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Randomised controlled trials for the prevention of cognitive decline or dementia: a systematic review

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Author contributions

NC: Data curation; Investigation; Methodology; Visualization; Writing - original draft

CG: Data curation; Investigation; Methodology; Visualization; Writing - original draft

PSA: Writing – reviewing and editing

BV: Writing – reviewing and editing

SA: Conceptualization; Methodology; Supervision; Writing – reviewing and editing

Highlights

- Over 110 prevention trials have now been published, but many were small-scale
- Pharmacological and lifestyle interventions have been tested; most showed no effect
- 2 large trials (testing multidomain or blood pressure interventions) were positive
- Ongoing trials are notably testing multidomain interventions and anti-amyloid drugs
- Methodological shifts concern target populations, endpoints and intervention design

Randomised controlled trials for the prevention of cognitive decline or dementia: a systematic review

Abstract

Dementia prevention research has progressed rapidly in recent years, with publication of several large lifestyle intervention trials, and renewed interest in pharmacological interventions, notably for individuals with Alzheimer's disease biomarkers, warranting an updated review of results and methodology. We identified 112 completed trials testing the efficacy of single-domain pharmacological (n=33, 29%), nutritional (n=27, 24%), physical activity (n=18, 16%) and cognitive stimulation (n=13, 12%), or multidomain (n=22, 20%) interventions on incident dementia, or a relevant intermediate marker (e.g. cognitive function, biomarkers or dementia risk scores) in people without dementia. The earliest trials tested pharmacological interventions or nutritional supplements, but lifestyle interventions predominated in the last decade. In total, 21 (19%) trials demonstrated a clear beneficial effect on the pre-specified primary outcome (or all co-primary outcomes), but only two (10%) were large-scale (testing blood pressure lowering (Syst-Eur) or multidomain (FINGER) interventions on incident dementia and cognitive change in cognitive function, respectively). Of the 116 ongoing trials, 40% (n=46) are testing multidomain interventions. Recent methodological shifts concern target populations, primary outcome measures, and intervention design, but study design remains constant (parallel group randomised controlled trial). Future trials may consider using adaptive trials or interventions, and more targeted approaches, since certain interventions may be more effective in certain subgroups of the population, and at specific times in the life-course. Efforts should also be made to increase the representativeness and diversity of prevention trial populations.

Keywords: dementia; Alzheimer's disease; cognitive decline; prevention; randomized controlled trials; clinical trial methodology

1. Introduction

Healthy ageing is a major concern around the world. Alzheimer's disease (AD) and other forms of dementia are key drivers of deteriorating late-life functioning, and, in the context of population ageing, the number of people living with such conditions is rapidly rising (G. B. D. Dementia Collaborators, 2019). Numerous longitudinal cohort studies have identified a group of modifiable risk factors (e.g. diet, physical activity, cognitive stimulation, hypertension, obesity) and a second group of non-modifiable risk factors (e.g. age, genetic factors) related to cognitive decline or dementia (Baumgart et al., 2015; Livingston et al., 2020). Around 40% cases of dementia potentially caused by this first group of risk factors may be preventable (Livingston et al., 2020). Accordingly, modification of these risk factors could influence cognitive trajectories in ageing. Randomised controlled trials provide the highest level of evidence to evaluate the impact of such changes and the effectiveness of the strategies implemented to achieve them, even if they present limitations, notably in terms of duration and population homogeneity.

Initial dementia prevention trials, reviewed in 2015 (Andrieu et al., 2015), demonstrated some degree of efficacy for certain interventions based on physical activity, cognitive training, or antihypertensive treatment, but methodological limitations, notably short follow-up periods and small sample sizes, meant that these results needed further confirmation in additional, adequately-designed, larger-scale trials. Furthermore, emerging evidence about potential beneficial effects of multidomain interventions on cognitive function required confirmation in additional large-scale studies, and longer-term effects of such interventions on dementia incidence needed to be assessed.

Finally, drug trials for dementia/cognitive decline prevention in individuals with evidence of biomarker or genetic risk factors for (sporadic forms of) Alzheimer's disease, in the absence of cognitive impairment, were starting to be designed and set up, but it was unclear if such trials would be feasible and acceptable to participants, and if anti-amyloid treatments, in particular, would be effective in such populations.

The field of interventional dementia prevention research has undergone rapid progression in recent years, including publication of the results of several large trials of blood pressure lowering, physical activity or multidomain interventions, and the initiation of additional trials testing anti-amyloid therapies in individuals with AD biomarkers. Therefore, in order to provide an overview of recent progress, in terms of both results and trial methodology, and to highlight future directions, we performed a systematic review to identify, analyse and synthesise completed and ongoing randomised controlled trials specifically designed to assess the efficacy of any kind of intervention on

incident dementia, or change over time in a relevant intermediate marker, such as cognitive function, dementia-related biomarkers or dementia risk scores, in people without dementia.

2. Methods

2.1 Search strategy

We updated our previous literature search, published in 2015 (Andrieu et al., 2015), using the same methodology. We searched PubMed from 11 May 2015 (the date of our last previous literature search) to 2 August 2022 for completed and ongoing randomised controlled trials, conducted in individuals without dementia, for the prevention of cognitive decline (i.e. decline in cognitive function over time) or sporadic forms of dementia. In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing trials (Supplementary Table 1). Certain additional articles were identified in our own files or in reference lists.

2.2 Eligibility criteria, study selection and data collection

As in our previous review (Andrieu et al., 2015), we included completed and ongoing randomised controlled trials with a pre-defined primary outcome measuring incident dementia (all-cause or Alzheimer's dementia) or mild cognitive impairment (MCI), or change from baseline in a relevant clinical or biological intermediate (surrogate) marker, such as cognitive function, dementia-relevant blood, imaging or cerebrospinal fluid (CSF) biomarkers, or dementia risk scores. We only included trials reporting an a priori sample size/power calculation for this primary outcome (i.e. those which were specifically designed to assess efficacy on this outcome), and those which were written in English. We excluded non-randomised controlled trials, trials that used a non-efficacy or cross-over study design, and pilot studies. We also excluded trials for individuals with diagnosed dementia or prodromal AD or for prevention of familial forms of AD, off-topic trials (e.g. those conducted in children, adolescents, pregnant women, or people with severe psychiatric antecedent, or those focused on depression, post-traumatic stress disorder, HIV, cancer, postoperative, smoking cessation, or phobia), and trials in which incident dementia or the relevant intermediate outcome was not the primary outcome.

2.3 Data extraction and classifications

The literature searches were performed by two of the authors (CG, NC). Articles were initially screened on the basis of titles and abstracts, and selected full-text articles were then read for the final step of data extraction. Any queries were resolved through discussion with a third author (SA). Data extracted from eligible studies included types of

intervention, duration of intervention and follow-up, primary outcome and eligibility criteria. Primary outcome measures were classified into four categories: incident dementia, cognitive function (measured using specific tests of global cognition or an individual cognitive domain, or composite cognitive scores combining scores from several different tests), biomarkers (blood, imaging or CSF), and other (e.g. dementia risk scores, incident MCI, other composite outcomes)), Based on each trial's eligibility criteria, we categorised study populations into 3 types: (i) "Mild Cognitive Impairment" (MCI), i.e. all trial participants met criteria for MCI (but were free of dementia and not diagnosed with prodromal AD); (ii) "At Risk", i.e. all participants were considered to be at increased risk of developing dementia (compared to the general population), on the basis of genetic, biological, imaging, clinical, family history or lifestyle risk factors; and (iii) "General Population", i.e. study participants were not selected on the basis of any specific risk factors other than age, or the study only included individuals with unimpaired cognition. All reference lists of included studies were checked to identify additional studies of interest.

Although all trials included in our review had to meet minimum methodological standards (i.e. being randomised and controlled, and having an a priori sample size calculation for a relevant primary outcome), we did not require a minimum sample size or follow-up duration. However, we developed a score enabling us to judge the scale of the included studies, and to identify large-scale trials, which are most likely to be able to detect clinically relevant intervention effects. The score was based on intervention duration (<12 months = 1 point, 12 months = 2 points, 13 - 24 months = 3 points, >24 months = 4 points) and sample size (<100 subjects = 1 point, 100 – 1000 subjects = 2 points, >1000 subjects = 3 points). The two parts of the score were summed to give the overall score, ranging from 2 to 7. Trials with a score of 6 or more were considered to be large-scale.

We classified the full set of completed trials, on the basis of their primary results, into the following four categories: (i) trials showing significant effects on (all of) the pre-specified (co-) primary outcome(s); (ii) trials showing significant effects on some, but not all co-primary outcomes (either the pre-specified co-primary outcomes, or all outcomes if none were clearly designated as primary), (iii) trials showing no significant effects on any primary outcome, and (iv) trials showing a significant detrimental effect on the primary outcome.

3. Results

3.1 Overall summary of results

In total, we identified 112 completed trials meeting our inclusion criteria, and 116 ongoing trials, as of 2 August 2022. The literature search flowchart and full description of the 48 completed trials published prior to May 2015 have been previously published (Andrieu et al., 2015) and the references for these trials can be found in Supplementary Table 2. The flowchart for the studies published since May 2015 can be found in Figure 1. The 64 completed trials published since May 2015 are summarised in Table 1. Full details of these trials, and of the ongoing trials, can be found in Supplementary Tables 3-12.

In total, 90 of the 112 completed trials tested single-domain interventions: 32 (29%) tested pharmacological interventions, 27 (24%) tested nutritional interventions, 18 (16%) tested physical activity interventions, 13 (12%) tested cognitive stimulation interventions. The remaining 22 trials (20%) tested multidomain interventions, which combined several different kinds of interventions simultaneously.

The number of completed prevention trials published has steadily increased over time (Figure 2). The first trial was published in 1998, and, like the majority of the earliest trials, tested a pharmacological intervention. The first lifestyle interventions began to be published from the mid-2000s, and mostly concerned nutritional or physical activity interventions for the first years. Lifestyle interventions tended to be the predominant type of intervention from 2010 onwards.

Figure 3 shows study scale ratings (ranging from 2 to 7) for the completed trials, by type of intervention. The pharmacological trials tended to be the largest-scale trials (average rating 5.6), followed by nutritional (average rating 3.8) and multidomain (average rating 3.7) trials. Cognitive stimulation trials were the smallest-scale trials, with an average rating of 2.9.

The primary results of the completed trials are summarised in Figure 4. 21 (19%) out of the 112 trials demonstrated a clear beneficial effect of an intervention on the pre-specified primary outcome (or all co-primary outcomes), of which 19 (90%) were small- or medium-scale trials, and nearly all measured changes in cognitive function as their primary outcome. Only two (7%) of the 28 large-scale trials, one testing a pharmacological (blood pressure lowering treatment) intervention, versus placebo, for the prevention of incident dementia (Forette et al., 1998), and one testing the effects of a multidomain intervention, compared to general health advice, on change in cognitive function (Ngandu et al., 2015), demonstrated a clear beneficial intervention effect. Three pharmacological interventions (testing an anti-amyloid drug (Sperling et al., 2021), a non-steroidal anti-inflammatory drug (Thal et al., 2005), or hormonal therapy (oestrogen plus progesterone)(Shumaker et al., 2003)) showed significant detrimental

effects of the investigative drug on the trial's pre-specified primary outcome (either incident dementia/AD or change in cognitive function), compared to placebo.

Of the 116 ongoing trials, 46 (40%) are testing multidomain interventions, 21 (18%) are testing nutritional interventions, 20 (17%) are testing physical activity interventions, 16 (14%) are testing cognitive stimulation interventions, and 13 (11%) are testing pharmacological interventions (Figure 5). Average study scale ratings are largest for the pharmacological trials (5.9), followed by multidomain trials (4.4). The other kinds of trials have average ratings between 3.8 (cognitive stimulation trials) and 3.4 (physical activity and nutritional trials).

Further details of the trials and their results, when available, are summarised below, by type of intervention.

3.2 Summary of trials by type of intervention

3.2.1 Pharmacological interventions

3.2.1.1 Antihypertensive treatment

Several of the initial trials of antihypertensive treatment showed promising results, notably the Syst-Eur trial, which found that nitrendipine treatment (with optional enalapril and/or hydro chlorothiazide) reduced incident dementia by 50% compared to placebo in 2418 hypertensive older adults, although there were few cases of dementia overall and follow-up time was only 2 years (Andrieu et al., 2015; Forette et al., 1998).

Two trials of anti-hypertensive treatments meeting our inclusion criteria have been published since May 2015 (Table 1, Supplementary Table 3). The largest, SPRINT MIND, compared an intensive blood pressure lowering intervention aimed at reducing systolic blood pressure to a target of <120 mmHg with standard treatment (<140 mmHg) in 8563 participants with hypertension aged 50 years or older (SPRINT MIND Investigators for the SPRINT Research Group et al., 2019). Investigating clinicians, who were not blinded to treatment allocation, could prescribe any major classes of antihypertensive agents. After a median of 3 years of treatment and 5 years of follow-up, no significant between-group differences were found for dementia incidence (HR, 0.83; 95% CI, 0.67-1.04). The study may have been underpowered, following early termination of treatment due to benefit on cardiovascular outcomes in the main SPRINT trial. However, intensive blood pressure treatment significantly reduced the risk of the secondary outcomes of MCI (HR, 0.81; 95% CI, 0.69-0.95) and the combined rate of MCI or probable dementia (HR, 0.85; 95%CI 0.74-0.97). It should be noted that in the main SPRINT trial, intensive blood pressure lowering was associated with increased adverse events (hypotension, syncope, electrolyte abnormalities, and acute renal failure) (Sprint Research

Group et al., 2015). Cognitive function was extensively assessed in a subgroup of 2921 SPRINT MIND participants, and there was no between-group difference in change in memory function over time, and slightly more decline in processing speed in the intensive treatment group (Rapp et al., 2020).

In the smaller-scale DANTE trial, there was no significant effect on overall cognition of discontinuation compared to continuation of antihypertensive treatment for 16 weeks in 385 individuals aged 75 or older with mild cognitive deficits and receiving antihypertensive treatment at inclusion (Moonen et al., 2015).

Two ongoing trials of anti-hypertensive treatment were identified (Supplementary Table 8), both of which are testing intensive blood pressure lowering interventions in individuals with raised blood pressure, either on change in cognitive function over 3.5 years in 920 patients attending primary care clinics predominantly managing underserved populations with health disparities (e.g. ethnic minorities, low-income groups, and residents of rural areas and inner cities) in the IMPACTS-MIND trial (NCT04797403), or on change in imaging markers of amyloid pathology over 2 years in 180 individuals with subjective memory complaints or a family history of dementia in the IPAT trial (NCT05331144).

3.2.1.2 Anti-amyloid treatments

Seven anti-amyloid studies were identified, of which four are ongoing, and three have been discontinued (Table 1, Supplementary Tables 3 and 8).

The A4 (Anti-Amyloid treatment in Asymptomatic Alzheimer's disease) study (NCT02008357) (Sperling et al., 2014), the first trial testing an anti-amyloid treatment in a preventive capacity, is still ongoing, and is investigating Solanezumab, a monoclonal antibody targeting soluble amyloid- β ($A\beta$), for the prevention of cognitive decline in 1150 clinically normal individuals aged 65-85 with PET evidence of brain amyloid pathology. The treatment dose and sample size were increased following the failure of Solanezumab trials in mild AD dementia patients (Honig et al., 2018).

The EARLY trial (A5; NCT02569398) involved 596 asymptomatic amyloid positive (CSF or PET) subjects aged 60-85 years at risk for developing Alzheimer's dementia (age ≥ 65 or family history of dementia, APOE $\epsilon 4$ genotype). Subjects were randomised to 5 or 25 mg daily of Atabecestat, an orally administered β -site amyloid precursor protein-cleaving enzyme 1 (BACE-1) inhibitor, or placebo. Dosing was discontinued in May 2018 because of hepatic adverse events (Henley et al., 2019). Following suggestions of negative effects of a different BACE-1 inhibitor on

cognition and function in prodromal AD patients (Egan et al., 2019), an expedited, ad hoc, interim analysis was performed which found that there was significantly greater decline in the high dose group compared to placebo on the primary outcome measure (a composite cognitive score measuring global cognitive function) (Henley et al., 2019), a result that was confirmed in the full analysis (Sperling et al., 2021). Furthermore, atabecestat treatment was associated increased adverse events, including neuropsychiatric events (Sperling et al., 2021).

The ongoing AHDEAD 3-45 program (NCT04468659) involves two trials (A3 and A45), both testing BAN2401 (lecanemab) for 4 years in cognitively normal individuals, with dosing regimens tailored to baseline amyloid level. Individuals with elevated amyloid will be enrolled in the A45 trial, which will measure change in cognitive function as its primary outcome, while those with intermediate amyloid will enter the A3 trial with PET amyloid as the primary outcome.

The GENERATION studies were designed to test two different anti-amyloid approaches in cognitively normal individuals who are APOE ϵ 4 carriers (Lopez Lopez et al., 2019). Generation Study 1 (NCT02565511) is assessing the efficacy of CAD106, a vaccine attacking brain beta-amyloid plaque deposits to stimulate A β -specific antibody and CNP520 (umibecestat), a BACE-1 inhibitor, administered separately, in cognitively unimpaired individuals at high risk of progression to MCI or AD on the basis of age (60–75 years) and APOE genotype (ϵ 4 homozygotes). Generation Study 2 (NCT03131453) is assessing the impact of CNP520 in cognitively unimpaired individuals aged 60–75 years who are APOE4 carriers. Those who are ϵ 4 heterozygotes must also have evidence of elevated brain amyloid. Dosing of CNP520 was stopped following an interim analysis showing worsening cognitive function with treatment (<https://www.nia.nih.gov/news/statement-discontinuation-bace-1-inhibitor-cnp520-alzheimers-prevention-initiative-generation>). The CAD106 arm was then also stopped. Neither study's results have so far been published. Two more recently initiated trials (TRAILBLAZER-ALZ 3 (NCT05026866), SKYLINE (NCT05256134)) are testing anti-amyloid antibodies (Donanemab, Gantenerumab) for 3.5-4 years in cognitively unimpaired individuals with evidence of amyloid, and, for the donanemab trial, tau pathology on changes in measures of cognitive or global function. These antibodies have shown some evidence of effects on AD biomarkers in dominantly inherited Alzheimer's disease (Salloway et al., 2021a) or on a composite measure of cognition and function in early AD (Mintun et al., 2021).

3.2.1.3 Non-steroidal anti-inflammatories (NSAIDs)

Initial trials of NSAIDs (including nonselective COX inhibitors (e.g., aspirin, naproxen) and COX-2 selective inhibitors (e.g., celecoxib and rofecoxib) did not provide evidence of dementia prevention, and some were stopped early due to safety concerns and recruitment difficulties (Andrieu et al., 2015). All were conducted in older populations, and had short treatment durations.

Three recent trials of NSAIDs were identified (Table 1, Supplementary Table 3). In INTREPAD (Meyer et al., 2019), 2 years' treatment with naproxen sodium in 195 cognitively normal individuals aged ≥ 60 years (or ≥ 55 years if within 15 years of youngest affected relative's onset) with parental or multiple sibling history of AD did not show a reduction in the change on a multimodal composite presymptomatic Alzheimer Progression Score (APS) compared to placebo, and increased adverse events. In addition, two very large placebo-controlled trials found no beneficial effect of 4.7-7.4 years treatment with 100mg aspirin daily, on incident dementia (rate ratio 0.91 [95% CI, 0.81–1.02, $p=0.11$) in 15,427 adults aged 40 and over with diabetes (Parish et al., 2022), or on a composite primary endpoint of death, dementia, or persistent physical disability (HR, 1.01; 95% CI, 0.92 to 1.11; $P=0.79$) in 19,114 individuals aged 70 (≥ 65 for blacks and Hispanics) and older (secondary analyses also showed no effect of aspirin on incident all-cause dementia, probable AD or MCI, or on change in cognitive function over time) (McNeil et al., 2018; Ryan et al., 2020). Aspirin was associated with an increased risk of major haemorrhage in both trials (Ascend Study Collaborative Group et al., 2018; McNeil et al., 2018).

No ongoing trials of NSAIDs were identified.

3.2.1.4 Hormone therapy

The first large-scale trial of hormone replacement therapy, the Women's Health Initiative Memory Study (WHIMS), showed a significantly increased risk of dementia, compared to placebo, after about 4 years of treatment with oestrogen and progestin in 4500 postmenopausal women (Shumaker et al., 2003), and non-significant increased risk with oestrogen alone (Shumaker et al., 2004). It was then hypothesised that hormone replacement therapy might only benefit cognition during the critical period around the time of menopause (Sherwin, 2009), but the more recently published ancillary Cognitive and Affective Study (KEEPS-Cog) of the Kronos Early Estrogen Prevention Study (KEEPS) found no effect of 4 years' oral or transdermal oestrogen plus progesterone, versus placebo, on global cognition nor on individual domains of cognitive function in 473 recently post-menopausal women (Table 1, Supplementary Table 3) (Gleason et al., 2015). Also, in the ELITE study ($N=567$), estradiol therapy initiated within six

years of menopause did not affect verbal episodic memory (primary outcome), executive function or global cognition compared to placebo or compared with when the therapy was begun ≥ 10 years after menopause (Henderson et al., 2016), and a small trial (N=37) in postmenopausal women aged 57-82 years with amnesic MCI (treated with donepezil) found no benefit of hormone therapy on cognitive function after 24 months, compared to placebo (Yoon et al., 2018).

In the Testosterone trials (Ttrials; N=493), no significant improvement of memory was found after 12 months of daily administration of testosterone gel in men with a low testosterone and age-associated memory impairment (Resnick et al., 2017).

No ongoing trials of hormone therapy were identified.

3.2.1.5 Other pharmacological interventions

Three other pharmacological trials were published since May 2015 (Table 1, Supplementary Table 3). The TOMMORROW trial randomised 3061 individuals aged 65-83 years at high risk of AD, based on a biomarker risk assignment algorithm, to either pioglitazone or placebo (Burns et al., 2021). The trial was stopped after a mean of approximately 2.5 years of treatment, following a pre-planned futility analysis. Pioglitazone did not delay the onset of MCI due to AD (MCI-AD; HR 0.80, 99% CI 0.45–1.40; $p=0.307$). The study also aimed to test and qualify the algorithm used to identify and stratify participants. Those designated “high risk” had a 3 times higher risk than the “low risk” group of developing MCI-AD, although this result did not meet the predefined level of statistical significance (HR 3.26, 99% CI 0.85–12.45; $p=0.023$). In the cognitive sub study of the Cardiovascular and Renal Microvascular outcome study with LINagliptin (CARMELINA), conducted in 1545 individuals with type 2 diabetes and cardiorenal disease, there was no effect of 2.5 years’ treatment with linagliptin on incident accelerated cognitive decline, compared to placebo (Biessels et al., 2019). Finally, a smaller-scale trial ($n=268$, 24 weeks’ follow-up), found no effect of a casein-derived angiotensin-converting enzyme inhibitory peptide (Met-Lys-Pro) on cognitive function (Yuda et al., 2020).

Five other ongoing pharmacological trials were identified (Supplementary Table 8). The largest of these, PREVENTABLE (NCT04262206), is testing the effects of up to 5 years’ treatment with atorvastatin on a composite outcome of death, dementia, and persistent disability in 20,000 individuals aged 75 and older. The other (small- and medium-scale) trials, involving between 80 and 370 participants, are testing lithium carbonate or metformin in

individuals with MCI, intranasal insulin in individuals with diabetes (Galindo-Mendez et al., 2020), and the sleep aid Suvorexant in individuals with raised amyloid.

3.2.2 Nutrition

Initial trials of nutritional interventions essentially tested nutritional supplements including homocysteine-lowering B-vitamins, antioxidants, omega-3 fatty acids, and flavonoids, and the only evidence of beneficial results on cognition came from small-scale trials of flavonoids (Andrieu et al., 2015; Desideri et al., 2012; Mastroiacovo et al., 2015). A medium-scale trial of B-vitamins also found a beneficial effect of B-vitamins on the rate of brain atrophy in individuals with MCI (Smith et al., 2010).

The results of several additional nutritional prevention trials have been published in the last 6 years (Table 1, Supplementary Table 4). In the largest of these, PREADViSE, 7540 men aged 60 years or older were randomised to receive vitamin E, selenium, both vitamin E and selenium, or placebo, and 3786 continued into an observational follow-up period and completed memory evaluations after treatment was stopped due to a futility analysis for the parent SELECT trial. After an average of 5.4 years of intervention and up to 10 years of follow-up, no difference in dementia incidence was found between the study arms (Kryscio et al., 2017). Study power was limited by the reduced treatment period and the relatively low incidence of dementia, likely because of selection bias, since participants had a relatively high educational level (Kryscio et al., 2013). The PREADViSE trial was an ancillary study to the SELECT trial, which found potentially major negative effects of these supplements (including possible increases of prostate cancer and diabetes) (Kryscio et al., 2017).

One other recent large-scale trial was identified (Kwok et al., 2017), but found no effect of 27 months' vitamin B12 supplementation on cognitive decline (i.e. an increase in clinical dementia rating scale (CDR) global score) in 271 older adults aged 70-100 years with low baseline vitamin B12.

As part of the MAPT trial, involving 1680 subjects presenting a memory complaint, limitation in one instrumental activity of daily living, and/or low gait speed, one of the study arms (n=423) was randomised to 3-years omega-3 fatty acid supplementation (other arms are detailed in the section on Multidomain interventions), and change in cognitive function was compared to placebo (n=420) (Andrieu et al., 2017). This study was the longest trial of omega-3 fatty acid supplementation to date for the prevention of cognitive decline. After three years of intervention, changes in composite cognitive scores did not differ between the omega-3 and placebo groups. Since the rate of

cognitive decline was found to be significantly greater in individuals with a low baseline omega-3 index, and there was some indication of a possible beneficial effect of supplementation in this subgroup (Andrieu et al., 2017; Coley et al., 2018), an ongoing trial has been set up to specifically assess the impact of omega-3 supplementation on change in cognitive function in individuals with a low omega-3 index (LO-MAPT NCT03691519). Two further trials, one testing omega-3 supplementation for 18 months in 400 community-dwelling adults aged 65-90 years (Danthiir et al., 2018), and another testing 1 year's supplementation with an omega-3 rich multivitamin in 99 dementia-free institutionalised individuals aged 75 and older (Baleztena et al., 2018), found no effect of supplementation cognitive function, compared to placebo.

Of the remaining recent trials testing supplements (Table 1, Supplementary Table 4) (Ahles et al., 2020; Asaoka et al., 2022; Evans et al., 2016; Evans et al., 2017; Harris et al., 2015; Schwarz et al., 2022; You et al., 2021; Zajac et al., 2020), none were large-scale, and only one, a 14-week placebo-controlled trial of resveratrol, a natural phenol, in 80 post-menopausal women, found a clear beneficial effect on cognitive function (Evans et al., 2017). The other trials (Coates et al., 2020; Nishimaki et al., 2018; Sakurai et al., 2020; Sala-Vila et al., 2020; Siddarth et al., 2020), which were small- or medium-scale, tested diets enriched with a specific food or drink (hydrogen-infused water, almonds, walnuts, pomegranate juice, Matcha green tea), but did not show a beneficial effect on all primary outcomes.

Among the additional 20 ongoing trials (Supplementary Table 9), the majority of the larger trials are testing interventions based on dietary patterns, rather than a single nutrient or supplement. Two trials ((Liu et al., 2021), NCT04337255) are testing the effects of the MIND Diet, a hybrid of the Mediterranean and DASH diets, on cognitive function, respectively for 3 years in 600 overweight individuals with a family history of dementia aged 65-84 years, and for 2-3 years in 500 individuals aged 60-80 years with a recent ischemic stroke. Two further trials ((Tussing-Humphreys et al., 2017), NCT03841539) are, respectively, testing an 8-month Mediterranean diet intervention, with or without caloric restriction/weight loss, in 180 overweight or obese individuals aged 55 and older, and a 1-year Mediterranean diet intervention, with or without omega-3 supplementation, in 200 individuals aged 65 and older. The other ongoing trials, many of which are small-scale, are all testing dietary supplements (including specific food supplements).

3.2.3 Physical activity

Encouraging results suggesting a beneficial effect of various types of physical activity on cognitive function in older adults were found in several of the earlier physical activity trials (Anderson-Hanley et al., 2012; Lautenschlager et al., 2008; Liu-Ambrose et al., 2010; Muscari et al., 2010), but given their small sample sizes and short intervention periods, evidence remained inconclusive (Andrieu et al., 2015). The results of the LIFE study (N=1635), which tested structured moderate-intensity physical activity (including walking, resistance training and flexibility) in sedentary individuals aged 70-89 years at high risk of mobility disability, were therefore eagerly awaited. After the 24-month program, global and domain-specific cognitive function was not improved in the physical activity group compared with a health education control group, even though the intervention group performed significantly more physical activity than the control group during the trial (Sink et al., 2015). Nevertheless, cognitive scores remained stable during follow-up for both groups. Similarly, the 2-year AIBL ACTIVE trial of home-based physical activity, in 108 participants aged ≥ 60 with subjective memory complaints, MCI or vascular risk factors, found no significant effect on its primary outcome, white matter hyperintensity load, or on the secondary outcome of hippocampal volume, regardless of baseline cognitive or beta amyloid status, or intervention adherence, although physical activity levels at the end of the trial were not different between the intervention and control groups (Venkatraman et al., 2020). Seven shorter and/or smaller physical activity trials have also been recently published (Table 1, Supplementary Table 5), of which, two both enrolling participants with MCI, respectively testing 3 months' choreographed aerobic dances, and 6 months' group aerobic and strength training, showed significant effects on the primary cognitive function outcomes (Bisbe et al., 2020; Langoni et al., 2019). Four of the five remaining trials showed significant effects of tai chi, golf training, aerobic exercise or resistance training on some but not all primary outcome measures of cognitive function (Marston et al., 2019; Shimada et al., 2018; Sungkarat et al., 2017; Tarumi et al., 2019), while the fifth found no significant effects of extensive aerobic or non-aerobic exercise (Stuckenschneider et al., 2020).

There is therefore still only relatively limited evidence of the benefit of physical activity on cognition from RCTs. Questions remain about the efficacy of different types, intensity, timing and duration of physical activity, and which outcomes are most susceptible to improve in which populations. Subgroup analyses of the LIFE trial suggested that moderate-intensity physical activity may have improved executive function in individuals aged 80 and older and those with poorer baseline physical function (Sink et al., 2015), but these exploratory results require confirmation. There are 20 ongoing trials of physical activity testing various types of aerobic and/or strength training exercises of different intensities delivered either in person, online or via mobile apps (Supplementary Table 10), of which the

largest is the Exercise for the Prevention of Dementia (EPD) trial which is testing long-term (3 hours a week for 4 years) supervised multimodal (aerobic, endurance and flexibility) exercise in 540 individuals aged 50 and older (Iuliano et al., 2019). Furthermore, the 3-year TIME study (NCT05310890), testing a tai chi intervention in 206 individuals with MCI due to AD, is the first physical activity trial to measure dementia incidence as its primary outcome.

3.2.4 Cognitive activity/stimulation, and social and self-development interventions

Although inconclusive, several early trials (Kwok et al., 2013; Smith et al., 2009; Willis et al., 2006; Wolinsky et al., 2013), notably the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial of 2832 adults aged 65 years and over (Willis et al., 2006), provided some evidence that cognitive stimulation or training could be beneficial for late-life cognitive or functional status. Intervention periods tended to be very short (Andrieu et al., 2015), but in some cases, intervention effects were detectable even after 10 years (Rebok et al., 2014).

The eight recently published trials were all relatively small-scale, involving at most 150 participants and no more than 3 months of intervention (Table 1, Supplementary Table 6). Two trials, respectively involving 124 participants aged ≥ 55 years and 160 participants aged ≥ 60 years with subjective memory complaints or MCI, found beneficial effects of a 3-month cognitive remediation program on a composite score of neurocognition and a 6 week robot-assisted cognitive training program on three primary outcome measures of global cognitive function (Montoya-Murillo et al., 2020; Park et al., 2021). Three further trials found significant benefits of board games (with face-to-face games giving rise to stronger effect sizes than online games), home-based adaptive computerised cognitive training, or visual, but not auditory, games-based computerised cognitive training on some but not all primary cognitive function outcomes (Faust et al., 2020; Iizuka et al., 2019; Simon et al., 2018), while the other three found no significant effects of jigsaw puzzles, interactive cognitive-motor step training (a combination of complex cognitive processing and motor movement stimulation using videogame technology) or tailored and adaptive computerised cognitive training (Bahar-Fuchs et al., 2020; Fissler et al., 2018; Fissler et al., 2017; Schoene et al., 2015).

There are 16 ongoing trials of cognitive stimulation interventions (Supplementary Table 11), including several which are larger and/or longer than the completed trials (Figure 3, Figure 5). The longest is testing the efficacy of up to 48-87 months of cognitive remediation plus transcranial direct current stimulation on the rate of cognitive decline in 375 individuals with MCI and/or remitted major depressive disorder (Rajji et al., 2020). Additional types of cognitive

stimulation interventions being tested include internet-based conversational engagement ((Yu et al., 2021)), choral singing (NCT02919748), piano playing (Hudak et al., 2019; James et al., 2020), foreign language training (NTR7336), and horticultural therapy (NCT03045718).

3.2.5 Multidomain interventions

Multidomain interventions are currently receiving great attention in the field of dementia prevention, notably following the results of the FINGER trial, the first large-scale (N=1200) multidomain trial to report results, which showed improved cognitive performance in individuals aged 60–77 years with an increased dementia risk score in Finland following 2-years of intensive multidomain intervention, compared to general health advice (Ngandu et al., 2015).

In recent years, several additional large-scale multidomain trials have been published (Table 1, Supplementary Table 7). In the Dutch PREDIVA study, 3526 subjects included by their general practice were randomised into a vascular care intervention group (personalised health advice and, if indicated, drug treatments for hypertension, dyslipidaemia or type 2 diabetes) or a control group. After >6 years of treatment, the incidence of dementia did not differ significantly between the two groups, with an incidence of 7% in each arm (Moll van Charante et al., 2016). Subgroup analyses suggested possible beneficial effects on all-cause dementia in subjects who were adherent to the intervention and those who were not treated for hypertension at baseline, although no effect of the intervention was found on dementia incidence following a 4-year additional observational follow-up period, even in subgroups (Hoevenaer-Blom et al., 2021).

The French MAPT study randomised 1680 individuals aged 70 and older with memory complaints and/or slow walking speed and/or an IADL limitation to a multidomain intervention (group-based cognitive training, physical activity and nutrition advice, and annual preventive consultation) and/or omega-3 supplementation and did not demonstrate any significant intervention effects on the rate of change in cognitive function, compared to placebo, after three years' intervention (Andrieu et al., 2017). Exploratory subgroup analyses suggested that multidomain intervention may have been beneficial on cognitive function in subjects with an increased dementia risk score, and those with PET evidence of amyloid accumulation. A 1-year cluster-randomised trial in Taiwan testing a similar intervention in a similar target population also found no significant effect on cognitive function, compared to a health education control group, although in a second cluster-randomised study, an “enhanced” version of the

intervention, “redesigned to empower and motivate” participants (through redesigned teaching materials, additional work-sheets and pedometers to support goal setting and monitoring, and greater community involvement) brought about significant improvements in cognitive function after 9 months, compared to the original intervention (Chen et al., 2020).

The final large-scale trial, the European DO-HEALTH study, randomised 2157 individuals aged 70 and older to vitamin D3 and/or strength training and/or omega-3 supplementation for 3 years, and found no effect of any intervention individually or in combination, compared to placebo, on cognitive function (measured using the MMSE) or any of the 5 other co-primary outcomes (Bischoff-Ferrari et al., 2020).

A further study by Rovner and colleagues randomised 221 black individuals aged 65 and older with amnesic MCI to receive either behavioural activation (involving goal setting and action planning to reinforce the practice of healthy cognitive, physical and social activities) or supportive therapy (a psychological treatment facilitating personal expression using discussions focused on the experience of aging (control)) for two years (Rovner et al., 2018). There was a significant difference in episodic memory decline between these groups.

Of the 13 remaining recent, smaller-scale, multidomain trials (including between 20 and 308 subjects with 8 to 40 weeks of follow-up) in individuals with or without MCI, one found a clear beneficial effect of a 6 month intervention combining aerobic exercise and the DASH diet on executive function in 160 sedentary individuals aged over 55 years with cognitive impairment no dementia (CIND) or cardiovascular disease/risk factor (Blumenthal et al., 2019), and one found a clear beneficial effect of a 6-month multicomponent intervention (dietary guidance, physical training, computer-aided cognitive training, and management and monitoring of metabolic indicators and vascular risk factors) on global cognitive function in 122 older adults with MCI (Yang et al., 2022). One very small trial also found a beneficial effect of 12-week exergame-based dual task training (motor and cognitive video games performed whilst walking on a treadmill) on measures of executive function and dual task performance (Wang et al., 2021). The 10 other trials found either no significant intervention effects, or significant effects on only some primary cognitive function outcome measures, compared to their respective control groups (Bae et al., 2019; Daly et al., 2015; Formica et al., 2020; Imaoka et al., 2019; Inoue et al., 2018; Law et al., 2022; Lebedev et al., 2020; Matsubara et al., 2021; McMaster et al., 2020; Nilsson et al., 2020; Shimada et al., 2018). Furthermore, there are 45 ongoing multidomain trials (Supplementary Table 12), many of which belong to the World-Wide FINGERS initiative (Rosenberg et al., 2020), which is aiming to evaluate the efficacy of locally-adapted versions of the FINGER intervention in multiple

countries across the world using harmonised methodologies. Further, the 2-year MET-FINGER trial is evaluating the efficacy of the FINGER multidomain intervention combined with metformin where indicated (i.e. no diagnosed diabetes + elevated adiposity OR mildly impaired fasting glucose) (NCT05109169). Other ongoing trials are testing digital multidomain interventions ((Eggink et al., 2021; Gray et al., 2022; Heffernan et al., 2019), NCT04465812, JPRN-UMIN000041926, ACTRN12619001392156, KCT0005231, NCT05407857, NCT05375513), including the PRODEMOS trial which is testing the efficacy of an 18-month coach-supported interactive mHealth application (based on the eHealth platform which brought about modest, but significant, decreases in cardiovascular and dementia risk scores in the HATICE trial (Richard et al., 2019)) encouraging participants to make lifestyle changes and manage risk factors on estimated dementia risk in 2400 individuals aged 55 - 75 years in the UK (with low socio-economic status) and in China (Eggink et al., 2021).

4. Discussion

We identified a total of 112 completed RCTs testing pharmacological and/or lifestyle interventions for the prevention of dementia or cognitive decline, or for the improvement of biomarker, imaging or dementia risk profiles, with a substantial increase in the number of trials, notably those testing lifestyle interventions, published in the last five years. While our inclusion criteria aimed to select only trials that were specifically designed and sufficiently powered for dementia prevention (or to assess intervention effects on a relevant surrogate marker), we did not specify a minimum sample size or study duration, and only a quarter of the trials were considered large-scale. Despite having a sample size calculation, many of the smaller trials were not designed or powered to detect long-term and/or clinically meaningful effects on dementia-relevant outcomes, and also often did not clearly specify their primary outcome measure (often using a battery of multiple cognitive tests, without specifying which test or comparison was the primary outcome, and/or without statistical correction for multiple comparisons). Only two large-scale trials demonstrated a clear beneficial intervention effect: one found antihypertensive treatment to significantly lower dementia incidence (Forette et al., 1998) and the other found a multidomain lifestyle intervention to significantly improve cognitive function (Ngandu et al., 2015). Both trials were conducted in individuals considered to be at increased risk of developing dementia (i.e. having raised blood pressure, or a raised dementia risk score (based on age, sex, level of education, blood pressure, body mass index and cholesterol)). However other large-scale trials of similar types of interventions found no clear beneficial effects, even in at-risk populations (Andrieu et al.,

2017; Bischoff-Ferrari et al., 2020; Moll van Charante et al., 2016; Peters et al., 2008; SPRINT MIND Investigators for the SPRINT Research Group et al., 2019; Tzourio et al., 2003). Additionally, 19 small- or medium-scale trials found beneficial effects, in individuals with MCI, at increased risk of developing dementia, or in the general population, of certain types of nutritional (Desideri et al., 2012; Evans et al., 2017; Mastroiacovo et al., 2015), cognitive stimulation (Kwok et al., 2013; Montoya-Murillo et al., 2020; Park et al., 2021; Smith et al., 2009; Wolinsky et al., 2013), physical activity (Anderson-Hanley et al., 2012; Bisbe et al., 2020; Langoni et al., 2019; Lautenschlager et al., 2008; Liu-Ambrose et al., 2010; Muscari et al., 2010), or multidomain interventions (Blumenthal et al., 2019; Rovner et al., 2018; Wang et al., 2021; Yang et al., 2022) on cognitive function or, in one case, brain atrophy (Smith et al., 2010), and several pharmacological interventions showed either significant detrimental effects on the primary outcome measure (Henley et al., 2019; Shumaker et al., 2004; Shumaker et al., 2003; Sperling et al., 2021; Thal et al., 2005) and/or increased adverse events (ADAPT Research Group, 2006; Kryscio et al., 2017; McNeil et al., 2018; Meyer et al., 2019; Sperling et al., 2021; Sprint Research Group et al., 2015).

Due to the substantial heterogeneity in intervention content, delivery and duration, target populations and outcome measures, we did not perform any meta-analysis, but it is evident that clear-cut evidence of the efficacy of interventions on clinically meaningful outcomes for dementia prevention remains lacking. This heterogeneity may explain much of the diversity in results.

4.1 Methodological issues

4.1.1 Target populations: shifting towards targeted dementia prevention

Prevention trial results may differ depending on the target population, which has varied so far, notably in terms of age, genetic, biological, lifestyle and cardiovascular risk factors, and cognitive performance. A given intervention may only be effective in certain subgroups, and it remains challenging to ensure that the right interventions are tested in the right target population at the right period of life. It is likely that many dementia prevention trials, both pharmacological and non-pharmacological, have been conducted in individuals who were too old and/or with insufficient dementia risk factors in order to demonstrate cognitive benefit from the interventions being tested. In the case of multidomain interventions targeting lifestyle behaviours and cardiovascular risk factors, for example, of four large-scale trials (Andrieu et al., 2017; Bischoff-Ferrari et al., 2020; Moll van Charante et al., 2016; Ngandu et al., 2015), only one showed a beneficial intervention effect on cognition in the primary analysis (Ngandu et al., 2015).

This trial was conducted in individuals who were slightly younger than those included in the other three trials, and had raised dementia risk scores, and cognitive function at the mean level or slightly lower than expected for age at baseline (Ngandu et al., 2015). In two of the other three large-scale trials, which included older individuals who were not selected on the basis of dementia risk scores, and did not exclude those with very high cognitive performance, although there were no beneficial effects detected in the primary analyses, there were significant intervention effects in certain subgroups defined by raised dementia risk scores (Andrieu et al., 2017), untreated cardiovascular risk factors (Moll van Charante et al., 2016), or raised amyloid biomarkers (Andrieu et al., 2017) (the third large-scale trial did not report any subgroup analyses). Another study found beneficial effects of a 2-year multidomain intervention on cognitive function in individuals with mild cognitive impairment (Rovner et al., 2018). There is also some indication from subgroup analyses that multidomain interventions might benefit cognition more in ApoE4 carriers than non-carriers (Andrieu et al., 2017; Berkowitz et al., 2018; Hafdi et al., 2021; Solomon et al., 2018). The available evidence, therefore points towards greater efficacy of multidomain interventions based around lifestyle and cardiovascular risk factors when they are targeted to certain at-risk populations.

Many of the ongoing multidomain trials are building on these findings (Supplementary Table 12), and enrolling only subjects with increased dementia risk profiles. Interestingly, some trials are specifically targeting populations, such as those with lower socio-economic status, at risk of health disparities, in whom management of dementia risk factors is likely to be sub-optimal ((Eggink et al., 2021), NCT04797403). However, recruitment of such populations is likely to be challenging, since they are typically less likely to participate in dementia prevention trials (Coley et al., 2021; Fitzpatrick et al., 2006; Ngandu et al., 2014).

Targeted risk-based approaches are also being employed for other kinds of interventions, with, for example, some pharmacological trials targeting individuals with genetic or biological risk factors for AD (Lopez Lopez et al., 2019; Sperling et al., 2014) (NCT02008357, NCT04468659). Such trials have raised ethical concerns about the disclosure of genetic/biomarker status, particularly to cognitively healthy individuals, in a research setting (Roberts et al., 2013). Nonetheless, these trials have shown that it is feasible to recruit cognitively normal biomarker or genetic risk factor positive individuals to relatively long-term pharmacological trials for AD prevention, and initial research suggests that, when following a specifically devised and standardised protocol for disclosure of risk factor status, participants generally understand what their results mean (Largent et al., 2020), and that psychological impact of disclosure may be not be as harmful as feared (Erickson et al., 2021; Grill et al., 2020). Furthermore, learning that they have a high

risk status may motivate individuals to make health behaviour changes and to think about potential future long-term care needs (Erickson et al., 2021; Largent et al., 2020). However, it is likely the individuals who are willing to participate in such trials and to learn their biomarker/genetic risk status are not representative of the general population (Ott et al., 2016). Furthermore, if a preventive treatment for asymptomatic individuals were found to be effective in a population defined by biomarkers, particularly those measured via lumbar puncture or imaging, it is uncertain how such a treatment could be integrated into general clinical practice, in the absence of widely available and affordable biomarkers. Indeed, in the case of anti-amyloid therapeutics, the rationale for treating biomarker-negative individuals is questionable. The recent FDA accelerated approval of aducanumab for MCI or mild dementia due to Alzheimer's disease, and the ensuing debate about which patients should actually receive the treatment in clinical practice, given that clinical trials of this treatment only included biomarker-positive individuals, demonstrates the challenges of rolling out treatments tested in biomarker-defined populations, even in symptomatic patients (Cummings et al., 2021). These challenges would be further increased in a prevention setting, although recent progress in blood-based biomarkers provides a potential pathway forward (Blennow, 2021).

4.1.2 Outcome measures: the rise of surrogates

Tests of cognitive function remain the most prominent type of primary outcome measure in prevention trials (Table 1, Figure 3, Figure 5), but there is little standardisation of the types of tests used across different studies, and no gold standard test or battery of tests (Supplementary Tables 3-12). Furthermore, there is generally little consideration of the clinical relevance of the expected or observed intervention effects, particularly in smaller-scale trials. Some larger trials continue to measure clinical events, such as incident dementia or MCI, as their primary outcome, however (Kryscio et al., 2017; Lin et al., 2018; Lopez Lopez et al., 2019; Moll van Charante et al., 2016; SPRINT MIND Investigators for the SPRINT Research Group et al., 2019) (JPRN-UMIN000041926, NCT04465812, NCT02967406). Recent trials are targeting individuals at increased risk of dementia in late mid- and early late-life, but the choice of outcome measure for such trials is problematic. Indeed, in the absence of extremely lengthy follow-up periods, it is unfeasible to measure dementia incidence, and even very sensitive cognitive test batteries struggle to detect changes in cognitive function in younger populations (Salloway et al., 2021b). Novel outcome measures, that may act as surrogate endpoints and thus reduce sample size and follow-up time, for these trials include biomarkers (e.g. imaging outcomes in the A3 study of the AHEAD platform), dementia risk scores (Coley et al., 2020), and

computerised cognitive tests (Bae et al., 2019; Formica et al., 2020) which may be more sensitive, and less prone to learning effects, than traditional pencil and paper tests (Brooker et al., 2020). Digital biomarkers, based on mobile and wearable technologies, are also under consideration (Kourtis et al., 2019). In all cases, these endpoints require thorough validation, including determining their clinical meaningfulness. For example, several multidomain trials have demonstrated significant intervention effects on dementia risk scores (Coley et al., 2020; Deckers et al., 2021; McMaster et al., 2020; Solomon et al., 2021), which include modifiable risk factors, such as blood pressure, body mass index, and physical activity, but none of these risk scores were specifically designed as an intervention trial outcome measure, and it is unclear what impact a relatively small and short-term change on a risk score will have on the long-term incidence of dementia (Coley et al., 2020). Likewise, it is difficult to determine the impact of modest changes in biomarkers or imaging on disease onset or progression (McDade et al., 2021). However, the FDA decision on aducanumab is based on the view that substantial reduction of brain amyloid as measured by PET scan is reasonably likely to predict clinically meaningful change, based in part on supportive data from other similar therapeutics (Mintun et al., 2021; Swanson et al., 2021). Furthermore, the use of invasive (e.g. requiring lumbar puncture or imaging), or technology-dependent outcome measures will depend upon acceptability amongst potential trial participants and may further enhance the selection biases already apparent in dementia prevention trials (Coley et al., 2021). The development of blood-based biomarkers is a significant advance in this respect (Blennow, 2021; Teunissen et al., 2021), since measurements are much less invasive and burdensome compared to other types of biomarkers.

4.1.3 Intervention delivery and dose, and adherence: balancing intensity and burden, and the importance of human interaction

Discrepancies in prevention trial results may also arise through differences in intervention design (Kivipelto et al., 2018). For pharmacological trials, this may include the dose and/or type of molecule tested, with, for example, suggestions of different results for different classes of antihypertensive treatments, hormone therapies, and anti-amyloid treatments (Coley et al., 2008). For non-pharmacological trials, intervention design is even more complex, and can include method of delivery, level of supervision and/or interaction with those delivering the intervention and other participants, the degree to which the intervention stimulates participant motivation, and the intensity, frequency and duration of the intervention, in addition to the actual content (e.g. the individual components of a

multidomain intervention, aerobic versus other kinds of physical activity, dietary supplement versus dietary guidelines in a nutritional intervention and/or the specific kind of supplement/diet (e.g. B-vitamins or omega-3 supplement, MIND versus DASH diet, etc.), type of cognitive training (pencil and paper or computerised, targeted cognitive abilities), etc.). There have generally been very few trials which have tested exactly the same type of intervention, even amongst pharmacological trials. Standardisation is even more complex for non-pharmacological trials, and even more so when one factors in cultural adaptations, but, for example, the Worldwide Fingers Network is attempting to address this issue to some extent (Kivipelto et al., 2020). Between-country differences in motivations for participating in and adhering to lifestyle-based prevention (Coley et al., 2019b), perhaps relating to cultural differences in attitudes to behaviour change, prevention and research participation, as well as differences in local healthcare systems, might also affect intervention design and efficacy.

It can be challenging to determine the optimal dose of pharmacological and especially lifestyle preventive interventions. In the case of multidomain interventions, there is so far little data about optimal dose (Belleville et al., 2022), but greater adherence to such interventions has been associated with better outcomes.(Coley et al., 2022; Moll van Charante et al., 2016; Ngandu et al., 2021). Furthermore, an insufficient dose and decreasing adherence were suggested as possible reasons for the lack of cognitive effect in the LIFE physical activity trial (although it cannot be completely excluded that there was a lack of effect because associations between physical activity and dementia risk in observational studies are attributable to reverse causality, rather than a true protective effect of physical activity) (Sabia et al., 2017; Sink et al., 2015). Maximising adherence to lifestyle interventions, particularly in the long-term, is challenging, and probably dependent on the intensity of the intervention (which itself may influence efficacy). For example, the FINGER multidomain intervention (Ngandu et al., 2015), which showed a beneficial effect on cognition, was more intensive than other multidomain interventions which did not show a beneficial effect on their primary outcomes (Andrieu et al., 2017; Bischoff-Ferrari et al., 2020; Moll van Charante et al., 2016), but adherence may have been lower than in other trials (Coley et al., 2019a). Indeed, adherence was found to be higher to less intensive components of both the FINGER and MAPT multidomain interventions (Coley et al., 2019a), but it should also be noted that some of these components were also supervised (compared to others which participants had to perform on their own), which may also have played a role, since maintaining social interaction and communication appears to be important for older individuals participating in prevention trials (Sano et al., 2019; van Middelaar et al., 2018). Nonetheless, adherence to a 24-month home-based physical activity

intervention was very high (91.67%) in one study of individuals aged 60 and older, although participants were already part of an imaging biomarkers study, and may have been very highly motivated to participate in research studies (Cox et al., 2019).

Trials employing digital interventions, which are becoming increasingly widespread, should strive to ensure they also maintain sufficient human contact. Providing human support for such interventions might also help to decrease disparities in their use (Coley et al., 2022), and, in the case of lifestyle interventions, help to provide motivation for behavioural change (Beishuizen et al., 2016). Strategies aiming to stimulate participants to make and sustain behaviour changes employed so far include motivational interviewing, goal setting and monitoring, and action plans (Andrieu et al., 2017; Chen et al., 2020; Richard et al., 2019; Rovner et al., 2018).

4.2 Conclusions, recommendations and future perspectives

Perhaps due to the methodological challenges of conducting dementia prevention trials, and despite the publication of more than 100 specifically designed RCTs in the last two decades, there is still no definitive evidence confirming the efficacy of any kind of pharmacological or non-pharmacological intervention for the prevention of cognitive decline or dementia. Although the WHO has published a set of pragmatic guidelines for dementia risk reduction (World Health Organization, 2019), essentially focusing on non-pharmacological interventions and the management of cardiovascular risk factors, it remains difficult to formulate public health messages given this lack of evidence from randomised trials, and public knowledge about dementia prevention remains low (Parial et al., 2021).

How can the field of dementia prevention trials move forward, and strive to provide the evidence of intervention efficacy that is so sorely needed? Box 1 presents our recommendations for future trials in the field.

Pharmacological trials have been able to build on innovations in biomarker and imaging research, and move towards testing putative specific anti-Alzheimer's treatments in populations whom benefit is truly likely to be detected, if the treatments are indeed effective. Furthermore, in the event that a short-term benefit on cognitive function is demonstrated, enrolling these specific at-risk populations may facilitate the long-term follow-up required to determine the true impact on disease progression. However, the safety of pharmacological interventions, particularly when used in a preventive capacity, remains a major concern.

The picture is also challenging for lifestyle interventions. Evidence is starting to suggest the importance of targeted and tailored interventions, but to further explore such hypotheses, and better design future trials to specifically test

them, harmonised studies are needed, to facilitate cross-study comparisons and enable sufficiently powered subgroup analyses through data pooling, which is currently hindered by dataset diversity (van Wanrooij et al., 2020). Also, observational studies have shown us that we need to take a life course approach when studying dementia risk factors (Livingston et al., 2020), so we need to incorporate a life course approach when designing and testing interventions, with careful consideration of the optimal timing of exposure to interventions. Additionally, we must consider how to harness the power and opportunities that the current era of big data provides, for example, through connected devices or data linkage to electronic health records, whilst maintaining the highest standards of privacy, integrity and scientific rigor. The field requires novel outcome measures that can be feasibly measured in the long-term and whose clinical relevance is clearly understood by both study participants and clinicians. More than ever, the methodology of dementia prevention trials requires continued innovation. While in recent years there have been some methodological shifts, in terms of target populations (with newer trials tending to target younger populations and/or those with specific risk factors), intervention design (e.g. increasing use of multidomain interventions and dietary pattern-based nutritional interventions, rather than dietary supplements), and outcome measures (a general shift from incident dementia to cognitive function outcomes, although with little use of validated surrogate outcomes), the standard study designs remains the classic parallel randomised controlled trial. Future trials may consider the use of adaptive designs or interventions, in addition to more personalised approaches. However, it should be remembered that prevention trial populations are not representative of the general population (Dangour et al., 2010), and that the use of complex or technology-dependent interventions or complex trial designs is likely to further emphasize disparities in access, participation and adherence in prevention trials (Coley et al., 2022; Coley et al., 2021). Further efforts need to be made in future trials to increase the representativeness and diversity of prevention trial populations. Furthermore, environmental-level, as opposed to individual-level, interventions might help to mitigate selection bias and facilitate and motivate lifestyle changes in those most at risk of dementia (Daly, 2021).

Finally, given the inter-relatedness of risk factors for dementia and other chronic diseases, we must also consider how to integrate dementia prevention into an overall public health life course approach targeting a healthy lifestyle and healthy ageing. Indeed, traditionally, prevention research in the field of ageing has focused on preventing specific-age related diseases, such as dementia, cancer or cardiovascular diseases, and has generally not taken into account the fact that these chronic conditions often occur simultaneously in older age (Marengoni et al., 2011) and

also share numerous risk factors. The WHO has proposed that functioning, rather than the presence or absence of a given disease or condition, may be the most important marker of healthy ageing, which it now defines as “the process of developing and maintaining the functional ability that enables well-being in older age” (Clegg et al., 2013). Developing and implementing successful interventions to maintain cognitive function during ageing will require sustained and integrated efforts from clinicians, researchers, public health professionals and policy makers alike.

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Table 1. Summary of completed randomized controlled trials for the prevention of dementia or cognitive decline published since May 2015

Trial name / 1st author	Year	N	Duration	Intervention(s)	Control	Type of primary outcome measure	Main eligibility criteria	Main result*
<i>Pharmacological interventions</i>								
DANTE	2015	385	16 weeks	Discontinuation of antihypertensive treatment	Continuation of antihypertensive treatment	Cognitive function	MCI, ≥75 years, receiving antihypertensive treatment	-
SPRINT MIND	2019	8563	3 to 5 years	Intensive antihypertensive treatment (<120 mmHg)	Standard antihypertensive treatment (<140 mmHg)	Dementia incidence	≥50 year, SBP 130-180	-
ELITE	2016	567	5 years	Estrogen (+/- progesterone)	Placebo	Cognitive function	Post-menopausal women within 6 - 10 years of menopause	-
Yoon	2018	37	2 years	Estrogen (+/- progesterone)	Placebo	Cognitive function	Post-menopausal women, MCI	-
KEEPS-Cog	2015	693	4 years	Estrogen + progesterone	Placebo	Cognitive function	Recently post-menopausal women	-
Ttrials	2017	493	1 year	Testosterone	Placebo	Cognitive function	Men, ≥65 years, low testosterone, poor physical status	-
INTREPAD	2019	95	1 year	Naproxen sodium	Placebo	Composite (cognitive function + biomarkers)	≥55 years, family history of AD	-
ASPREE	2018	19114	4.7 years (median)	Aspirin	Placebo	Composite (dementia, death or persistent physical disability)	≥70 years (or ≥65 years among blacks and Hispanics)	-
ASCEND	2022	15427	7.4 years (mean)	Aspirin	Placebo	Dementia incidence	≥40 years, diabetes, no history of cardiovascular disease	-
A5¹	2019	596	Up to 18 months	Atabecestat	Placebo	Cognitive function	Asymptomatic amyloid positive, aged 60-85 years, ≥1 AD risk factor (age ≥65, family history of dementia, APOE ε4)	X

Trial name / 1st author	Year	N	Duration	Intervention(s)	Control	Type of primary outcome measure	Main eligibility criteria	Main result*
TOMMORROW	2021	3061	2.5 years (mean)	Pioglitazone	Placebo	Incident MCI due to AD	Cognitively healthy, age 65–83 years, at high risk of developing MCI due to AD according to biomarker risk assignment algorithm	-
Yuda	2020	268	24 weeks	Met-Lys-Pro (casein-derived angiotensin-converting enzyme inhibitory peptide)	Placebo	Cognitive function	Community-dwelling adults aged ≥ 40 (mean age 68)	-
CARMELINA-COG	2019	1545	2.5 years	Linagliptin	Placebo	Cognitive function	Adults with type 2 diabetes (mean age 67.8y) at high cardiovascular or renal risk	-
<i>Nutritional interventions</i>								
Harris	2015	116	16 weeks	Multivitamin supplement	Placebo	Cognitive function	55 to 65 years	-
Kwok	2017	271	27 moths	Vitamin B12	Placebo	Cognitive function	70 to 100 years, low vitamin B12	-
PREADVISE	2017	7540	5 years	Vitamin E, Selenium, or both	Placebo	Dementia incidence	Men, ≥60 years	-
Baleztena	2018	99	1 year	PUFA-rich multivitamin supplement	Placebo	Cognitive function	MCI, ≥75 years, institutionalized	-
Evans	2016	80	14 weeks	Resveratrol	Placebo	Cognitive function	Post-menopausal women, 45 to 85 years	+
Danthiir	2018	403	18 months	DHA + EPA	Placebo	Cognitive function	65 to 90 years	-
Niskimaki	2018	73	1 year	Hydrogen-infused water	Placebo	Cognitive function	MCI, ≥67 years	-
Coates	2020	128	12 weeks	Almond-enriched diet	Isocaloric nut-free diet	Cognitive function	50-80 years, overweight/obese, free of cognitive impairment	-
WAHA	2020	708	2 years	Walnut-enriched diet	Walnut-free control diet	Cognitive function	Age 63-79 years	-
Siddarth	2020	261	1 year	Pomegranate juice	Polyphenol-free placebo drink	Cognitive function	Age 50–75 years	+/-
Sakurai	2020	61	12 weeks	Matcha green tea powder drink	Placebo black tea flavoured powder	Cognitive function	Age >60 years, normal cognition	-
You	2021	48	12 weeks	<i>Cosmos caudatus</i> supplement	Placebo	Cognitive function	Age 60 to 75; MCI	+/-
Zajac	2020	436	24 weeks	Vitamin D2-enriched mushroom powder, Vitamin	Placebo	Cognitive function	Age 60–90 years	-

Trial name / 1st author	Year	N	Duration	Intervention(s)	Control	Type of primary outcome measure	Main eligibility criteria	Main result*
				D3, or Standard mushroom powder				
Ahles	2020	102	24 weeks	High or low-dose anthocyanin-containing <i>Aronia melanocarpa</i> extract	Placebo	Cognitive function	Overweight, aged 40–60 years	+/-
Asaoka	2022	130	24 weeks	Probiotic (<i>B. breveronia</i> MCC1274)	Placebo	Cognitive function	Age 65-89 years, MCI	-
SmartAge	2022	100	1 year intervention; 18m follow-up	Spermidine-rich nutritional supplementation	Placebo	Cognitive function	Age 60-90 years, cognitively normal (free of MCI/dementia), subjective cognitive decline	-
Physical activity interventions								
LIFE	2015	1635	2 years	Walking, resistance training	Health advice	Cognitive function	70 to 89 years, sedentary, at risk of mobility disability	-
Sungkarat	2017	66	15 weeks	Tai Chi	Health advice	Cognitive function	MCI, ≥60 years	+/-
Shimada	2018	106	24 weeks	Golf	Health advice	Cognitive function	≥65 years	+/-
Marston	2019	45	12 weeks	resistance training	Health advice	Cognitive function	41 to 69 years	+/-
Bisbe	2020	36	12 weeks	Choreographed aerobic dances	Multimodal physical Therapy	Cognitive function	65-85 years, aMCI	+
AIBL ACTIVE	2020	108	2 years	Home-based physical activity workshop	Education and usual care control	Biomarker (imaging)	Age ≥60; SMC or MCI and ≥1 vascular risk factor	-
Langoni	2019	60	6 months	Group aerobic and strength training	Usual care control	Cognitive function	Sedentary individuals with MCI, aged 60 years or older	+
Tarumi	2019	70	1 year	Aerobic exercise training	Stretching and toning control	Cognitive function	Age 55–80 years, aMCI	+/-
NeuroExercise	2020	183	1 year	Extensive aerobic exercise, or stretching and toning (non-aerobic) exercise	Non-exercise control group	Cognitive function	50 years and over, aMCI, sedentary	-
Multidomain interventions								
Rovner	2018	221	2 years	Behavioral activation	Supportive therapy	Cognitive function	MCI, ≥65 years, Afro-Americans	+
MAPT	2017	1525	3 years	Cognitive training + physical activity & nutrition advice, and/or PUFA supplement	Placebo	Cognitive function	≥65 years, memory complaint or pre-frail	-

Trial name / 1st author	Year	N	Duration	Intervention(s)	Control	Type of primary outcome measure	Main eligibility criteria	Main result*
PreDIVA	2016	3454	6-8 years	Multidomain vascular care	Usual care	Dementia incidence	70 to 78 years	-
Bae	2019	83	24 weeks	Physical, cognitive and social activities	Health advice	Cognitive function	MCI, ≥65 years	+/-
Shimada	2018	308	40 weeks	Physical and cognitive activities	Health advice	Cognitive function	MCI, ≥65 years	+/-
Inoue	2018	38	12 weeks	Resistance training + probiotic	Resistance training + placebo	Cognitive function	≥65 years	-
DO-HEALTH	2020	2157	3 years	Vitamin D3 and/or strength-training and/or omega-3	Placebo	Cognitive function	Aged ≥70 years (target 40% at high risk of frailty)	-
ENLIGHTEN	2019	160	6 months	Aerobic exercise and/or DASH diet	Health education control	Cognitive function	Sedentary, age >55 years, CIND, CVD or additional CV risk factor	+ ²
Imaoka	2019	67	3 months	Memory training + aerobic exercise	Exercise + soy peptide	Cognitive function	Aged ≥60 years	-
Lebedev	2020	63	4 weeks	L-dopa/ benserazide + cognitive training	Placebo + cognitive training	Cognitive function	65-75 years	+/-
Matsubara	2021	55	8 months	Oral health intervention (+ group health promotion)	Group health promotion lectures	Cognitive function	Aged ≥65 years, MMSE-J ≥21 to ≤26	+/-
Nilsson	2020	139	12 weeks	Physical exercise + cognitive training (either before or after physical training)	Physical exercise or cognitive training alone	Cognitive function	Age 65 - 75 years	-
BBL-CD	2020	119	8 weeks intervention; 6 months follow-up	Online health education + dietitian and exercise physiologist sessions, and online brain training	Online health education	Dementia risk score + Cognitive function	Aged >65; owning a computer with Internet access; MCI or SCD	+/-
STEPS	2020	154	24 weeks	Resistance training + lean meat	Resistance training + carbohydrate	Cognitive function	65 years and over, cognitively healthy	-
Chen	2020	1082	1 year	Cognitive training + physical activity & nutrition advice	Health education	Cognitive function	≥65 years, memory complaint or pre-frail	-
Yang	2022	122	6 months	Dietary guidance, physical training, computer-aided cognitive training, and management and monitoring of metabolic	Usual care	Cognitive function	Age ≥65 years, MCI	+

Trial name / 1st author	Year	N	Duration	Intervention(s)	Control	Type of primary outcome measure	Main eligibility criteria	Main result*
				indicators and vascular risk factors				
Wang	2021	20	12 weeks	Exergame-based dual-task training	Multicomponent exercise training	Cognitive function	Age ≥65 years, MMSE ≥ 24	+
Law	2022	145	8 weeks intervention; 5 months follow-up	Functional task exercise (physical activity + cognitive training), or cognitive or exercise training alone	Wait-list control	Cognitive function	Age ≥60 years, MCI	+/-
<i>Cognitive stimulation interventions</i>								
Schoene	2015	81	16 weeks	Interactive cognitive motor-step training	Advice on fall prevention	Cognitive function	≥70 years	-
PACE	2018	100	5 weeks	Jigsaw puzzles + cognitive health counselling	Cognitive health counselling	Cognitive function	≥50 years	-
Iizuki	2019	72	3 months	Face-to-face or tablet delivered board games	Health education	Cognitive function	≥65 years	+/-
SAGE	2018	82	5 weeks	Adaptive computerized cognitive training	Non-adaptive computerized cognitive training	Cognitive function	≥65 years	+/-
Bahar-Fuchs	2020	84	8 weeks intervention (+ 3-month booster); 6 months follow-up	Tailored and adaptive computerized cognitive training + one of 3 randomly assigned self-efficacy interventions	Generic, non-tailored or adaptive computerized cognitive training + one of 3 randomly assigned self-efficacy interventions	Cognitive function	≥65 years, diabetes, access at home to a computer & internet, ≥6 years of education	-
Faust	2020	151	8-10 weeks intervention; 3 months follow-up	Visual and/or auditory games-based computerized cognitive training	No cognitive training control	Cognitive function	Age ≥60 years	+/-
Montoya-Murillo	2020	124	3 months; 12-month follow-up	Cognitive remediation program	Occupational therapy	Cognitive function	≥ 55 years, attending senior day centres	+
Park	2021	160	6 weeks	Robot-assisted or traditional cognitive training	No intervention control	Cognitive function	Age ≥60 years, subjective memory complaints or MCI	+

¹Trial terminated early due to safety. Results are based on an expedited, ad hoc, interim analysis; ² for exercise or exercise+DASH diet (but not for DASH diet alone)

* - indicates no significant effect on the primary outcome measure(s); +/- indicates a significant beneficial effect on some, but not all, primary outcome measures; + indicates significant beneficial effects on all pre-specified primary outcome measures; X indicates significant detrimental effect on the primary outcome measure

Figure 1. Flowchart for studies identified since May 2015

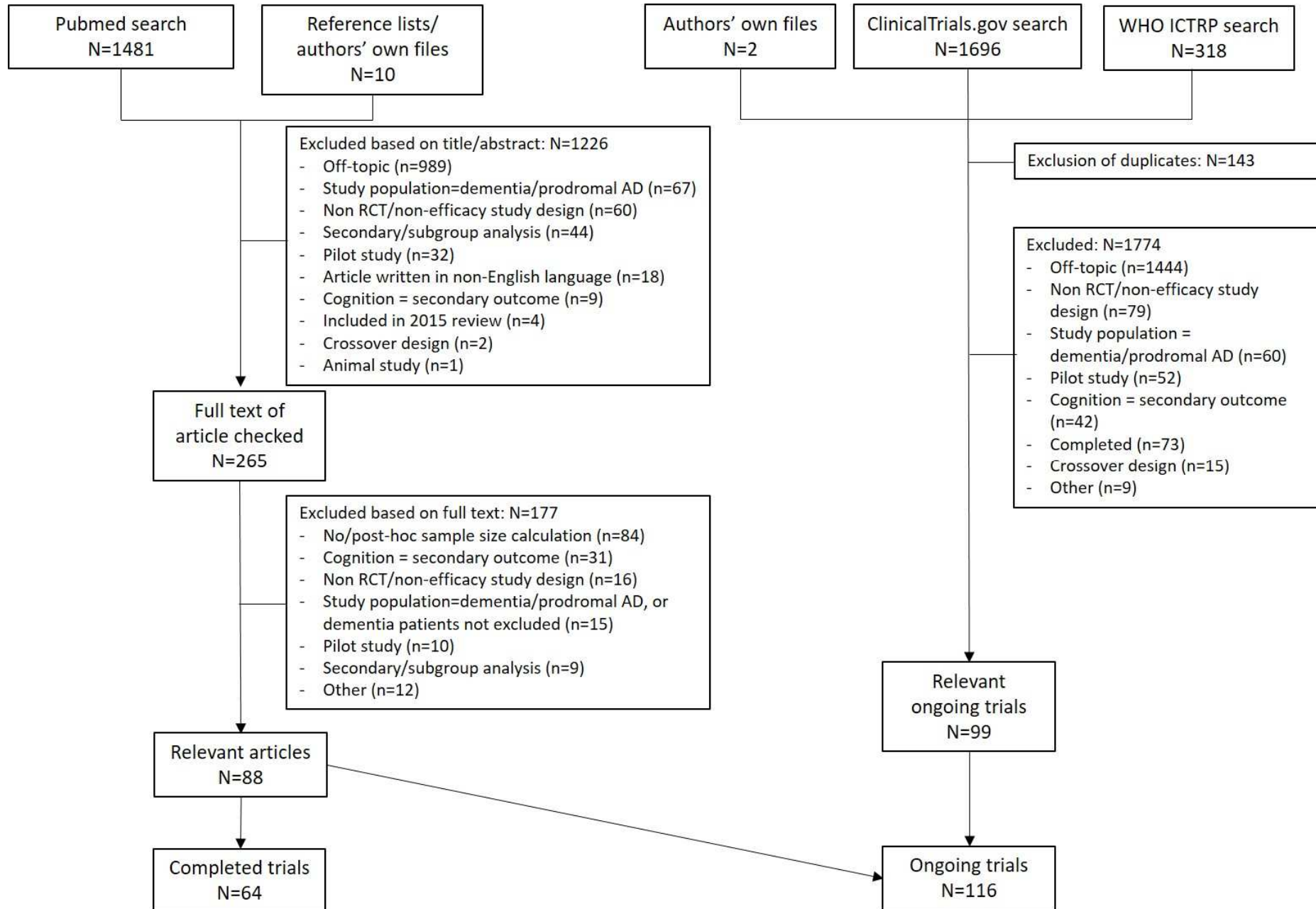


Figure 2. Number of completed trials published per 5-year period to 2020, and number of ongoing trials, by type of intervention

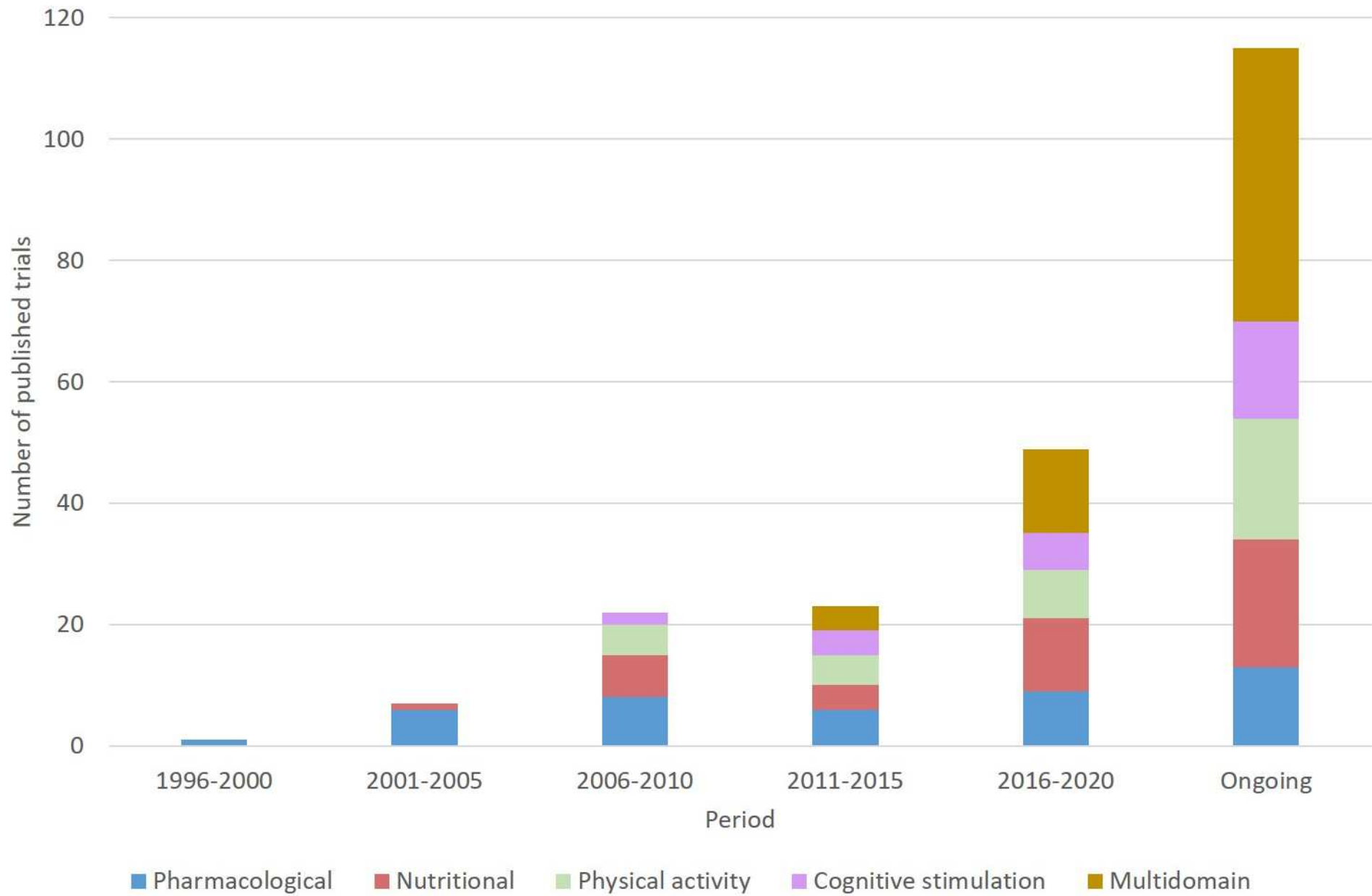
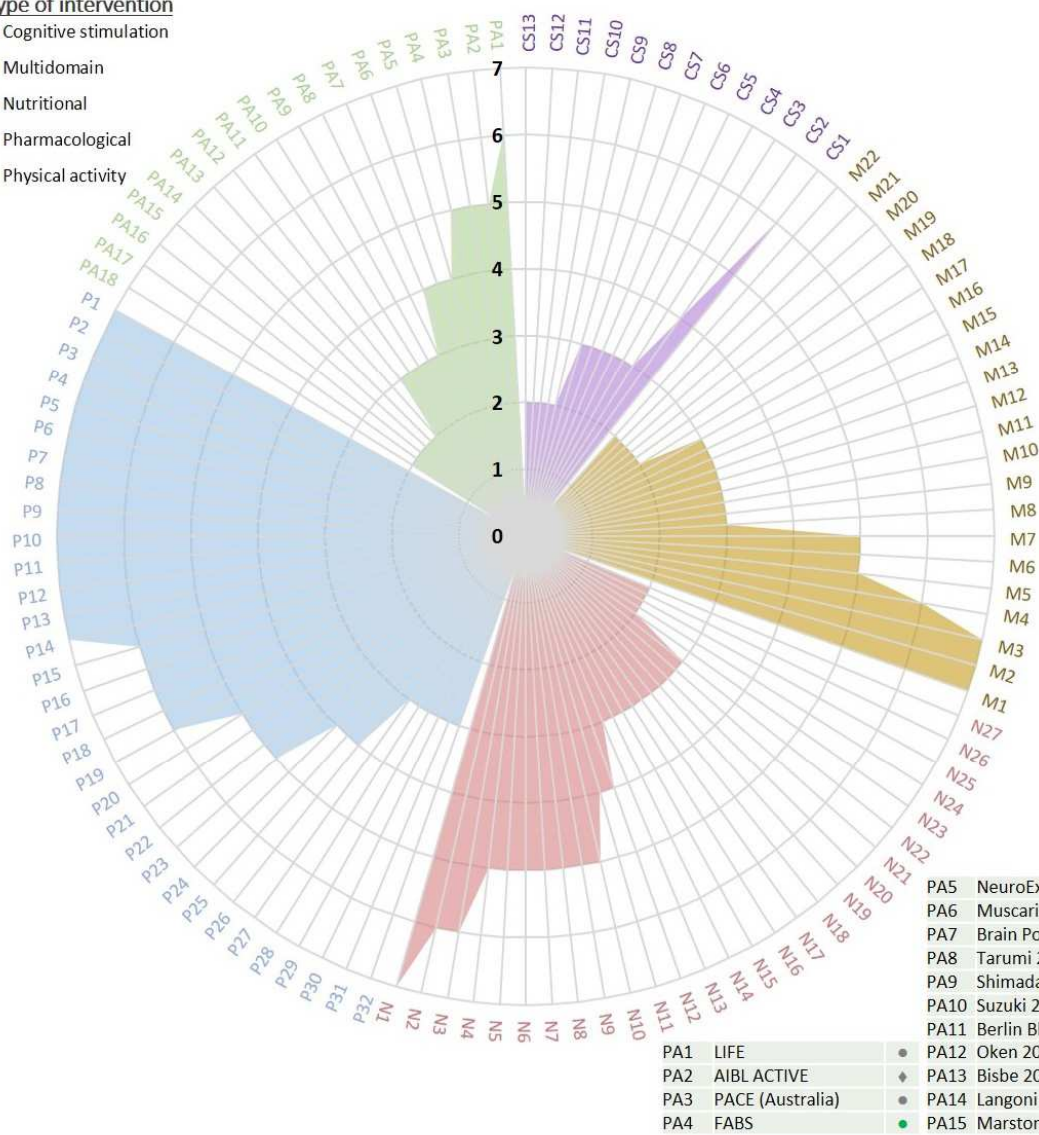


Figure 3: Study scale ratings for completed trials published since 1998, by type of intervention

Type of intervention

- Cognitive stimulation
- Multidomain
- Nutritional
- Pharmacological
- Physical activity

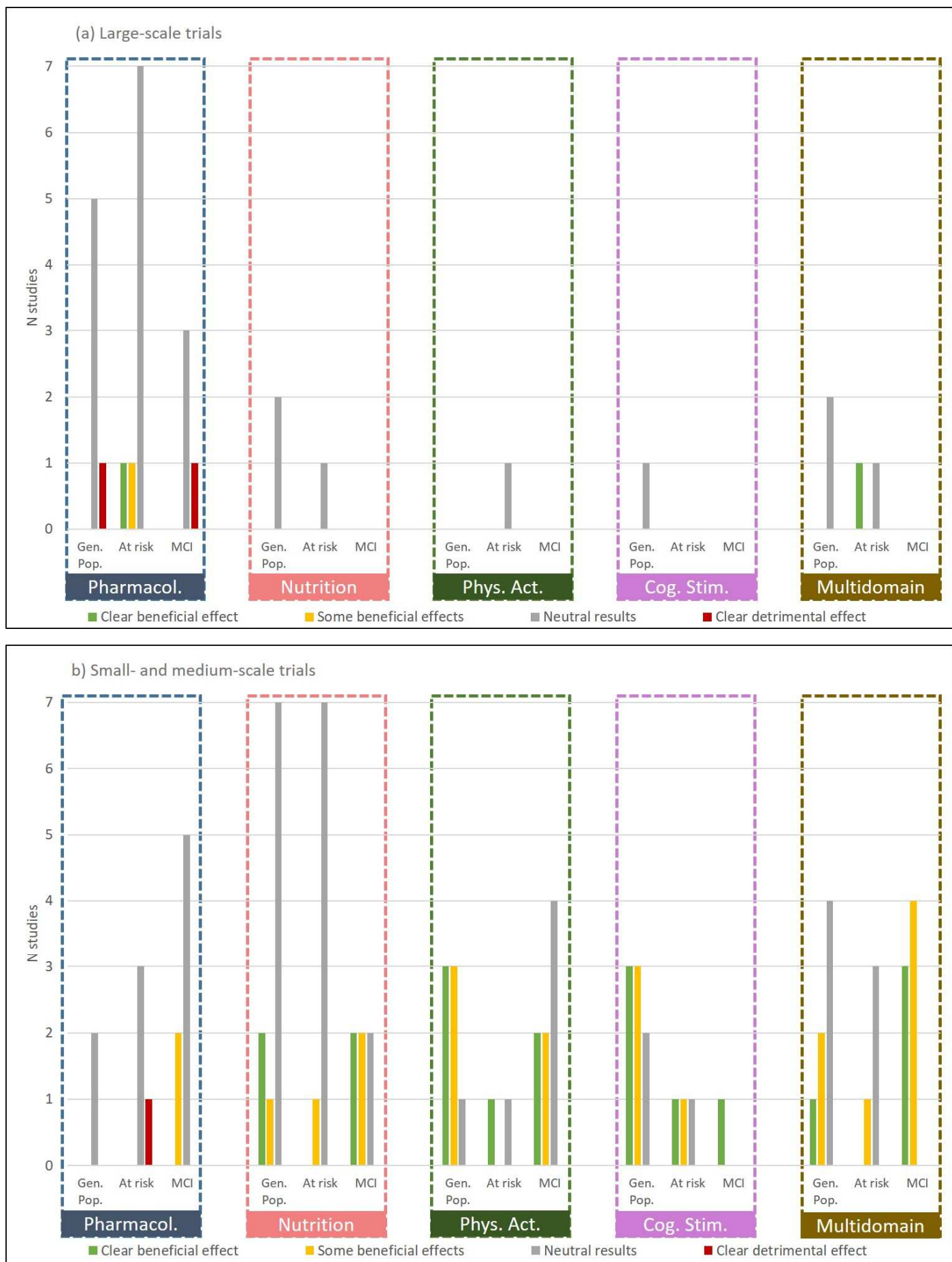


CS1	ACTIVE	●	M1	DO-HEALTH	●
CS2	Iowa Healthy and Active Minds Study	●	M2	MAPT	●
CS3	Park 2021	●	M3	PreDIVA	▶
CS4	Faust 2020	●	M4	FINGER	●
CS5	Montoya-Murillo 2020	●	M5	Chen 2020	●
CS6	PACE (Germany)	●	M6	Rovner 2018	●
CS7	Kwok 2013	●	M7	Lee 2014	●
CS8	IMPACT	●	M8	Law 2022	●
CS9	Bahar-Fuchs 2020	●	M9	Yang 2022	●
CS10	Iizuki 2019	●	M10	STEPS	●
CS11	SAGE	●	M11	BBL-CD	■
CS12	Schoene 2015	●	M12	Nilsson 2020	●
CS13	Diamond 2015	●	M13	ENLIGHTEN	●
P1	ASCEND	▶	M14	Shimada 2018 (M)	●
P2	TOMMORROW	■	M15	Ihle-Hansen	●
P3	CARMELINA-COG	●	M16	MAX	●
P4	SPRINT MIND	●	M17	Wang 2021	●
P5	ASPREE	■	M18	Matsubara 2021	●
P6	GuidAge	▶	M19	Lebedev 2020	●
P7	ACCORD-MIND	▶	M20	Imaoka 2019	●
P8	HYVET-COG	▶	M21	Bae 2019	●
P9	GEM	▶	M22	Inoue 2018	●
P10	InDDEX	▶	N1	PREADVISE	▶
P11	Rofecoxib Protocol 078	▶	N2	Kwok 2017	●
P12	WHIMS [E]	▶	N3	Kwok 2012	●
P13	WHIMS [E+P]	▶	N4	WAHA	●
P14	PROGRESS	▶	N5	Danthiir 2018	●
P15	ELITE	▶	N6	VITACOG	◆
P16	KEEPS-Cog	●	N7	OPAL	●
P17	GAL-INT-11/18	▶	N8	Ford 2010	●
P18	ADCS donepezil and vitamin E trial	▶	N9	McMahon 2006	●
P19	Syst-Eur-vascular dementia project	▶	N10	VISP	◆
P20	INTREPAD	▶	N11	SmartAge	●
P21	A5	●	N12	Siddarth 2020	●
P22	Tierney 2009	●	N13	Asaoka 2022	●
P23	TRIMCI	●	N14	Ahles 2020	●
P24	Yoon 2018	●	N15	Zajac 2020	●
P25	Ttrials	●	N16	Coates 2020	●
P26	ADAPT	▶	N17	Baleztena 2018	●
P27	Yuda 2020	▶	N18	Niskimaki 2018	●
P28	DANTE	●	N19	Harris 2015	◆
P29	Peters 2012	●	N20	MIDAS	●
P30	AVEC	●	N21	van de Rest 2008	●
P31	Doody 2009	●	N22	Eussen 2006	●
P32	Donepezil 401 study	●	N23	You 2021	●
PA5	NeuroExercise	●	N24	Sakurai 2020	●
PA6	Muscari 2010	●	N25	Evans et al 2017	●
PA7	Brain Power	●	N26	CoCoA-cognitively normal arm	●
PA8	Tarumi 2019	●	N27	CoCoA-MCI arm	●
PA9	Shimada 2018 (PA)	●			
PA10	Suzuki 2013	◆			
PA11	Berlin Bleibt Fit (BBF)	◆			
PA12	Oken 2006	◆			
PA13	Bisbe 2020	●			
PA14	Langoni 2019	●			
PA15	Marston 2019	●			

Study scale ratings range from 2 to 7 and were calculated as the sum of ratings for sample size (<100 subjects = 1 point, 100 – 1000 subjects = 2 points, >1000 subjects = 3 points) and intervention duration (<12 months = 1 point, 12 months = 2 points, 13 - 24 months = 3 points, >24 months = 4 points).

Each “spoke” of the radar graph represents an individual study, and the label at the end of the spoke can be used to identify the study name in the table on the right hand side of the figure. Shapes on the right hand side of the study name tables indicate the type of primary outcome measure(s) used in each trial: ● cognitive function, ► incident dementia, ◆ biomarker, ■ other (MCI due to Alzheimer’s disease, composite endpoint or dementia risk score). The colour of the shape indicates the primary study result: green=clear beneficial effect, yellow=some beneficial effects, grey=neutral results, red=clear detrimental effect. Full details of the trials published since May 2015 can be found in Table 1 and Supplementary Tables 3-7. Full details of the trials published up to May 2015 can be found in *Lancet Neurol.* 2015 Sep;14(9):926-944, and references for these trials are given in Supplementary Table 2

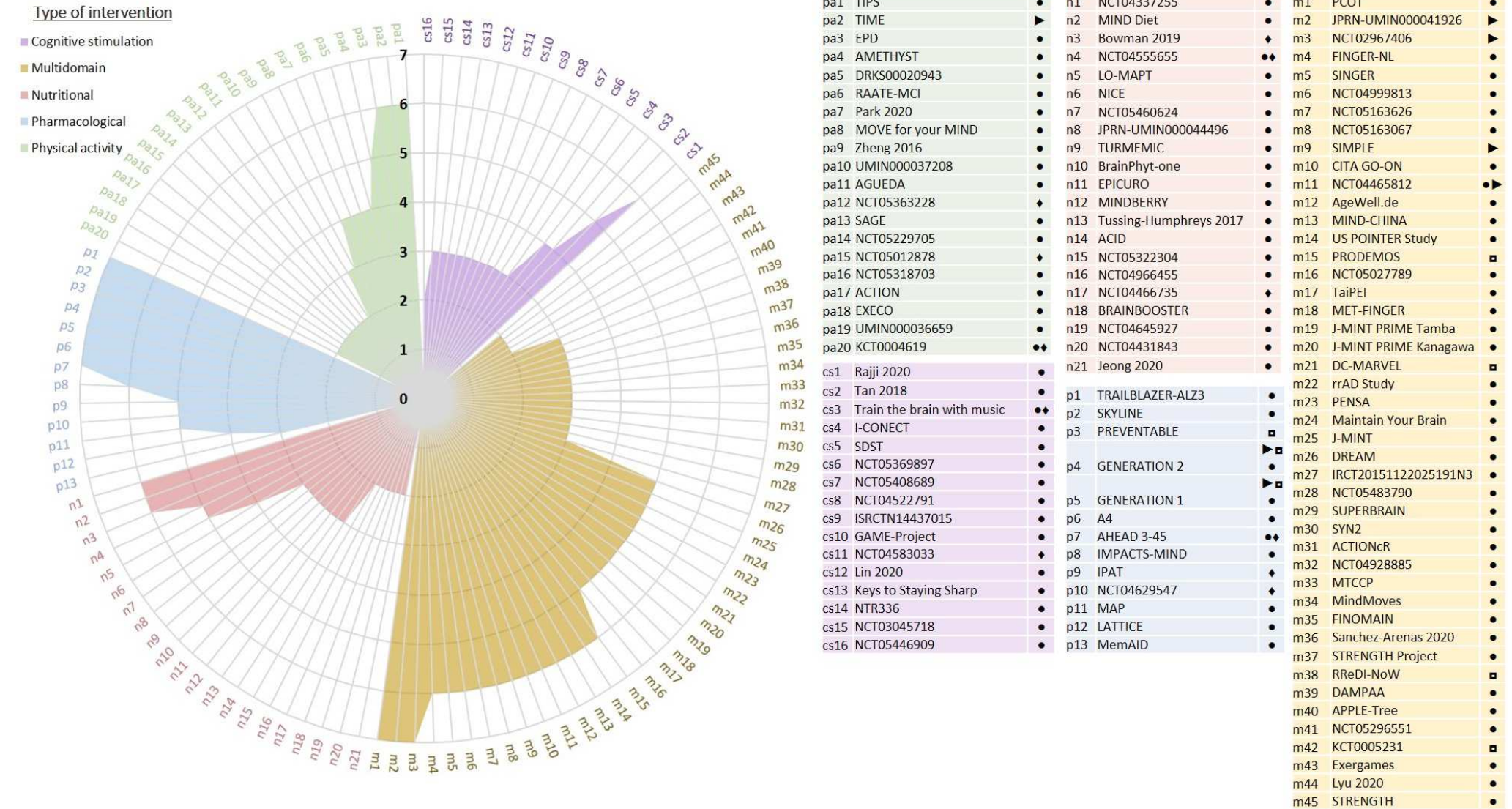
Figure 4. Summary of trial results by type of intervention and study population



Studies were considered as large-scale if they had a total rating ≥ 6 , calculated as the sum of ratings for sample size (<100 subjects = 1 point, 100 – 1000 subjects = 2 points, >1000 subjects = 3 points) and intervention duration (<12 months = 1 point, 12 months = 2 points, 13 - 24 months = 3 points, >24 months = 4 points).

Study populations were categorized as (i) General population (Gen. Popn.), i.e. i.e. study participants were not selected on the basis of any specific risk factors other than age, or the study only included individuals with unimpaired cognition; (ii) At risk, i.e. all participants were considered to be at increased risk of developing dementia (compared to the general population), on the basis of genetic, biological, imaging, clinical, family history or lifestyle risk factors; or (iii) Mild cognitive impairment (MCI all trial participants met criteria for MCI (but were free of dementia and not diagnosed with prodromal AD).

Figure 5: Study scale ratings for ongoing trials, by type of intervention



Study scale ratings range from 2 to 7 and were calculated as the sum of ratings for estimated sample size (<100 subjects = 1 point, 100 – 1000 subjects = 2 points, >1000 subjects = 3 points) and planned intervention duration (<12 months = 1 point, 12 months = 2 points, 13 - 24 months = 3 points, >24 months = 4 points).

Each “spoke” of the radar graph represents an individual study, and the label at the end of the spoke can be used to identify the study name in the table on the right hand side of the figure. Shapes on the right hand side of the study name tables indicate the type of primary outcome measure(s) used in each trial: ● cognitive function, ► incident dementia, ◆ biomarker, ■ other (MCI incidence, dementia risk factor profile or risk score, brain health activities score, or dementia knowledge). Full details of the trials can be found in Supplementary Tables 8-12. The ChiCTR2000037305 trial is not included in this figure as no information is available about the duration of follow-up, meaning that a study scale rating could not be calculated.

Box 1: Recommendations for the design of future prevention trials

General	<ul style="list-style-type: none">• Efforts should be made to harmonise outcome measures and intervention designs across trials to facilitate cross-study comparisons and data pooling for meta-analysis
Target population & recruitment	<ul style="list-style-type: none">• Interventions should be targeted to those most likely to obtain benefit, and they should be conducted at the right period of the life-course for a sufficiently long duration• More effort should be made to increase the representativeness and diversity of prevention trial populations. Specific recruitment strategies should be developed in this regard.
Outcome measures	<ul style="list-style-type: none">• Primary outcome measures and study objectives must be clearly specified in protocols and publications.• Validated intermediate outcome measures are required to enable evaluation of interventions beginning earlier in the life-course. The clinical relevance of changes on such measures needs to be considered.• Efforts are also needed to develop longer-term outcome measures and follow-up approaches, which can systematically be used in all trials.• Big data approaches could help to develop novel outcome measures – e.g. through connected devices or linkage to health records. However, data privacy is paramount, and reliability and validity should not be overlooked.• Blood biomarkers, that may be used for participant selection and/or as outcome measures, would, compared to biomarkers measured by imaging or in CSF, greatly reduce trial cost and burden, and would enable measurement in larger samples. Better understanding of such biomarkers, and their relationship with other biomarkers and clinical measures, is required.
Intervention design	<ul style="list-style-type: none">• For lifestyle interventions, methods should be developed to help define the optimal dose, timing and duration of the intervention• Alternative forms of intervention delivery, and/or additional support or motivation, should be considered, for example on the basis of motivation or self-efficacy or risk of non-adherence, which could be evaluated in run-in periods, or on the basis of known determinants.

Supplementary Appendix

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Supplementary Table 1. Search strategies

Source	Types of trials targeted	Search terms	Date of last search
PubMed	Completed and ongoing	(((((Alzheimer* OR dementia OR memory OR cognition*) AND prevent*) AND Randomized Controlled Trial[Publication Type])))	2 August 2022
Clinicaltrials.gov	Ongoing	Interventional Studies (prevent OR prevention OR preventive) AND (cognition OR cognitive OR dementia OR Alzheimer OR Alzheimer's OR memory)	2 August 2022
WHO ICTRP	Ongoing	Title: (prevent OR prevention OR preventive) AND (cognition OR cognitive OR dementia OR Alzheimer OR Alzheimer's OR memory)	2 August 2022

Supplementary Table 2. References of trials identified in the 2015 literature search

Study Name	Reference(s)
Pharmacological interventions	
Syst-Eur	Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. <i>Lancet</i> . 1998 Oct 24; 352 (9137):1347-51.
AVEC	Hajjar I, Hart M, Chen YL, et al. Effect of antihypertensive therapy on cognitive function in early executive cognitive impairment: a double-blind randomized clinical trial. <i>Arch Intern Med</i> . 2012 Mar 12; 172 (5):442-4.
PROGRESS	Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. <i>Arch Intern Med</i> . 2003 May 12; 163 (9):1069-75.
InDDEX	Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEX study. <i>Lancet Neurol</i> . 2007 Jun; 6 (6):501-12.
Doody 2009	Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. <i>Neurology</i> . 2009 May 5; 72 (18):1555-61.
Donepezil 401 study	Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. <i>Neurology</i> . 2004 Aug 24; 63 (4):651-7.
ADCS donepezil and vitamin E trial	Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. <i>N Engl J Med</i> . 2005 Jun 9; 352 (23):2379-88.
TRIMCI	Gomez-Isla T, Blesa R, Boada M, et al. A randomized, double-blind, placebo controlled-trial of triflusal in mild cognitive impairment: the TRIMCI study. <i>Alzheimer Dis Assoc Disord</i> . 2008 Jan-Mar; 22 (1):21-9.
HYVET-COG	Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. <i>Lancet Neurol</i> . 2008 Aug; 7 (8):683-9. 49
ACCORD-MIND	Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. <i>Lancet Neurol</i> . 2011 Nov; 10 (11):969-77.
WHIMS [Estrogen arm]	Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. <i>JAMA</i> . 2004 Jun 23; 291 (24):2947-58.
WHIMS [Estrogen + Progesterone arm]	Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. <i>JAMA</i> . 2003 May 28; 289 (20):2651-62.
Rofecoxib Protocol 078	Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. <i>Neuropsychopharmacology</i> . 2005 Jun; 30 (6):1204-15.
ADAPT	Lyketsos CG, Breitner JC, Green RC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. <i>Neurology</i> . 2007 May 22; 68 (21):1800-8.
GEM	DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. <i>JAMA</i> . 2008 Nov 19; 300 (19):2253-62.
GuidAge	Vellas B, Coley N, Ousset PJ, et al. Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. <i>Lancet Neurol</i> . 2012 Oct; 11 (10):851-9.
Peters 2012	Peters O, Lorenz D, Fesche A, et al. A combination of galantamine and memantine modifies cognitive function in subjects with amnesic MCI. <i>J Nutr Health Aging</i> . 2012; 16 (6):544-8.
GAL-INT-11/18	Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. <i>Neurology</i> . 2008 May 27; 70 (22):2024-35.
Tierney 2009	Tierney MC, Oh P, Moineddin R, et al. A randomized double-blind trial of the effects of hormone therapy on delayed verbal recall in older women. <i>Psychoneuroendocrinology</i> . 2009 Aug; 34 (7):1065-74.

Nutritional interventions	
VITACOG	Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. <i>PLoS One</i> . 2010; 5 (9):e12244.
MIDAS	Yurko-Mauro K, McCarthy D, Rom D, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. <i>Alzheimers Dement</i> . 2010 Nov; 6 (6):456-64.
CoCoA – MCI arm	Desideri G, Kwik-Urbe C, Grassi D, et al. Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) study. <i>Hypertension</i> . 2012 Sep; 60 (3):794-801.
CoCoA – cognitively normal arm	Mastroiacovo D, Kwik-Urbe C, Grassi D, et al. Cocoa flavanol consumption improves cognitive function, blood pressure control, and metabolic profile in elderly subjects: the Cocoa, Cognition, and Aging (CoCoA) Study--a randomized controlled trial. <i>Am J Clin Nutr</i> . 2015 Mar; 101 (3):538-48.
Eussen 2006	Eussen SJ, de Groot LC, Joosten LW, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. <i>Am J Clin Nutr</i> . 2006 Aug; 84 (2):361-70.
Ford 2010	Ford AH, Flicker L, Alfonso H, et al. Vitamins B(12), B(6), and folic acid for cognition in older men. <i>Neurology</i> . 2010 Oct 26; 75 (17):1540-7.
McMahon 2006	McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. <i>N Engl J Med</i> . 2006 Jun 29; 354 (26):2764-72.
VISP	Viswanathan A, Raj S, Greenberg SM, et al. Plasma Abeta, homocysteine, and cognition: the Vitamin Intervention for Stroke Prevention (VISP) trial. <i>Neurology</i> . 2009 Jan 20; 72 (3):268-72.
van de Rest 2008	van de Rest O, Geleijnse JM, Kok FJ, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. <i>Neurology</i> . 2008 Aug 5; 71 (6):430-8.
OPAL	Dangour AD, Allen E, Elbourne D, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. <i>Am J Clin Nutr</i> . 2010 Jun; 91 (6):1725-32.
Kwok 2012	Kwok TC, Lam LC, Sea MM, Goggins W, Woo J. A randomized controlled trial of dietetic interventions to prevent cognitive decline in old age hostel residents. <i>Eur J Clin Nutr</i> . 2012 Oct; 66 (10):1135-40.
Physical activity interventions	
FABS	Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. <i>JAMA</i> . 2008 Sep 3; 300 (9):1027-37.
Muscari 2010	Muscari A, Giannoni C, Pierpaoli L, et al. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. <i>Int J Geriatr Psychiatry</i> . 2010 Oct; 25 (10):1055-64.
Cybercycle study	Anderson-Hanley C, Arciero PJ, Brickman AM, et al. Exergaming and older adult cognition: a cluster randomized clinical trial. <i>Am J Prev Med</i> . 2012 Feb; 42 (2):109-19.
Brain Power	Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: a 12-month randomized controlled trial. <i>Arch Intern Med</i> . 2010 Jan 25; 170 (2):170-8.
BBF	Klusmann V, Evers A, Schwarzer R, et al. Complex mental and physical activity in older women and cognitive performance: a 6-month randomized controlled trial. <i>J Gerontol A Biol Sci Med Sci</i> . 2010 Jun; 65 (6):680-8.
Oken 2006	Oken BS, Zajdel D, Kishiyama S, et al. Randomized, controlled, six-month trial of yoga in healthy seniors: effects on cognition and quality of life. <i>Altern Ther Health Med</i> . 2006 Jan-Feb; 12 (1):40-7.
Suzuki 2013	Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. <i>PLoS One</i> . 2013; 8 (4):e61483. 50

Makizako 2012	Makizako H, Doi T, Shimada H, et al. Does a multicomponent exercise program improve dual-task performance in amnesic mild cognitive impairment? A randomized controlled trial. <i>Aging Clin Exp Res.</i> 2012 Dec; 24 (6):640-6.
Cognitive training interventions	
Kwok 2013	Kwok T, Wong A, Chan G, et al. Effectiveness of cognitive training for Chinese elderly in Hong Kong. <i>Clin Interv Aging.</i> 2013; 8 :213-9.
IMPACT	Smith GE, Housen P, Yaffe K, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. <i>J Am Geriatr Soc.</i> 2009 Apr; 57 (4):594-603.
Iowa Healthy and Active Minds Study	Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Dotson MM. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults. <i>PLoS One.</i> 2013; 8 (5):e61624.
ACTIVE	Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. <i>JAMA.</i> 2006 Dec 20; 296 (23):2805-14.
Diamond 2015	Diamond K, Mowszowski L, Cockayne N, et al. Randomized controlled trial of a healthy brain ageing cognitive training program: effects on memory, mood, and sleep. <i>J Alzheimers Dis.</i> 2015; 44 (4):1181-91.
PACE	Vidovich MR, Lautenschlager NT, Flicker L, Clare L, McCaul K, Almeida OP. The PACE study: a randomized clinical trial of cognitive activity strategy training for older people with mild cognitive impairment. <i>Am J Geriatr Psychiatry.</i> 2015 Apr; 23 (4):360-72
Multidomain interventions	
FINGER	Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. <i>Lancet.</i> 2015; 385 (9984):2255-63.
Lee 2014	Lee KS, Lee Y, Back JH, et al. Effects of a multidomain lifestyle modification on cognitive function in older adults: an eighteen-month community-based cluster randomized controlled trial. <i>Psychother Psychosom.</i> 2014; 83 (5):270-8.
MAX	Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. <i>JAMA Intern Med.</i> 2013 May 13; 173 (9):797-804.
Ihle-Hansen 2014	Ihle-Hansen H, Thommessen B, Fagerland MW, et al. Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: a 12-month randomized controlled trial. <i>Int J Stroke.</i> 2014 Oct; 9 (7):932-8.

Supplementary Table 3: Completed pharmacological trials published since May 2015

Completed pharmacological trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
DANTE ¹ (Netherlands)	385	16 weeks	Cognitive function / Global cognitive function composite Z-score (TMT-A & B, Stroop Color-Word Test, Verbal Learning Test, Visual Association Test, Letter Digit Substitution Test)	<ul style="list-style-type: none"> Discontinuation of antihypertensive treatment (until a maximum increase of 20 mm Hg in SBP). vs. Control: Continuation of antihypertensive treatment 	MCI	75 years and over, MMSE 21-27, Mild cognitive deficits without serious cardiovascular disease who received antihypertensive treatment	<ul style="list-style-type: none"> Systolic and diastolic BP significantly increased in the intervention group compared to the control group, but there was no difference in change in overall cognition compound score
Ttrials ² (USA)	493	12 months	Cognitive function / Episodic memory	<ul style="list-style-type: none"> 5g daily of testosterone gel 1% concentration (AndroGel, AddVie) vs. Placebo 	At risk	65 years and over; Men; Low serum testosterone concentrations (<275 ng/d)L; decreased libido, mobility disability or low vitality; MMSE ≥24	<ul style="list-style-type: none"> No significant improvement of memory or other cognitive functions in treatment group compared with placebo.
ELITE ³ (USA)	567	5 years	Cognitive function / Verbal episodic memory	<ul style="list-style-type: none"> Oral 17β-estradiol 1 mg/d vs. Placebo or Women with a uterus received cyclic micronized progesterone vaginal gel vs. 	General population	41-84 years, Healthy women within 6 years of menopause or 10+ years after menopause	<ul style="list-style-type: none"> Estradiol initiated within 6 years of menopause did not affect verbal memory, executive functions, or global cognition differently than therapy begun 10+ years after menopause. Neither had any effect on cognition, compared to placebo

Completed pharmacological trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				<ul style="list-style-type: none"> • Placebo 			
KEEPS Cog ⁴ (USA)	693	4 years	Cognitive function / Global cognition (3MSE) & domain scores for verbal learning/memory, auditory attention/working memory, visual attention/executive function, and speeded language/mental flexibility	<ul style="list-style-type: none"> • 0.45 mg/d oral conjugated equine estrogens (o-CEE) plus 200 mg/d micronized progesterone (m-P) for the first 12 d of each month • 50 µg/d transdermal estradiol (t-E2) plus 200 mg/d m-P for the first 12 d of each month vs. <ul style="list-style-type: none"> • Placebo 	General population	Women aged 42-58 years, in the late menopausal transition and early postmenopausal periods (within 6–36 months of last menstrual period); dementia free and not at high risk of cardiovascular disease.	<ul style="list-style-type: none"> • There were no effects of treatment on any of the primary cognitive outcomes
SPRINT MIND ⁵ (USA)	8563	Median 3.34 years (5.11 years)	Incident dementia: <i>adjudicated probable dementia</i>	<ul style="list-style-type: none"> • Intensive treatment: SBP goal <120 mmHg vs. <ul style="list-style-type: none"> • Standard treatment: SBP goal <140 mmHg 	At risk	50 years and over; SBP 130-180 mm Hg; free of dementia, diabetes and history of stroke	<ul style="list-style-type: none"> • No significant reduction in the risk of probable dementia in the intensive treatment group (7.2 vs 8.6 cases per 1000 person-years; HR, 0.83; 95% CI, 0.67-1.04). • Intensive BP control significantly reduced the risk of the secondary outcomes of MCI (14.6 vs 18.3 cases per 1000 person-years; HR, 0.81;

Completed pharmacological trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
							95% CI, 0.69-0.95) and the combined rate of MCI or probable dementia (20.2 vs 24.1 cases per 1000 person-years; HR, 0.85; 95% CI, 0.74-0.97).
INTREPAD ⁶ (Canada)	195	12 months (24 month follow-up)	Cognitive function & biomarkers / Alzheimer Progression Score (APS), composite score incorporating multimodal imaging, neurosensory, cognitive, and Cerebrospinal fluid markers	<ul style="list-style-type: none"> • Naproxen sodium tablets 220 mg twice daily for two years vs. • Placebo 	At risk	55 years and over, free of dementia or MCI, history or documentation of AD dementia in at least one parent, or in two siblings	<ul style="list-style-type: none"> • No difference in rate of change on the APS between groups • Individuals treated with Naproxen showed an excess of adverse events.
ASPREE ⁷ (US, Australia)	19114	4.7 years (median)	Composite / Dementia, death or persistent physical disability	<ul style="list-style-type: none"> • Enteric-coated aspirin [100 mg/d] vs. • Placebo 	General population	≥70 years (or ≥65 years among US blacks and Hispanics); free of and cardiovascular disease, dementia, or physical disability	<ul style="list-style-type: none"> • No effect of aspirin on the composite primary endpoint (HR, 1.01; 95% CI, 0.92 to 1.11; P=0.79) • The rates of major hemorrhage and all-cause mortality were significantly higher in the aspirin group • Secondary analyses showed no effect of aspirin on all-cause dementia, probable AD or MCI, or on cognitive change over time

Completed pharmacological trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
ASCEND ⁸ (UK)	15427	mean 7.4 years (with approximately 2 years additional follow-up)	Incident dementia / “broad dementia” (i.e. dementia, cognitive impairment, or confusion, ascertained through participant, carer of general practitioner report, or hospital admission diagnosis, or use of dementia medication, or referral to a memory clinic, or cognitive impairment cited as reason for not completing cognitive assessment)	<ul style="list-style-type: none"> • Aspirin (100 mg/d) vs. <ul style="list-style-type: none"> • Placebo 	At risk	Adults aged 40 and over with diabetes and no history of cardiovascular disease, free of dementia	The broad dementia outcome occurred in 548 participants (7.1%) in the aspirin group, compared to 598 (7.8%) in the placebo group, rate ratio 0.91 [95% CI, 0.81–1.02, p=0.11]
Yoon 2018 ⁹ (Korea)	37	2 years	Cognitive function / global cognition (ADAS-Cog, K-MMSE, MoCA_K)	<ul style="list-style-type: none"> • Menopausal hormone therapy (MHT; percutaneous estradiol [E2] gel [0.1%, 2 mg/d] and oral micronized progesterone [MP4] [100mg/d]) vs. <ul style="list-style-type: none"> • Placebo <p>All participants also received donepezil</p>	MCI	Postmenopausal women with multiple domain, amnesic subtype MCI	<ul style="list-style-type: none"> • There was no significant difference in time trend between the two groups in all measures for general cognition. • 24 month K-MMSE and MoCA_K scores, but not ADAS-Cog, were significantly better in the MHT group
A5 (EARLY) ^{10,11} (14 countries in North/Central	596	Up to 18 months (planned 54 months; trial	Cognitive function/ global cognition (Preclinical Alzheimer Cognitive Composite score)	<ul style="list-style-type: none"> • Atabecestat, 5 mg daily • Atabecestat, 25mg daily 	At risk	60-85 years, asymptomatic (CDR = 0) amyloid positive, ≥1 AD risk factor (age	<ul style="list-style-type: none"> • Following early termination of the trial due to hepatic-related AEs, cognitive decline was

Completed pharmacological trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
America, Europe and Asia)		suspended due to adverse events)		vs. • Placebo		≥65, family history of dementia, APOE ε4)	significantly greater in the high dose group compared to placebo • There were increased systemic and neuropsychiatric-related treatment-emergent AEs in atabecostat groups
TOMMORROW ¹² (Australia, Germany, Switzerland, UK, USA)	3061	Mean 2.5y (stopped early following futility analysis)	Incident MCI due to AD	• oral pioglitazone (0.8 mg/day sustained release) vs. • placebo	At risk	cognitively healthy, community living participants aged 65–83 years, CDR 0, MMSE >24, at high risk of developing MCI due to AD within 5 years based on biomarker risk assignment algorithm	• The trial was prematurely terminated after a planned futility analysis. • Pioglitazone did not delay the onset of mild cognitive impairment
Yuda 2020 ¹³ (Japan)	268	24 weeks	Cognitive function (ADAS-Cog)	• Met-Lys-Pro (casein-derived angiotensin-converting enzyme inhibitory peptide; 200µg/d) vs. • placebo	General population	Community-dwelling adults aged ≥ 40 (mean age 68) without dementia	There was no significant between-group difference on the ADAS-Cog
CARMELINA-COG ¹⁴ (27 countries in North, Central &	1545	2.5 years	Cognitive function / accelerated cognitive decline (MMSE)	• Linagliptin (5 mg/d) vs. • Placebo	At risk	Adults with type 2 diabetes (mean age 67.8y) at high	There was between-group difference in the incidence of accelerated cognitive decline

Completed pharmacological trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
South America, Europe, Asia, and Africa)						cardiovascular or renal risk, MMSE ≥ 24	

Supplementary Table 4: Completed nutritional trials published since May 2015

Completed nutritional trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
Harris 2015 ¹⁵ (Australia)	116	16 weeks	Cognitive function / Attention, processing speed, recognition memory, working memory, response to inflammation	<ul style="list-style-type: none"> Multi-Vitamin (Swisse Ultivite Mineral & Anti-Oxidant with Herbs 50+ Years™; different formulas for Men and Women) vs. <ul style="list-style-type: none"> Placebo 	General population	55-65 years, free of cognitive disorders, MMSE 27-30	<ul style="list-style-type: none"> No cognitive improvements were observed after supplementation with either formula.
Kwok 2017 ¹⁶ (Hong Kong, Netherlands)	271	27 months	Cognitive decline / Clinical Dementia Rating scale (CDR)	<ul style="list-style-type: none"> Vitamin B12, 1mg, daily, 2 tablets vs. <ul style="list-style-type: none"> Placebo 	At risk	70-100 years, type 2 diabetes, free of dementia, low vitamin B12: 150 - 300 pmol/L	<ul style="list-style-type: none"> At month 27, there was no significant group difference in changes in CDR scores
PREADVISE ¹⁷ (USA, Canada, Puerto Rico)	7540 (3786 continued into the observational cohort phase after early termination of treatment)	Median 5.5 years (up to 10 years)	Dementia incidence / Dementia diagnosis (type non-specified)	<ul style="list-style-type: none"> Vitamin E (400 IU/day) Selenium (200 µg/day) Vitamin E (400 IU/day) + selenium (200 µg/day) vs. <ul style="list-style-type: none"> Placebo 	General population	Men aged 60 years and over, free of dementia	<ul style="list-style-type: none"> Treatment was stopped prematurely following a futility analysis. Approximately half of subjects continued to be followed-up in the observational extension period. Neither supplement had any effect of dementia incidence compared to placebo
Baleztena 2018 ¹⁸ (Spain)	99	1 year	Cognitive function / MMSE, Global Deterioration Scale,	<ul style="list-style-type: none"> 1 capsule of multivitamins rich in n-3 PUFA, 3 x day 	At risk	75 years and over, MCI or without cognitive impairment, Global	<ul style="list-style-type: none"> There were no significant differences in cognitive decline between

Completed nutritional trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
			Verbal Fluency, Clock Test	(350 mg n-3 PUFA/capsule) vs. • Placebo		Deterioration Scale 1-3, free of dementia, Institutionalized in a nursing home	the intervention and placebo groups on any of the cognitive tests
Evans 2017 ^{19,20} (Australia)	80	14 weeks	Cognitive function / Global cognitive performance composite score (Episodic memory, semantic memory, attention and working memory, executive functions)	• Resveratrol supplementation (75mg twice daily) vs. • Placebo	General population	Postmenopausal women aged 45-85 years, free of dementia	• There was a significant improvement in overall cognitive performance in the resveratrol group compared to the placebo group
Danthiir 2018 ²¹ (Australia)	403	18 months	Cognitive function/reasoning, working memory, short-term memory, retrieval fluency, cognitive speech-related constructs	• DHA (1720mg/d) + EPA (600mg/d) vs. • Low polyphenic olive oil	General population	Community-dwelling adults ages 65-90y	Supplementation did not maintain or improve cognitive function
Nishimaki 2018 ²² (Japan)	73	1 year	Cognitive (ADAS Cog)	• Hydrogen (H ₂) infused water vs. • Placebo	MCI	67 years or older, MCI, GDS ≤6, MMSE ≥24, free of dementia, not using anti-Alzheimer drugs	• No significant between-group differences in the primary analysis
Coates 2020 ²³ (Australia)	128	12 weeks	Cognitive/ working memory	• almond-enriched diet vs. • isocaloric nut-free diet	At risk	50-80 years, overweight/ obese, free of cognitive impairment (MoCA ≥18)	• No significant effects on cognitive performance

Completed nutritional trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
WAHA ²⁴ (Spain, US)	708	2 years	Cognitive function/global cognition composite	<ul style="list-style-type: none"> diet enriched with walnuts at ~15% energy (30-60 g/d) vs. control diet (abstention from walnuts) 	General population	Free-living elders, age 63-79 y, free of neurodegenerative disease	<ul style="list-style-type: none"> There were no between-group differences in change in the global cognition composite
Siddarth 2020 ²⁵ (USA)	261	1 year	Cognitive function/memory (Brief Visuospatial Memory Test-Revised (BVM-T-R) and Buschke Selective Reminding Test)	<ul style="list-style-type: none"> pomegranate juice (8 oz [236.5 mL]/day) vs. placebo drink (without polyphenols) 	General population	Age 50–75 y; normal cognition or MCI	<ul style="list-style-type: none"> There was a significant between-group difference on one measure of visual memory performance (out of 6 primary outcome measures, after adjustment for multiple testing).
Sakurai 2020 ²⁶ (Japan)	61	12 weeks	Cognitive function / global (MoCA, MMSE) cognition & memory (Wechsler Memory Scale-Delayed Recall)	<ul style="list-style-type: none"> Matcha green tea powder drink (twice daily) vs. Placebo black tea flavoured powder 	General population	Age >60 years, free of dementia and MCI	<ul style="list-style-type: none"> There were no significant differences in any outcome measures between groups
You 2021 ²⁷ (Malaysia)	48	12 weeks	Cognitive function / MMSE, digit span, RAVLT, VR, DSST	<ul style="list-style-type: none"> <i>Cosmos caudatus</i> supplement (250 mg twice daily) vs. placebo 	MCI	Aged 60 to 75; MCI; BMI 20–30 kg/m ² ; non-smokers	<ul style="list-style-type: none"> There was a significant difference in favour of the intervention on the MMSE, but not the other primary outcome measures
Zajac 2020 ²⁸ (Australia)	436	24 weeks	Cognitive function / C-CAB battery	<ul style="list-style-type: none"> vitamin D2-enriched mushroom powder 	General population	Aged 60–90 years of age; MMSE >24; free of	<ul style="list-style-type: none"> There were no significant effects of treatment on any of the

Completed nutritional trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				<ul style="list-style-type: none"> • vitamin D3 • standard mushroom powder vs. <ul style="list-style-type: none"> • placebo 		dementia and depression	measures of cognitive function or mood.
Ahles 2020 ²⁹ (Netherlands)	102	24 weeks	Cognitive function / psychomotor speed, attention, and cognitive flexibility (pegboard test, number cross-out test, Stroop test)	<ul style="list-style-type: none"> • Anthocyanin-containing <i>Aronia melanocarpa</i> extract (90 mg/d) • <i>Aronia melanocarpa</i> extract (150 mg/d) vs. <ul style="list-style-type: none"> • placebo 	At risk	Healthy overweight middle aged adults aged 40–60 years, BMI 25 - 35 kg/m ²	<ul style="list-style-type: none"> • The 90 mg AME supplementation group showed significantly better cognitive performance compared to placebo on one test of psychomotor speed, but there were no significant differences for any other outcomes/doses.
Asaoka 2022 ³⁰ (Japan)	130	24 weeks	Cognitive function / global cognition (ADAS-Jcog)	<ul style="list-style-type: none"> • Probiotic (<i>B. breveronia</i> MCC1274, 2×10¹⁰ CFU, once daily) vs. <ul style="list-style-type: none"> • placebo 	MCI	Age 65-89 years, MCI (DSM-5), memory complaint, MMSE 22-26, CDR 0.5	There was no significant between-group difference in change from baseline on ADAS-Jcog scores.
SmartAge ^{31,32} (Germany)	100	1 year intervention / 18 months follow-up	Cognitive function/ memory performance (mnemonic similarity task)	<ul style="list-style-type: none"> • Spermidine-rich nutritional supplementation (750 mg/d) vs. <ul style="list-style-type: none"> • placebo 	At risk	Cognitively normal older individuals aged 60-90 years with subjective cognitive decline (free of MCI & dementia)	There was no significant between-group difference in mnemonic discrimination performance

Supplementary Table 5: Completed physical activity trials published since May 2015

Completed physical activity trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
LIFE ³³ (USA)	1635	24 months	Cognitive function / Working memory, attention, episodic memory	<ul style="list-style-type: none"> Moderate-intensity physical activity program that included walking, resistance training, and flexibility exercises (twice weekly centre-based + 3-4 times per week home-based) vs. Health education control (educational workshops and upper extremity stretching weekly) 	At risk	70-89 years, Free of dementia and cognitive impairment, sedentary, at high risk for mobility disability, could walk 400 m in 15 minutes	<ul style="list-style-type: none"> There were no improvements in global or domain-specific cognitive function compared to the control group
Sungkarat 2017 ³⁴ (Thailand)	66	15 weeks	Cognitive function / memory, visuospatial ability, and executive function	<ul style="list-style-type: none"> Tai Chi training (50 minutes per sessions, 3 x week) vs. Control group: received educational material covering information related to cognitive impairment and fall prevention 	MCI	60 years and over, Amnesic-MCI, MMSE \geq 24 and MoCA < 26, Exercise <30 minutes/day	<ul style="list-style-type: none"> After 15 week-follow-up, performance on Logical Memory delayed recall, Block Design and TMT B–A were significantly better for the Tai Chi group than the control group but not performance on Digit Span.
Shimada 2018 ³⁵ (Japan)	106	24 weeks	Cognitive function / MMSE & National Centre for Geriatrics and Gerontology-Functional Assessment	<ul style="list-style-type: none"> Golf training (weekly 90-120 min sessions + home-based practice) vs. 	General population	Age 65 and older, free of dementia, little to no experience of playing golf (< 2	<ul style="list-style-type: none"> The intervention group showed significantly less decline/more improvement on 3 logical memory scores, but not on the 7 other

Completed physical activity trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
			Tool (NCGG-FAT; including tests of memory, attention, & processing speed)	<ul style="list-style-type: none"> • Health education control (2*90 min classes) 		times/year), engaging in vigorous exercise <3 times/week.	primary cognitive outcome measures (with no adjustment for multiple testing)
Marston 2019 ³⁶ (Australia)	45	12 weeks	Cognitive function / Cogstate	<ul style="list-style-type: none"> • High load, long rest resistance training (twice weekly) • Moderate load, short rest resistance training (twice weekly) vs. <ul style="list-style-type: none"> • Non-exercising control 	General population	Middle-aged and older adults (41-69 years), MoCA ≥26, no resistance training in previous 6 months	<ul style="list-style-type: none"> • Both resistance training groups showed improved delayed verbal memory performance after the intervention, compared to the control group, but there were no differences on the other 5 primary cognitive outcome measures (and 3 further cognitive measures were not analysed due to data integrity issues).
Bisbe 2020 ³⁷ (Spain)	36	12 weeks	Cognitive function/verbal memory performance (Verbal recognition - Word List Learning test from the WMS-III)	<ul style="list-style-type: none"> • Choreography (choreographed aerobic dances; 60-min, twice weekly) Vs. <ul style="list-style-type: none"> • Multimodal physical Therapy (strength, endurance, flexibility, balance, coordination & gait training; 60-min, twice weekly) 	MCI	aMCI, aged 65-85 years	<ul style="list-style-type: none"> • In the primary per protocol analysis, there was significantly greater improvement in verbal recognition memory in the choreography group compared to the Physical Therapy group
AIBL ACTIVE ³⁸ (Australia)	108	2 years	Imaging/ MRI WMH	<ul style="list-style-type: none"> • Home-based physical activity workshop (target 	At risk	Participants of AIBL flagship study aged ≥60 with SMC or	<ul style="list-style-type: none"> • In the primary (per protocol) analysis, there was no significant effect on WMH

Completed physical activity trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				150 min/wk moderate intensity PA) vs. • Education and usual care control		MCI and ≥ 1 vascular risk factor	load. There was also no effect on the secondary outcome of hippocampal volume
Langoni 2019 ³⁹ (Brazil)	60 (52 analysed)	6 months	Cognitive function / MMSE	• Group aerobic and strength training (60 min. twice weekly) vs. • Usual care control	MCI At risk	Sedentary individuals with MCI, aged 60 years or older, independent in activities of daily living	The mean post-intervention MMSE score was significantly higher in the intervention group compared to the control group.
Tarumi 2019 ⁴⁰ (USA)	70	1 year	Cognitive function / memory, executive function (California Verbal Learning Test-second edition, Delis–Kaplan Executive Function System)	• Aerobic exercise training (up to 5 sessions/week, with increasing frequency and intensity over time) vs. • Stretching and toning control	MCI	Age 55–80 years, aMCI, CDR=0.5 ; MMSE ≥ 24 , free of dementia	• There was significantly more improvement in the control group on one of six outcome measures, but no significant between-group differences for any other measures
NeuroExercise ^{41,42} (Germany, Ireland, Netherlands)	183	1 year	Cognitive function / global cognition (composite score)	• Standardized extensive aerobic exercise intervention (3 units of 45minutes/week) • Stretching and toning (non-aerobic) exercise (3 units of 45 min/week) vs. • Non-exercise control group	MCI	50 years and over Amnesic MCI, MoCA [18-26], free of dementia Sedentary	• There were no significant between-group differences in the composite cognitive score (or in any cognitive domain)

Supplementary Table 6: Completed cognitive stimulation trials published since May 2015

Completed cognitive stimulation trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
Schoene 2015 ⁴³ (Australia)	81	16 weeks	Cognitive function / Executive function	<ul style="list-style-type: none"> Intervention group: Interactive Cognitive-Motor Step Training: four stepping games that required them to divide attention, inhibit irrelevant stimuli, switch between tasks, rotate objects and make rapid decisions (20-minute sessions/week) unsupervised at home vs. Control group: evidence-based brochure on fall prevention 	General population	70 years and over, Free of neurodegenerative disease, no major cognitive impairment (Mini-Cog \geq 3), able to step unassisted, free of health problems that affect stepping ability	<ul style="list-style-type: none"> No significant improvement was found in the Stroop Stepping Test for the intervention group
PACE ⁴⁴ (Germany)	100	5 weeks	Cognitive function / Global visuospatial cognition with composite z-score	<ul style="list-style-type: none"> Jigsaw puzzle group (at least 1 h per day) and telephone based cognitive health counselling vs. Cognitive health counselling group 	General population	50 years and over, MMSE \geq 24, free of dementia, free of neurological disorder	<ul style="list-style-type: none"> No significant improvement was found for global visuospatial cognition in Jigsaw puzzle group compared to the control group.
Iizuka 2019 ⁴⁵ (Japan)	72	3 months	Cognitive function / working memory	<ul style="list-style-type: none"> Face-to-face group board game (Go) sessions (1/week + daily homework exercises) • tablet computer- delivered board game (Go) sessions (1/week + daily homework exercises) 	General population	65 years and older, free of dementia, able to perform activities of daily living independently, no previous experience of playing Go	<ul style="list-style-type: none"> Compared to the control group, scores at follow-up were significantly better for two (working memory, but not verbal working memory) out of three primary outcome measures in the face to face Go group, and

Completed cognitive stimulation trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				vs. • Health education control group (2hr lecture once a month, for 3 months)			for one (working memory) of the three primary outcome measures for the non-face-to-face Go group, with a greater effect size, compared to the control group, in the face-to-face group than the non-face-to-face group.
SAGE ⁴⁶ (USA, Sweden)	82	5 weeks	Cognitive function / working memory tests	• Home-based (40 mins, 5d-wk) Cogmed adaptive computerized cognitive training (CCT) vs. • Home-based (5d-wk) non-adaptive CCT	General population	65 years or older, IQ ≥90, MMSE ≥26, cognitive performance within 1SD of mean for age-based norms, GDS<15	• Participants in the adaptive CCT group improved significantly more on one of three working memory primary outcome measures (after adjustment for multiple comparisons) compared to the control group, but not on the other two primary outcome measures
Bahar-Fuchs 2020 ⁴⁷ (Israel)	84	8 weeks intervention (+ booster session at 3 months)/6 months follow-up	Cognitive function / global cognition (composite score based on battery of 9 tests)	• Tailored and adaptive computerized cognitive training (CogniFit, 3 times per week (2 sessions per day), total 48 sessions + 1-week booster training at 3 months) + one of 3 randomly assigned self-efficacy interventions vs. • Generic, non-tailored or adaptive computerized cognitive training (CogniFit, 3 times per week (2 sessions per day), total 48 sessions +	At risk	Community-dwelling older adults with diabetes, free of dementia, access at home to a computer & internet, ≥6 years of education	Cognition significantly improved immediately post-training and at 6 months in both groups, but there were no between-group differences.

Completed cognitive stimulation trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				1-week booster training at 3 months) + one of 3 randomly assigned self-efficacy interventions			
Faust 2020 ⁴⁸ (USA)	151	8-10 weeks / 3 months	Cognitive function / visual processing and verbal memory (RBANS)	<ul style="list-style-type: none"> • Computerized cognitive training (CCT; 30–40 ~40 min sessions - visual games • CCT - auditory games • CCT - both types of games vs. • Control (no CCT) 	General population	Community dwelling, age ≥60 years, MMSE ≥ 24	The visual games group showed significant improvement on 2 of 3 primary outcome measures compared to the control group. The auditory games and both games groups showed no difference compared to the control group.
Montoya-Murillo 2020 ⁴⁹ (Spain)	124	3 months (12-month follow-up)	Cognitive function / overall neurocognition (composite score)	<ul style="list-style-type: none"> • Cognitive remediation program (REHACOP) vs. • Control group: occupational therapy 	General population	55 years and over attending senior day centres, MMSE > 10th percentile for participant age and education level Independent in ADL, free of dementia	After the intervention, the experimental group showed significantly better performance in neurocognition in comparison with the control group
Park 2021 ⁵⁰ (Korea)	160	6 weeks	Cognitive function / global cognition (MMSE-DS, SMCQ, CERAD-K)	<ul style="list-style-type: none"> • Robot-assisted cognitive training (RACT; 2 sessions/week) • Traditional cognitive training (TCT; 2 sessions/week) vs. • No intervention control group 	At risk/MCI	Older adults aged 60 and older with subjective memory complaints or MCI, with no ADL or IADL limitations and free of major neurocognitive disorder	<p>There were significant group*time effects for all primary outcome measures.</p> <p>In within-group analyses, compared to pre-intervention, MMSE-DS scores significantly improved in the RACT group only, and SMCQ and CERAD-K scores significantly improved in the</p>

Completed cognitive stimulation trials							
Trial name/1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
							RACT and TCT groups, but not the control group,

Supplementary Table 7: Completed multidomain trials published since May 2015

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
Rovner 2018 ⁵¹ (USA)	221	24 months	Cognitive function / Episodic memory	<ul style="list-style-type: none"> • Behavioural activation, 5 in-home 60-minute treatment sessions over 4 months and 6 in-home follow-up maintenance sessions over the next 20 months vs. • Supportive therapy (control) 	MCI	65 years and over, Amnesic MCI, free of dementia, African American,	<ul style="list-style-type: none"> • The 2-year incidence of memory decline was significantly lower in the behavioural activation group compared to the supportive therapy group (1.2% (95% CI, 0.2-6.4 vs 9.3% (95% CI, 5.30-16.4; RR, 0.12; 95% CI, 0.02-0.74; P = .02). • Behavioural activation was associated with stable everyday function, whereas supportive therapy was associated with decline
MAPT ⁵² (France, Monaco)	1525	3 years	Cognitive function / Global cognitive performance with composite Z-score	<ul style="list-style-type: none"> • Multidomain intervention • Omega 3 supplement (400 mg daily of oil mixture containing natural fish oil with a minimum of 65% docosahexaenoic acid and maximum of 15% eicosapentaenoic acid) + Multidomain intervention (cognitive training, advice on physical exercise, 	At risk	70 years and over; MMSE ≥ 24; free of dementia; self-reported memory complaint, low gait speed, and/or limitation in one instrumental activity of daily living	<ul style="list-style-type: none"> • No significant differences in 3-year cognitive decline between any of the three intervention groups and the placebo group.

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				nutrition and social activities) • Omega 3 vs. • Placebo			
PreDIVA ⁵³ (Netherlands)	3454	6-8 years	Dementia incidence / all-cause dementia	• Multidomain cardiovascular intervention (every 4 months individually tailored lifestyle advices and/or drug treatment, if indicated, based on cardiovascular risk factors assessment) vs. • Control (usual care)	General population	70-78 years, free of dementia,	• No difference in dementia incidence between the two groups (HR 0.92, 95% CI 0.71–1.19; p = 0.54).
Bae 2019 ⁵⁴ (Japan)	83	24 weeks	cognitive function / NCGC-FAT tablet-based assessment of word list recall, spatial working memory, attention, executive function, processing speed; and global cognitive function (MMSE)	• 2*90 minute supervised sessions per week, with participation in self-selected physical (N=16), cognitive (N=16) and social (N=16) activities vs. • Health education control group (2*90 min. classes on oral care & nutrition)	MCI	65 years and over, MCI, MMSE≥24, free of ADL disability & dementia	• The intervention group showed significantly greater improvement in only one (spatial working memory) of 6 cognitive tests
Shimada 2018 ³⁵ (Japan)	308	40 weeks	Cognitive function / MMSE, WMS-R	• Combined cognitive and physical activity (weekly 90 min sessions involving	MCI	65 years and over, MCI, free of dementia, enrolled in the OSHPE	• Compared with the control group, the combined activity group

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
			Logical Memory II, RAVLT	aerobic, muscle strength, balance and dual-task training + daily home- based muscle strength exercises and walking) vs. • Health education control (3*90 min health promotion sessions + 3 mailed leaflets)		population-based study	showed significantly less decline/more improvement on two of three primary cognitive outcome measures
Inoue 2018 ⁵⁵ (Japan)	38	12 weeks	Cognitive function / MoCA-J	• Resistance training (1h30 per week) + probiotic <i>Bifidobacterium</i> supplementation vs. • Resistance training + Placebo	General population	Aged >65 years, having undergone stretch training for the previous 12 months, free of dementia	• There was no difference in change on the MoCA-J between the two groups
DO-HEALTH ⁵⁶ (Switzerland, France, Germany, Portugal, Austria)	2157	3 years	6 co-primary outcomes, including cognitive function/MoCA	• Vitamin D3 (2000 IU/d) + omega-3s (1 g/d) + strength-training exercise • vitamin D3 + omega-3s • vitamin D3 + exercise • vitamin D3 alone • omega-3s + exercise • omega-3s alone • exercise alone Vs. • Placebo	General population	Aged ≥70 years, community-dwelling, MMSE ≥24, no major health events in the 5 years prior to enrolment, sufficient mobility to come to study centres without help (target of 40% with a history of falling in previous 12 months, i.e. at high risk of frailty)	• There were no statistically significant effects of any intervention individually or in combination for cognition or any of the 5 other end points at 3 years

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
ENLIGHTEN ⁵⁷ Blumenthal et al 2019. (USA)	160	6 months	Cognitive function / composite measure of executive function	<ul style="list-style-type: none"> • Aerobic exercise (3*45 mins/week for 6 months (supervised for 1st 3 months)) • DASH diet (with weekly (1st 12 weeks) or bi-weekly (2nd 12 weeks) 30 minute sessions with a nutritionist) • Aerobic exercise + DASH diet Vs. <ul style="list-style-type: none"> • Health education control (weekly 30-minute educational phone calls for 3 months and then biweekly for 3 months) 	At risk	Sedentary men and women, age >55 years, CIND (Mail-in Cognitive Function Screening Instrument score ≥ 0.5 ; and MoCA score 19-25 or letter fluency ≤ 12 or animal fluency ≤ 15), CVD or additional CV risk factor	<ul style="list-style-type: none"> • Compared to the control group, participants in the aerobic exercise conditions showed significant improvements in executive function (b = 4.2 [0.2–8.2], d = 0.32, p = 0.046), but no significant changes were observed for those in the DASH diet condition (b = 3.7 [-0.2 to 7.7], d = 0.30, p = 0.059)
Imaoka 2019 ⁵⁸ (Japan)	67	3 months	Cognitive function / MMSE, TMT	<ul style="list-style-type: none"> • Exercise (15 min. memory training, 45 min. aerobic exercise, once a week) Vs. <ul style="list-style-type: none"> • Exercise + soy peptide 	General population	Aged ≥ 60 years, independent in ADLs, free of dementia	<ul style="list-style-type: none"> • In this unblinded trial, there were no between-group differences in the main cognitive outcome measures
Lebedev 2020 ⁵⁹ (Sweden)	63	4 weeks (primary outcome measured immediately post-	Cognitive function / latent variables of spatial and verbal fluid intelligence	<ul style="list-style-type: none"> • L-dopa/ benserazide (100/25 mg, prior to each cognitive training session) + cognitive training (1 hour, 5 times/week) Vs.	General population	65-75 years, MMSE >25	<ul style="list-style-type: none"> • The subjects receiving L-dopa improved significantly less in one (spatial intelligence) of the two co-primary outcomes, compared to

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
		intervention, although 6 months follow- up was performed)		<ul style="list-style-type: none"> • Placebo + cognitive training 			the placebo group. There was no between-group difference for the second co-primary outcome.
Matsubara 2021 ⁶⁰ (Japan)	55	8 months	Cognitive function / MMSE-J, Dementia Assessment Sheet in Community-based Integrated Care System (DASC-21), TMT-A & B	<ul style="list-style-type: none"> • Monthly oral health intervention (oral hygiene, oral function exercises + education on nutrition) + monthly group health promotion lectures Vs. • Group health promotion lectures (twice monthly) 	MCI	Community-dwelling older adults aged ≥65 years, MMSE-J ≥21 to ≤26, no dental clinic visit in the previous year	<ul style="list-style-type: none"> • There was a significant intervention effect on the TMT, but not on the other cognitive outcome measures.
Nilsson 2020 ⁶¹ (Sweden)	139 randomized; 97 analysed	12 weeks	Cognitive function/ 8 cognitive composite scores	<ul style="list-style-type: none"> • Physical exercise (35 min. aerobic exercise) immediately before cognitive training (35 min. adaptive working memory training, 3 times/wk) • Physical exercise immediately after cognitive training • Physical exercise only • Cognitive training only 	General population	Healthy participants between 65 and 75 years, MMSE ≥26	<ul style="list-style-type: none"> • There were no between group differences in cognitive outcomes
BBL-CD ⁶² (Australia)	119	8 weeks / 6 months	Dementia risk score / ANU-ADRI And cognitive function / composite	<ul style="list-style-type: none"> • Online health education + dietitian and exercise physiologist sessions, and online brain training 	At risk	Community-dwelling individuals aged >65; owning a computer with Internet access;	<ul style="list-style-type: none"> • The intervention group had a significantly better ANU-ADRI score at 3 months (but not at

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
			Z score (ADAS-Cog-Plus)	Vs. • Online health education		with MCI or subjective cognitive decline (SCD)	other time points), and had significantly a better cognition score at 3 and 6 months, but not immediately post-intervention
STEPS ^{63,64} (Australia)	154	24 weeks	Cognitive function / executive function (Cogstate battery)	• Progressive resistance training + lean meat (3 days*week) vs. • Progressive resistance training + carbohydrate	General population	65 years and over, cognitively healthy (Short Portable Mental Status Questionnaire \leq 2), no current or prior participation in resistance exercise and/or moderate-intensity physical activity	• No between-group difference in changes in executive function
Chen 2020 ⁶⁵ (Taiwan)	1082 (40 clusters)	1 year	Cognitive function / global cognitive function (MoCA)	• 16, 2 h sessions/year comprising communally partaken physical and cognitive training plus nutrition and disease education vs. • ~3-monthly telephone consultations providing health education	At risk	\geq 65 years; prefrail/frail (subjective memory impairment and/or loss of \geq 1 instrumental activities of daily living (IADL), and/or timed 6 m walk speed \leq 1 m/s); community-dwelling; free of dementia	• There was no significant between-group difference in cognitive decline after 1 year.
Yang 2022 ⁶⁶ (China)	122	6 months	Cognitive function / global cognitive function (MoCA)	• Mutlicomponent intervention (dietary guidance, physical training, computer-aided	MCI	Age \geq 65 years, MCI	Participants in the intervention group had significantly greater improvement in

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
				cognitive training, and management and monitoring of metabolic indicators and vascular risk factors) delivered by community healthcare workers vs. • Usual care			cognitive function compared to the control group.
Wang 2021 ⁶⁷ (Taiwan)	20	12 weeks	Cognitive function / executive function and dual task performance (EXIT25, TMT, Stroop, motor and cognitive timed up and go dual task tests)	• exergame-based dual-task training (motor and cognitive video games performed whilst walking on a treadmill) vs. • home-based multicomponent exercise training	General population	Community dwelling, age ≥65 years, able to walk 10m independently, MMSE ≥ 24, ≥ 6 years education	There were significant time · group interaction effects for all outcomes.
Law 2022 ⁶⁸ (Taiwan)	145	8 weeks (5 months follow-up)	Cognitive function / global cognition, executive function, everyday problem-solving ability, functional status (NCSE, Category Verbal Fluency Test, TMT-A, TMT-B, Problems in Everyday Living Test (PEDL) ADL, IADL)	• Functional task exercise (physical activity + cognitive training) • Cognitive training • Exercise training vs. • Wait-list control	MCI	Community dwelling adults aged ≥60, MCI	Immediately post-intervention and at 5-month follow-up, there were significant between-group differences in changes in verbal fluency, everyday problem solving and functional status, but not in other outcome measures. Post-hoc pairwise comparisons

Completed multidomain trials							
Trial name/ 1st author (Country)	N	Length of intervention (and follow-up if different)	Type of primary cognitive endpoint / precisions	Details of intervention and control	Type of study population	Main eligibility criteria	Main result (primary endpoint), and, where relevant, significant secondary results
							suggested that the FTE group performed better than others.

Supplementary Table 8: Ongoing pharmacological trials

Ongoing pharmacological trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
Generation Study 2 ^{69,70} NCT03131453 (24 countries in North/Central/South America, Europe, Asia and Africa)	2000	5-8 years (duration will be event-driven)	Dementia or MCI incidence and cognitive function (<i>the study will be considered positive if a significant effect is detected on either endpoint, following multiplicity adjustment</i>)	<ul style="list-style-type: none"> • CNP520 (umibecestat) 15 mg • CNP520 50 mg vs. <ul style="list-style-type: none"> • Placebo 	At risk	60-75 years; Cognitively unimpaired (MMSE \geq 24, RBANS delayed memory index \geq 85, CDR=0); APOE4 carriers; evidence of elevated brain amyloid if ϵ 4 heterozygote
Generation Study 1 ^{69,70} NCT02565511 (USA, Australia, Belgium, Canada, Finland, Germany, Netherlands, Spain, Switzerland, UK)	1340	5-8 years (duration will be event-driven)	Dementia or MCI incidence and cognitive function (<i>the study will be considered positive if a significant effect is detected on either endpoint, following multiplicity adjustment</i>)	<ul style="list-style-type: none"> • CAD106 (450 μg) + Alum (450 μg) given i.m. at week 1, 7, 13 and quarterly thereafter • Placebo to CAD106 + Alum (450 μg) given i.m. at week 1, 7, 13 and quarterly thereafter • CNP520 (50 mg) oral capsules vs. <ul style="list-style-type: none"> • Placebo to CNP520 oral capsules 	At risk	60-75 years; Cognitively unimpaired (MMSE \geq 24, RBANS delayed memory index \geq 85, CDR=0); APOE4 homozygotes
A4 ⁷¹ NCT02008357 (USA, Australia, Canada, Japan)	1150	240 weeks	Cognitive function	<ul style="list-style-type: none"> • Solanezumab (400- 1600 mg) intravenously every 4 weeks vs. <ul style="list-style-type: none"> • Placebo iv every 4 weeks 	At risk	65 years and over; Free of dementia (CDR 0), MMSE 25-30, logical Memory II score 6–18, Florbetapir PET scan evidence of brain amyloid pathology
AHEAD 3-45 (NCT04468659) (USA, Canada, Australia, Japan, Netherlands, Singapore, Spain, UK)	1400	216 weeks (approx. 4 years)	A45 trial: Cognitive function / global cognitive function (Preclinical Alzheimer Cognitive Composite 5 (PACC5))	<ul style="list-style-type: none"> • Lecanemab (BAN2401; A45: 5 mg/kg intravenously every 2 weeks for 8 weeks, then 10 mg/kg every 2 weeks up to 96 weeks, then every 4 weeks; A3: 5 mg/kg intravenously every 4 	At risk	Age 55-80 years, MMSE \geq 27, CDR 0, elevated (A45 trial) or intermediate (A3 trial) levels of brain amyloid pathology (PET). If <65 years, 1 additional risk factor is required (first-degree relative with dementia onset

Ongoing pharmacological trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
			A3 trial: biomarker / PET amyloid	weeks for 8 weeks, then 10 mg/kg every 4 weeks) vs. • Placebo		<75y, ApoE+, or prior CSF or PET evidence of raised amyloid)
TRAILBLAZER-ALZ 3 NCT05026866 (USA, Japan, Puerto Rico)	3300	3.5 years	Cognitive function / Time to clinical progression on CDR	• Intravenous donanemab (LY3002813) vs. • placebo	At risk	Age 55-80 years, intact cognitive function, presence of amyloid and early tau pathology (p-tau), free of MCI or dementia
SKYLINE NCT05256134 (USA, Argentina, Australia, Canada, Italy, Poland, Spain, Sweden)	1200	4 years	Cognitive function / global cognition (PACC-5)	• Subcutaneous Gantenerumab vs. • placebo	At risk	Age 60-80 years, cognitively unimpaired (CDR=0, RBANS delayed memory index ≥80), evidence of cerebral amyloid accumulation, free of MCI and dementia
LATTICE NCT03185208 (USA)	80	2 years	Cognitive function	• Lithium carbonate (initiated at 150 mg / day and increased based on blood levels until a steady blood level between 0.6 and 0.8 meq/L is achieved) vs. • Placebo	MCI	60 years and over MCI, free of major neurologic illness No major psychiatric illness, no contraindication to lithium
MAP NCT04098666 (USA)	370	2 years	Cognitive function / FCSRT total recall	• extended release metformin (up to 4 * 500 mg tablets/day) vs. • Placebo	MCI	aMCI, MMSE ≥ 24 (≥ 20 if <8 years of education); CDR 0.5; Age 55-90; free of diabetes; BMI ≥ 25
PREVENTABLE NCT04262206 (USA)	20000	up to 5 years (estimated median of 3.8 years)	Incident dementia / composite of death, dementia, and persistent disability	• Atorvastatin 40 mg vs. • Placebo	General population	Community-dwelling adults 75 years of age or older without clinically evident cardiovascular disease, significant disability, or dementia
NCT04629547 (USA)	200	2 years	Imaging / change in in PET amyloid-β	• Suvorexant (sleep aid) 20 mg vs. • Placebo	At risk	Age ≥65, CDR 0, PET PIB standard uptake value ratio (SUVR) between >1.42 to <3

Ongoing pharmacological trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
IMPACTS-MIND NCT04797403 (USA)	920	3.5 years	Cognitive function / global cognition (composite score)	<ul style="list-style-type: none"> • Intensive blood pressure lowering (SPRINT protocol) vs. • Usual care 	At risk	Age ≥40 (2/3 of participants ≥60 years) attending primary care clinics predominantly managing underserved populations with health disparities (ethnic minorities, low-income groups, and residents of rural areas and inner cities), SBP ≥140 mmHg (or ≥130 mmHg if taking antihypertensive medication), free of dementia
IPAT NCT05331144 (USA)	180	2 years	Biomarker / PET amyloid	<ul style="list-style-type: none"> • Intensive blood pressure lowering treatment (ARBs and CCBs; target SBP <120mmHg) vs. • Usual care (ARBs and CCBs; target SBP <140mmHg) 	At risk	Age 60-80 years, family history of dementia or subjective memory complaints, MMSE ≥26, SBP ≥ 130 and ≤ 180, free of dementia
MemAID ⁷² NCT02415556 (USA)	210	24 weeks / 48 weeks	Cognitive function /memory and general cognitive function (CANTAB)	<ul style="list-style-type: none"> • Intranasal insulin (40 IU/d) vs. • placebo (saline) 	At risk General population	Age 50–85 years, either type 2 diabetic or control subjects with fasting plasma glucose <126 mg/dL and HbA1c <6.5%, free of dementia, MMSE>20 (between-group comparisons will be stratified by diabetes status)

Supplementary Table 9: Ongoing nutritional trials

Ongoing nutritional trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
MIND Diet ⁷³ NCT02817074 (USA)	604	3 years	Cognitive function	<ul style="list-style-type: none"> • MIND Diet (based on Mediterranean and DASH diets) + mild caloric restriction for weight loss vs. • Usual Diet + mild caloric restriction 	At risk	65-84 years Family history of dementia, free of cognitive impairment BMI >= 25, suboptimal diet, no heavy alcohol use
LO-MAPT NCT03691519 (France, Spain)	400	18 months (36-month follow-up)	Cognitive function	<ul style="list-style-type: none"> • Omega-3 treatment (DHA + EPA), 1.53 g/day vs. • Placebo 	At risk	70 years and over Subjective memory complaint or family history of AD, MMSE≥24, free of dementia, RBC DHA/EPA index ≤ 4.83%
ACID ⁷⁴ NCT03419039 (Norway)	220	24 weeks	Cognitive function	<ul style="list-style-type: none"> • Anthocyanins: Medox tablet containing 80mg anthocyanins, 2 capsules x 2 daily, 320mg daily vs. • Placebo 	At risk	60-79 years MCI or 2 or more risk factors of cognitive impairment or dementia (cardiovascular diseases, cerebrovascular disease, hypercholesterolemia, hypertension, diabetes mellitus type 1, metabolic syndrome), free of dementia,
Nutrition Interventions for Cognitive Enhancement (NICE) NCT03841539 (USA)	200	1 year	Cognitive function	<ul style="list-style-type: none"> • Mediterranean diet + Omega 3 • Mediterranean diet + Placebo • Low-fat diet + Omega 3 vs. • Low-fat diet + Placebo 	General population	65 years and over MMSE>25, free of dementia

Ongoing nutritional trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
Bowman 2019 ⁷⁵ NCT01953705 (USA)	102	3 years	Imaging / cerebral white matter hyperintensities (WMH)	<ul style="list-style-type: none"> • Marine n-3 polyunsaturated fatty acids (PUFA) vs. • Placebo (soybean oil) 	At risk	Age 75 and older, CDR≤ 0.5, MMSE≥ 24, free of dementia, MRI derived total WMH ≥ 5 cm ³ , blood n-3 PUFA (EPA + DHA) < 110 ug/mL or < 5.5 wt%)
Jeong 2020 ⁷⁶ (Korea) KCT0003570	80	12 weeks	Cognitive function / Seoul verbal learning test-elderly's version (SVLT-E)	<ul style="list-style-type: none"> • Jujadokseo-hwan (traditional Chinese herbal medicine) vs. • Placebo 	MCI	Age 45-85 years; mild neurocognitive disorder (DSM-5); CDR=0.5, GDS (global deterioration scale)=2-3; MoCA-K=22; no limitations in activities of daily living; > 6 years (elementary) education
MINDBERRY NCT04317612 (Sweden)	100	12 weeks	Cognitive function / episodic memory (verbal recognition memory); attention, psychomotor speed & executive function (TMT-A & B); selective attention & processing (Stroop color-word test); Verbal fluency	<ul style="list-style-type: none"> • Active berry product vs. • Reference product 	MCI	Age 55 or older; cognitive impairment (DSM-5 criteria & Global Deterioration Scale stage 3); MMSE ≥24
NCT04431843 (Korea)	80	12 weeks	Cognitive function/ visual learning, visual working memory, verbal learning	<ul style="list-style-type: none"> • Spirulina maxima extract (1.5g/d) vs. • placebo 	General population	Age ≥60, Korean MMSE 25-28
BRIDGE Tussing-Humphreys 2017 ⁷⁷ NCT03129048 (USA)	180	8 months (14-month follow-up)	Cognitive function	<ul style="list-style-type: none"> • MedDiet lifestyle intervention with caloric restriction/weight loss • MedDiet Alone, without caloric restriction/weight loss vs. • Typical Diet Control 	At risk	55 years and over MoCA≥19, overweight or obese (BMI 30.0-50.0 kg/m ²), with access to a phone

Ongoing nutritional trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
NCT04555655 (Taiwan)	276	2 years	Cognitive function / ADCOMS + Imaging / Florbetaben (18F) PET	<ul style="list-style-type: none"> • Chicken extract supplement (70ml/d) • Peptide supplement (70ml/d) vs. <ul style="list-style-type: none"> • Placebo (caesinate) 	MCI or At risk	Age 55-75 years, normal cognition with subjective cognitive decline or MCI, free of dementia
NCT04645927 (Canada)	60	6 months	Cognitive function / memory (CANTAB memory score)	<ul style="list-style-type: none"> • Flax (omega-containing) beverage (30g/day flaxseed, i.e. 3.75 mg omega-3) vs. <ul style="list-style-type: none"> • Placebo beverage 	MCI or At risk	Age 60-84, MCI or minor cognitive disorder, MoCA score 19-25, free of dementia
EPICURO NCT04705220 (Italy)	100	6 months	Cognitive function / global cognitive function (MMSE, MoCA)	<ul style="list-style-type: none"> • Turmeric supplementation (MERIVA®, 1g/day (approx. 200mg curcuminoids)) vs. <ul style="list-style-type: none"> • Placebo 	At risk	Aged 60+ years with Metabolic Syndrome, MMSE ≥ 24
BrainPhyt-one NCT04832412 (Ireland)	144	24 weeks	Cognitive function / spatial working memory (COMPASS score)	<ul style="list-style-type: none"> • Low dose BrainPhyt (bioactive compound derived from marine microalgae) supplement + sunflower oil • High dose BrainPhyt supplement + sunflower oil vs. <ul style="list-style-type: none"> • Placebo (sunflower oil) 	General population	Age 55-75 years, free-living, age-related mild cognitive decline (MMSE ≥ 24 , MAC-Q ≥ 25), normal cognition (AD8 dementia screening score < 2) free of significant anxiety & depression symptoms
TURMEMIC NCT04860050 (Ireland)	152	24 weeks	Cognitive function / working memory (CDR system)	<ul style="list-style-type: none"> • Turmeric supplement (Turmipure Gold®) vs. <ul style="list-style-type: none"> • Placebo 	At risk	Age 60-85 years, subjective memory impairment with preserved global cognitive functions, everyday activities and no dementia, MMSE ≥ 24

Ongoing nutritional trials						
Trial name/ 1st author/ trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
BRAINBOOSTER NCT04910399 (France)	56	3 months	Cognitive function / verbal recognition memory (CANTAB Paired Associated Learning test)	<ul style="list-style-type: none"> • Blue fish hydrolysate (BrainBooster; containing peptides and n-3 polyunsaturated fatty acids; 4 capsules/day) vs. • Placebo 	General population	Age 60-73 years, MMSE 27-29, free of AD
JPRN-UMIN000044496 (Japan)	100	24 weeks	Cognitive function / global cognition (MMSE, MoCA)	<ul style="list-style-type: none"> • DHA containing food vs. • Placebo 	General population	Age 65-85 years, MMSE ≥ 22 , free of dementia
NCT04337255 (USA)	500	2-3 years	Cognitive function / global cognition (z-score of 19 cognitive tests)	<ul style="list-style-type: none"> • MIND diet vs. • Usual care 	At risk	Age 60-80 years, free of dementia, discharged home following hospitalization for acute ischemic stroke
NCT04466735 (Canada)	56	6 months	Imaging / Acetoacetate and glucose brain uptake (PET)	<ul style="list-style-type: none"> • Exogenous ketone salt supplement (2 x 12 g/d) vs. • Placebo 	At risk	Age 55-80, subjective memory complaint, MoCA 20-25, free of major cognitive decline or neurodegenerative disease
NCT04966455 (Spain)	80	3 months	Cognitive function / global cognition (MoCA)	<ul style="list-style-type: none"> • Raisins (50g/d) vs. • No intervention 	General population	Age 70-80 years, MMSE ≥ 24
NCT05460624 (USA)	128	12 weeks	Cognitive function / memory, executive function (CNSVS verbal and visual memory tests and shifting attention test)	<ul style="list-style-type: none"> • Egg-containing breakfast (12 eggs/week) vs. • Typical American-style breakfast excluding eggs (matched to the intervention foods on total energy and saturated fat) 	General population	Age 65-90 years, CNSVS standard score of 85-105 for either the domain composite memory or the domain executive function, and 80-110 for the other domain
NCT05322304 (country not specified)	60	24 weeks	Cognitive function / global cognition (CANTAB)	<ul style="list-style-type: none"> • Almonds (20% of energy) vs. • Isocaloric diet 	At risk	Age 40-60 years, Asian Indians with prediabetes, no previous diagnosis of neurodegenerative disease

Supplementary Table 10: Ongoing physical activity trials

Ongoing physical activity trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
MOVE for Your MIND NCT03384602 (Switzerland)	195	12 months	Cognitive function	<ul style="list-style-type: none"> • Dalcroze Eurhythmics Program (music-based multi-task exercise in group) 1x60min/week • Home exercise strength program (simple strength exercise program to perform individually at home) 3x30min/week vs. <ul style="list-style-type: none"> • Control group 	At risk	70 years and over Free of MCI, subjective cognitive decline, free of depressive symptomatology, no risk of recurrent falling
Zheng 2016 ⁷⁸ ChiCTR-ICR-15005795 (China)	135	24 weeks (37-week follow-up)	Cognitive function	<ul style="list-style-type: none"> • 24-week Baduanjin exercise intervention (60 min per session, three sessions per week) • 24-week brisk walking intervention (60 min per session, three sessions per week) vs. <ul style="list-style-type: none"> • 24-week usual physical activity control group (60 min per session, three sessions per week) 	MCI	60 years and over, MCI, living in the community, no regular physical exercise for at least half a year
EPD ⁷⁹ NCT02236416 (Italy)	540	48 months	Cognitive function (MMSE)	<ul style="list-style-type: none"> • Multimodal supervised exercise (3*1 hour group classes per week, including aerobic, endurance and flexibility exercises) vs.	General population	Community dwelling individuals aged 50 years or more; sedentary or normally-active lifestyle; normal cognition, subjective memory complaints

Ongoing physical activity trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				<ul style="list-style-type: none"> • Usual lifestyle 		or MCI; MMSE \geq 24; free of dementia
KCT0004619 (South Korea)	52	20 weeks	Cognitive function & Biomarker / (neuropsychological tests not specified) & MRI	<ul style="list-style-type: none"> • Structured exercise program (aerobic, strength, balance and flexibility exercises; 50 mins, 3 times a week) vs. <ul style="list-style-type: none"> • Regular walking exercise (50 mins, 3 times a week) 	At risk	60 years and older; \geq 1 dementia risk factor (Hypertension, Diabetes mellitus, Dyslipidemia, Obesity, Smoking, Excessive drinking, <9 years education, Physically inactive); free of dementia
UMIN000036659 (Japan)	60	3 months	Cognitive function / (not specified)	<ul style="list-style-type: none"> • Exercise intervention at cardiac oxygen demand threshold vs. <ul style="list-style-type: none"> • No intervention control 	General population	Community-dwelling, age 50 and over, no mental illness
UMIN000037208 (Japan)	100	6 months	Cognitive function / memory, attention, executive function, processing speed, special recognition, working memory	<ul style="list-style-type: none"> • dual task pole walking for 6 months vs. <ul style="list-style-type: none"> • health education control (1 lecture) 	MCI	65-75 years old, MCI
PAAD-2 Park 2020 ⁸⁰ NCT03876314 (USA)	240	1 year	Cognitive function/ PAAD-2 cognitive test battery	<ul style="list-style-type: none"> • Physical activity (group aerobic & strength training, 3days/wk) vs. <ul style="list-style-type: none"> • usual activities + biweekly education materials control 	At risk	Cognitively normal, middle aged (40-65 years) sedentary adults with family history of AD
EXECO NCT04504643 (France)	45	8 weeks	Cognitive function/ working memory (HappyNeuron software), inhibition processes (Stroop), switching capacities (TMT-A & B), visuospatial capacities (Rey complex figure), dual task	<ul style="list-style-type: none"> • Technology-assisted circuit training • Conventional circuit training including single and dual task Vs. <ul style="list-style-type: none"> • Nordic walking 	General population	Cognitively healthy (MMSE \geq 26) community dwellers aged 65 to 80

Ongoing physical activity trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
			capacities (walking oral TMT-A & B), global cognition (MoCA)			
RAATE-MCI NCT04956549 (USA)	144	1 year	Cognitive function / executive function (NIH-Toolbox cognitive battery executive function subdomain, i.e. Flanker Inhibitory Control and Attention Test and Dimensional Change Card Sort Test)	<ul style="list-style-type: none"> Physical activity program (2*80 min group sessions/week, consisting of aerobic, strength, flexibility, and balance training) Vs. Low intensity Successful Aging control (1 session/ week for first 6 mo, then 1 session every 2 weeks, covering stretching, balance training, flexibility, relaxation, and successful aging education) 	MCI	Age 65-85, African American, MCI, free of dementia, not engaging in regular physical activity, SPPB ≥4
DRKS00020943 (Poland)	198	1 year	Cognitive function / global cognitive function (NTB, MoCA)	<ul style="list-style-type: none"> mobile application encouraging participants to increase their physical activity up to a moderate level (>10,000 steps per day) Vs. Usual physical activity 	MCI	Age 50-65, mild cognitive impairment (MoCA 19-26), free of dementia
ACTION NCT04384263 (USA)	20	12 weeks	Cognitive function / executive function, memory, information processing, attention (Stroop test, letter and category fluency, HVL, TMT-A&B, CalCAP, NIH Toolbox Flanker Inhibitory Control and Attention Test)	<ul style="list-style-type: none"> Online instructor-led Tai Chi sessions (3*45 min sessions/wk) + offline practice with instructional videos Vs. Usual physical activity 	At risk	Age 55 and older, established hypertension, MMSE≥25, physically inactive
NCT05318703 (USA)	69	16 weeks	Cognitive function / global cognitive function, attention and working memory, executive function (MoCA,	<ul style="list-style-type: none"> Online cognitively enhanced tai ji quan exercise Vs. 	MCI	Age 65-95, MCI (CDR ≤0.5, informant-corroborated self-

Ongoing physical activity trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
			Digit Span, TMT-B, Category Fluency, Everyday Cognition)	<ul style="list-style-type: none"> • Stretching 		reported memory decline), MMSE ≥ 24
NCT05012878 (US)	87	12 weeks	Biomarker/cerebral blood flow	<ul style="list-style-type: none"> • High intensity interval training (HIIT) • Moderate intensity continuous training (MICT) Vs. <ul style="list-style-type: none"> • Exercise advice 	At risk	Age 40 and older, eligible for cardiac rehabilitation following a cardiac-related hospital admission, or diagnosed coronary artery disease
TIME NCT05310890 (China)	206	3 years follow-up	Dementia incidence	<ul style="list-style-type: none"> • Tai chi training + quarterly group activities (e.g. popular science lectures or interactive games) Vs. <ul style="list-style-type: none"> • Quarterly group activities (e.g. popular science lectures or interactive games) 	MCI	Age 55-75 years, MCI-AD (NIA-AA criteria), free of dementia
TIPS NCT05485025 (China)	134	3 years	Cognitive function / global cognitive function (RBANS)	<ul style="list-style-type: none"> • Tai chi training + quarterly group activities (e.g. popular science lectures or interactive games) Vs. <ul style="list-style-type: none"> • Quarterly group activities (e.g. popular science lectures or interactive games) 	At risk	Age 60-75 years, subjective cognitive impairment (SCI), CDR=0
NCT05229705 (Canada)	70	6 months	Cognitive function / executive function (TMT)	<ul style="list-style-type: none"> • Progressive resistance training Vs. <ul style="list-style-type: none"> • Balance and tone control 	At risk	Age 60-80 years, MMSE > 24 , IADL $> 6/5$, at-risk for diabetes (blood glucose level of 6.1-7 mmol/L; BMI > 25 ; or CANRISK diabetes questionnaire > 21)

Ongoing physical activity trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
AMETHYST NCT05232968 (Slovakia)	120	2 years	Cognitive function / global cognitive function (MoCA)	<ul style="list-style-type: none"> • Long-term (2 years) exercise program (individualized aerobic strength training) • Short-term (4 months) exercise program (individualized aerobic strength training) Vs. <ul style="list-style-type: none"> • Sedentary volunteers 	MCI	Age 55-85 years, non-smokers, MCI, sedentary lifestyle ≥ 2 years prior this study
SAGE NCT05036304 (Canada)	68	12 weeks	Cognitive function / working memory (list sorting performance, digit span)	<ul style="list-style-type: none"> • Outdoor aerobic exercise Vs. <ul style="list-style-type: none"> • Indoor aerobic exercise 	MCI	Age 65-80, MCI
NCT05363228 (Czech Republic)	90	3 months	Biomarker / blood Irisin levels	<ul style="list-style-type: none"> • Movement therapy (tai chi) • Dance and movement therapy Vs. <ul style="list-style-type: none"> • No activity 	General population	Age 65-80 years, independent in instrumental activities of daily living,
AGUEDA NCT05186090 (Spain)	88	24 weeks	Cognitive function / executive function (comprehensive neuropsychological battery assessing several domains of executive function)	<ul style="list-style-type: none"> • Supervised resistance training (3*60 min sessions/week) Vs. <ul style="list-style-type: none"> • Wait-list control 	At risk	Age 65-80 years, cognitively normal, physically inactive

Supplementary Table 11: Ongoing cognitive stimulation trials

Ongoing cognitive stimulation trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
Tan 2018 ⁸¹ NCT02919748 (Singapore)	360	2 years	Cognitive function	<ul style="list-style-type: none"> • Choral Singing 1h weekly vs. <ul style="list-style-type: none"> • Health education talk and group activities 1h weekly 	At risk	60 years and over Subjective cognitive complaints or objective cognitive impairment based on neuropsychological test scores, free of dementia
I-CONNECT ⁸² NCT02871921 (USA)	360	12 months	Cognitive function	<ul style="list-style-type: none"> • Conversational engagement: 30-minute face-to-face communications with study staff through internet/webcam 4 times per week for 24 weeks (6 months), followed by sustaining dose of 2 times per week of 30 minutes session for additional 6 months vs. <ul style="list-style-type: none"> • Control Group: phone call weekly less than 10 minutes 	At risk	80 years and over; socially isolated; MCI or normal cognition, free of dementia; living alone independently, not severely depressed, no severe hearing or vision impairment,
NTR7336 (Netherlands)	190	3 months (12-month follow-up)	Cognitive function	<ul style="list-style-type: none"> • Foreign language training vs. <ul style="list-style-type: none"> • Music training 	At risk	65-80 years; Self-perceived decline in cognition, free of MCI or dementia; Native language Dutch, monolingual, access to computer or tablet.
NCT03045718 (Singapore)	100	9 months	Cognitive function / CDR, Colour Trails Tests, Digit Span, Rey Auditory Verbal Learning Test (RAVLT), Block Design, semantic Verbal Fluency scores.	<ul style="list-style-type: none"> • Horticultural Therapy 1h weekly (designed to stimulate the senses through interaction with the tasks and the environment, promote social interaction and also to promote a sense of self-worth through completion of projects) 	At risk	60-100 years; MCI, subjective memory impairment and/or dementia risk factors (e.g. family history, cerebrovascular disease, cardiovascular risk factors);

Ongoing cognitive stimulation trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				vs. • Waitlist Control		free of dementia and depression
Keys To Staying Sharp study ⁸³ (USA)	360	10 weeks	Cognitive function / central auditory processing, verbal fluency, executive function	• Piano training (group sessions, 90 mins/day, twice/week) vs. • Music listening instruction (group sessions, 90 mins/day, twice/week)	General population	60 years and older, with or without MCI; MoCA \geq 20, without previous music training
Train the brain with music (TBM) ⁸⁴ NCT03674931 (Germany, Switzerland)	155	1 year (18 months)	Cognitive function (working memory, executive functions, speed of information processing, auditory selective attention, abstract thinking) and functional and structural brain plasticity [<i>the only outcome discussed for the SS calculation is white matter DTI, but unclear if this is the primary outcome</i>]	• Piano instruction (1 hour training/wk + home practice 30 min./day) vs. • Music listening awareness (1 hour training/wk + home practice 30 min./day)	General population	retired healthy elderly (64–78) years, no prior musical education, free of MCI or dementia
Lin 2020 ⁸⁵ ChiCTR1900021526 (China)	111	24 weeks	Cognitive function / global cognitive function (MoCA-CS)	• Creative Expressive Arts-based Storytelling (CrEAS) programme (one 90 min session/wk, including 60 min of art-making and 30 min of storytelling) vs. • Usual activity	MCI	Age 60–85 years; MCI (Peterson criteria)
Rajji 2020 ⁸⁶ (Canada)	375	Up to 48-87 months (participants receive the intervention until they progress from a normal cognitive	Cognitive function / composite cognitive score	• cognitive remediation (CR) plus transcranial direct current stimulation (tDCS) (for 5 days/week for 8 weeks followed by boosters for 5 days/week once	At risk and/or MCI	MCI and/or remitted major depressive disorder (MDD), without current severe depressive symptoms; age \geq 60 years for those with MCI

Ongoing cognitive stimulation trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
		status to MCI or from MCI to dementia or until the study ends		every 6 months until participants progress from a normal cognitive status to MCI or from MCI to dementia or the study ends (max 7 y FUP) Vs. • Sham-CR+sham-tDCS		and ≥65 years for those with MDD (+/-MCI)
NCT04583033 (USA)	100	12 weeks / 2 years	Imaging / MRI brain volume	• Online cognitive Behavioural Therapy (CBT) aiming to improve sleep quality vs. • No contact control	At risk	Age 55 or older, cognitively normal (free of MCI & dementia), poor sleep quality
GAME-Project NCT04835909 (Spain)	112	16 weeks	Cognitive function/ battery of 11 cognitive tests	• Modern board and card games (group sessions, 2*≥1 hour/week) • cognitive paper and pencil tasks (group sessions, 2*≥1 hour/week) vs. • Wait-list control	MCI	Age 60 and older, amnesic MCI, Global Deterioration Scale 2-3, free of dementia
ISRCTN14437015 (Germany)	100	6 months	Cognitive function / global cognition (MoCA)	Individualised computerised cognitive training (targeted exercises for memory span, information processing, visual-spatial cognition, etc.) vs. • Basic computerised cognitive training (basic exercises for memory span, information processing, visual-spatial cognition, etc.)	MCI	Age ≥60 years, MCI (MMSE≥24, MoCA<24), computer/tablet owner with basic internet skills, free of dementia
NCT04522791 (USA)	114	2 months	Cognitive function / autonomic nervous system	• Resonance frequency breathing + processing speed and attention	MCI	Age 60-89y, MCI

Ongoing cognitive stimulation trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
			flexibility and executive function (EXAMINER z-score)	oriented cognitive training (8 weeks intervention + 2-week booster sessions at 3- and 9-months after intervention) • imagery-guided relaxation + processing speed and attention oriented cognitive training vs. • imagery-guided relaxation		
NCT05446909 (USA)	40	3 months	Cognitive function / working memory, subjective cognitive decline	• i IBMT mindfulness vs. • health education	At risk	Age 40-65 years, normal cognitive performance, self-reported cognitive decline
NCT05408689 (Hong Kong)	120	10 weeks / 14 weeks	Cognitive function / global cognitive function, executive function, memory (MoCA, Digit Span, Visual memory span, Stroop color word test, Face Recognition, Picture recognition)	• T1 spine transcutaneous electrical nerve stimulation (TENS ; 30 min per day, 3 days per week, for 10 weeks) • Concha (left outer ear) TENS vs. • placebo T1 TENS	MCI	
NCT05369897 (Poland)	100	12 weeks	Cognitive function / working memory, attention (CNSVS working memory and complex attention domains)	• Virtual reality cognitive training (≥ 10 minutes for ≥ 3 days/week) vs. • Sham virtual reality activity (360° images and videos, but not interactive cognitive training)	General population	Age 65-85 years, independent in everyday functioning, free of MCI and dementia, MoCA ≥ 26
SDST NCT05380284 (Taiwan)	100	5 weeks / 12 months	Cognitive function / set shifting, working memory, executive function (Wisconsin Card Sorting Test, Digit Span, Stroop)	• Senior driving simulation training (30-mins training, twice/week) vs. • Waiting list control	At risk, MCI	subjective cognitive decline or MCI

Supplementary Table 12: Ongoing multidomain trials

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
Maintain Your Brain (MYB) ⁸⁷ ACTRN12618000851268 (Australia)	8500	12 months (3-year follow-up)	Cognitive function	<ul style="list-style-type: none"> • Coaching group: online module that aims to improve either physical activity, nutrition, cognitive activity or peace of mind vs. • The information group: information about relevant dementia risk factors 	General population	55-77 years Free of dementia Enrolled in the “45 and Up Study”, have home internet and computer access
NCT02967406 (Thailand)	3600	10 years	Dementia incidence	<ul style="list-style-type: none"> • Lifestyle modification 4 x 4 lifestyle modification intervention (physical activity, diet, smoking and alcohol drinking and different levels: individual, household, knowledge management and community levels) every 3 months vs. • Control: no intervention 	General population	45-75 years; Free of dementia; Have resided in the Ubon Ratchathani's villages for at least 1 year, able to move or get physical exercise
MIND-CHINA ChiCTR1800017758 (China)	3000	2 years	Cognitive function	<ul style="list-style-type: none"> • Multimodal intervention including lifestyle and nutritional guidelines, daily physical exercise, vascular risk factor management, social and intellectual activity vs. • Drug and health education 	General population	60-79 years Free of dementia Living in rural communities
PENSA NCT03978052 (Spain)	200	2 years	Cognitive function / ADCS-PACC-Plus-exe	<ul style="list-style-type: none"> • Epigallocatechin gallate (EGCG) + personalized multimodal lifestyle intervention • EGCG + non-personalized lifestyle recommendations 	At risk	Subjective cognitive decline, age 60-80, APO4 carriers

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				<ul style="list-style-type: none"> • Placebo + personalized multimodal lifestyle intervention • Placebo + non-personalized lifestyle recommendations 		
STRENGTH NCT04146818 (Italy)	300	6 months (3 years follow-up)	Cognitive function / Corsi test	<ul style="list-style-type: none"> • Adapted Tango (90 min/wk) + comprehensive cognitive intervention (music therapy, engagement in social activities, cognitive training and psycho-education; 90 min/wk) Vs. <ul style="list-style-type: none"> • psycho-education and healthy lifestyle advice (once a month) 	MCI	MCI, 60 years and older
DREAM NCT04259047 (USA)	200	2 years	Cognitive function / Hopkins Verbal Learning Test total recall (HVLt)	<ul style="list-style-type: none"> • Behavioural treatment for diabetes mellitus (in-home DM education tailored to AAs with MCI; use of action plans to reinforce diabetes self-care; 3) telehealth visits with a DM nurse educator to improve DM self-care and address participants' health beliefs; and 4) increase primary care physicians' (PCP) awareness of participants' cognitive deficits and health beliefs to optimize treatment of DM) Vs. <ul style="list-style-type: none"> • Enhanced usual care 	MCI	African Americans with amnesic multiple domain mild cognitive impairment (MCI) and poorly controlled diabetes
U.S. POINTER STUDY NCT03688126 (USA)	2000	2-years	Cognitive function / modified NTB	<ul style="list-style-type: none"> • Structured Lifestyle Intervention (diet, physical exercise, and intellectual and social stimulation) Vs.	At risk	60-79 years; Sedentary; Poor diet; First-degree family history of a significant memory impairment; no cognitive impairment; SBP and/or

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				<ul style="list-style-type: none"> Self-Guided Lifestyle Intervention (education, support, and tangible tools to assist developing and carrying out healthier lifestyle practices) 		HbA1c and/or lipids not conforming to current health guidelines for age
RReDI-NoW ACTRN12619001392156 (Australia)	650	4 weeks (6 months)	Other / Modifiable Dementia Risk Factor profile & Knowledge of Dementia Risk Reduction	<ul style="list-style-type: none"> Preventing Dementia Online Course (PD MOOC, 2 hrs/wk; the goal of the is to build knowledge and self-efficacy in management of these modifiable dementia risk factors) PDMOOC plus community initiatives Vs. <ul style="list-style-type: none"> Static online dementia prevention information 	General population	Age 50 years and older
APPLE-Tree ISRCTN17325135 (pmid 35883143) (UK)	704	6 months (2 years follow-up)	Cognitive function / modified NTB	<ul style="list-style-type: none"> 10 group video sessions (targeting cardiometabolic dysfunction, physical inactivity, social isolation, mental illness, alcohol and smoking) + shorter video call 'tea breaks' (less structured, facilitated social interactions) + monthly goal setting phone calls Vs. <ul style="list-style-type: none"> Usual care plus written information about dementia prevention 	At risk	Age 60+; Subjective cognitive impairment (Cognitive Change Index score>16); Quick MCI score within educational and age normal range for MCI or SCD; CAIDE Dementia Risk Score ≥6 points (modifiable risk factors)
J-MINT JPRN-UMIN000038671 (Japan)	440	18 months	Cognitive function / composite score	<ul style="list-style-type: none"> Multidomain intervention (management of lifestyle-related disease, exercise, nutritional guidance, cognitive training) Vs.	MCI	65-85 years; cognitive impairment (age-adjusted decline at least 1.5 SD from the reference threshold in any cognitive domains measured by using NCGG-FAT); MMSE ≥24

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				<ul style="list-style-type: none"> • Usual care + documents regarding lifestyle and behaviours for the prevention of dementia 		
DAMPAA ACTRN12619000656134 (Australia)	320	6 months (18 months follow-up)	Cognitive function / KICA-Cog assessment (Kimberley Indigenous Cognitive Assessment)	<ul style="list-style-type: none"> • exercise, education and cardiovascular risk management program Vs. <ul style="list-style-type: none"> • Usual Care and education program 	MCI	Aboriginal Australians aged 45 to 90 years; community dwelling; cognitive impairment with no dementia (score of 32-36 out of 39 on KICA Cog), and no functional decline due to cognitive impairment
PRODEMOS ⁸⁸ ISRCTN15986016 (UK, China)	2400	18 months	Dementia risk / CAIDE risk score	<ul style="list-style-type: none"> • Coach-supported interactive mHealth application encouraging participants to make lifestyle changes and manage risk factors Vs. <ul style="list-style-type: none"> • Usual Care + static app with general healthy lifestyle information 	At risk	55 - 75 years; low socioeconomic status (SES) in the UK and from the general population in Beijing; possession of a smartphone; ≥ 2 dementia risk factors (cardiovascular disease, physical inactivity, smoking, hypertension, overweight, diabetes mellitus, depression, or dyslipidaemia)
STRENGTH Project ⁸⁹ (Italy)	300	6 months (2 years follow-up)	Cognitive function / spatial learning	<ul style="list-style-type: none"> • multimodal intervention (adapted tango, music therapy, social activities, cognitive stimulation, and psycho-education; 180 min sessions, once a week for 6 mo) Vs. <ul style="list-style-type: none"> • Psycho-education + healthy lifestyle advice for dementia prevention (once a month) 	MCI	Age ≥60 years, MCI
Lyu 2020 ⁹⁰ (China)	96	6 months	Cognitive function	<ul style="list-style-type: none"> • multicomponent integrative intervention (cognitive training, dietary instruction, physical activity, 	MCI	Age ≥65 years, MCI

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				and management of vascular risk factors) Vs. • Usual care & health education materials		
AgeWell.de ⁹¹ DRKS00013555 (Germany)	1152	2 years	Cognitive function / NTB	• Multi-component intervention (nutritional counselling, physical activity, cognitive training, optimization of medication, management of vascular risk factors, social activity, and, if necessary, further specific interventions targeting grief and depression) Vs. • Usual care & general health advice	General population	Community-dwelling primary care patients aged 60-77 years; CAIDE Dementia Risk Score ≥ 9 ; free of dementia
rrAD Study ⁹² NCT02913664 (US)	640	2 years	Cognitive function / ADCS-PACC, NIH Toolbox cognition battery	• Intensive reduction of vascular risk factors (IRVR; i.e. intensive pharmacological control of blood pressure and cholesterol) • Exercise training (EX) • IRVR+EX Vs. • Usual care	At risk	Cognitively normal (MMSE ≥ 26) older adults aged 60-85 years with hypertension (SBP 130-180mmHg, or 110-130mmHg if treated) and subjective memory concerns or a first-degree relative with dementia, and sedentary lifestyle
Sanchez-Arenas 2020 ⁹³ NCT04068376 (Mexico)	300	6 months / 1 year	Cognitive function / General cognitive function (MoCA)	• Coach-led double-task (aerobic and cognitive) square-stepping exercise programme for 24 • 12-week coach led, followed by 12-week caregiver led double-task square-stepping exercise programme Vs.	At risk	Age 60–65 years; self-reported cognitive concerns; one or more vascular risk factor; free of dementia; functionally independent

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				<ul style="list-style-type: none"> • Coach-led aerobic-balance-stretching exercise control group 		
FINOMAIN NCT04301544 (Philippines)	72	1 year	Cognitive function / General cognitive function Adas-Cog, Mnemonic Similarity score, executive function composite score)	<ul style="list-style-type: none"> • Dance and kinesthetic (two hourly sessions/week) + nutrition counselling & standardized vascular care Vs. • Nutrition counselling & standardized vascular care 	MCI	Age ≥60, MCI
Exergames ⁹⁴ NCT04311736 (USA)	96	3 months	Cognitive function / Episodic memory (NIH toolbox app)	<ul style="list-style-type: none"> • Moderate intensity cycling + concurrent virtual reality cognitive training (3 times per week) • Moderate intensity cycling Vs. • Stretching control (3 times per week) 	At risk	Age ≥65, subjective cognitive complaint, free of MCI and dementia, not engaging in aerobic exercise or cognitive training >2 days/week, 30 minutes a session in the past 3 months
NCT04465812 (China)	824	1 year (short-term primary outcome) / 5 years (long-term primary outcome)	Cognitive function (short-term primary outcome) / composite z-score & Dementia incidence (long-term primary outcome)	<ul style="list-style-type: none"> • Self-monitoring and personalized feedback smartphone app targeting vascular risk factors, sleep quality, mental health and cognitive training Vs. • Standard health counselling at baseline 	At risk	Age 45-74 years; high risk of stroke (with ≥ 3 of 8 stroke risk factors, including hypertension, dyslipidemia, diabetes, atrial fibrillation or valvular heart disease, smoking history, obvious overweight or obesity, lack of exercise, family history of stroke, or with transient ischemic attack); free of dementia
MindMoves ⁹⁵ NCT04556305 (USA)	254	24 weeks / 72 weeks follow-up	Cognitive function / (East Boston Memory Test, Category Fluency, Digit Span, oral TMT-A & B, digit ordering test)	<ul style="list-style-type: none"> • Mind - BrainHQ cognitive training intervention (three 30-minute sessions per week, for a total of 36 hours, via iPad) 	At risk	Women aged ≥ 65 years, history of CVD, MoCA score ≥19 (i.e. no significant cognitive impairment or dementia)

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				<ul style="list-style-type: none"> • Move - lifestyle physical activity intervention (Core elements include a personal lifestyle physical activity goal and five group meetings) • MindMoves - cognitive training and lifestyle physical activity Vs. <ul style="list-style-type: none"> • Usual care 		
DC-MARVEL ⁹⁶ NCT04559789 (USA)	200	2 years	Dementia risk score /ANU-ADRI	<ul style="list-style-type: none"> • Digital lifestyle intervention (MindMate cognitive health app + digital health coaching) Vs. <ul style="list-style-type: none"> • Health education materials (delivered electronically) 	At risk	Age 45-75, ≥2 AD risk factors (low education, overweight/obese, diabetes, hypertension, high cholesterol, smoking, TBI), ≤1 AD protective factor (high physical activity, fish consumption or cognitive engagement), smartphone owner, free of dementia and MCI
MTCCP ⁹⁷ NCT04727450 (Hong Kong)	228	4 months/6 months	Cognitive function / executive function (Wisconsin Card Sorting Test), attention (color TMT), memory (Rivermead Behavioral Memory Test)	<ul style="list-style-type: none"> • Cognitive training (group games requiring thinking skills) + physical training (instructor-led line dancing) + combined cognitive and physical training (BIGMAP program) • Cognitive training + physical training • Physical training + combined cognitive and physical training • Cognitive training + combined cognitive and physical training Vs. <ul style="list-style-type: none"> • No intervention control 	At risk	Age 60+, MoCA score >19, free of AD, not currently performing regular physical or cognitive exercise

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
CITA GO-ON NCT04840030 (Spain)	1094	2 years	Cognitive function / global cognitive performance (modified NTB)	<ul style="list-style-type: none"> Structured multimodal intervention (individual + group visits) focusing on cognitive stimulation, socio-emotional skills, nutrition, physical activity, and vascular risk factors Vs. Standard health advice 	At risk	Age 60-85 years, CAIDE dementia risk score ≥ 6 , lower than expected cognitive performance in at least 1 of 3 brief cognitive tests, free of dementia or moderate cognitive impairment (MMSE ≥ 20)
NCT04928885 (USA)	240	12 weeks / 6 months	Cognitive function / global cognition (PROMIS cognitive function measure)	<ul style="list-style-type: none"> Multimodal Wits Workout brain health workshops (addressing factors affecting cognitive health such as physical activity, diet, intellectual engagement, social isolation, stress, sleep, and self-efficacy) Vs. Waitlist control 	General population	Age 50+, free of dementia, TICS score ≥ 28
ChiCTR2000037305 (China)	290	Not stated	Cognitive function / global cognition (MMSE)	<ul style="list-style-type: none"> Individual comprehensive intervention for modifiable risk factors Vs. health education 	At risk	Age 60 years old or older with one or more dementia risk factor; free of dementia and moderate to severe cognitive impairment
J-MINT PRIME Kanagawa study JPRN-UMIN000041887 (Japan)	240	18 months	Cognitive function / global cognition (composite cognitive score)	<ul style="list-style-type: none"> Intensive multidomain lifestyle intervention (management of lifestyle-related disease, multicomponent exercise program, nutritional guidance, computerized cognitive training) Vs. Usual care + health education 	At risk	Age 65-85 years, treated or at risk for lifestyle-related disease, MMSE ≥ 24 , free of dementia
J-MINT PRIME Tamba study JPRN-UMIN000041938	200	18 months	Cognitive function / global cognition	<ul style="list-style-type: none"> Intensive multidomain lifestyle intervention (management of lifestyle-related disease, 	At risk	Age 65-85 years, ≥ 1 vascular risk factor (treated hypertension, SBP ≥ 140 mmHg, DBP ≥ 85 mmHg,

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
(Japan)			(composite cognitive score)	multicomponent exercise program, nutritional guidance, computerized cognitive training) Vs. • Usual care + health education		treated diabetes or HbA1c $\geq 6.0\%$), MMSE ≥ 24 , free of dementia
JPRN-UMIN000041926 (Japan)	3498	30 months	Incident dementia	• Smartphone-delivered self-management activity and walking program (twice/wk, facilitating physical, social and cognitive activity) Vs. • Health education	General population	Age ≥ 60 , free of dementia, MMSE ≥ 23 if $<12y$ education, ≥ 24 if 12-15y education, ≥ 26 if $\geq 16y$ education
KCT0005231 (Korea)	80	8 weeks	Risk score / Brain health activities score	• Health education + motivational enhancement smartphone application promoting lifestyle improvement for brain health Vs. • Health education	General population	Age 60-79 years, Users of an Android phone with a Wi-Fi connection, free of dementia, MMSE z-score ≥ 1.5
SIMPLE ⁹⁸ NCT03119051 (China)	250	36 months	Dementia incidence	• Online computerized training • Online computerized training + Tai Chi vs. • No training control group	MCI	50-85 years; MCI, MMSE [24-28], free of dementia; Hamilton Depression Scale/17-item score ≤ 10 , education level \geq primary school
MET-FINGER NCT05109169 (Finland, Sweden, UK)	600	2 years	Cognitive function / global cognitive function (NTB z-score)	• Structured intensive lifestyle intervention (individual consultations + group sessions covering diet, physical activity, cognitive training, and cardiovascular/metabolic risk monitoring) + those eligible for metformin treatment (i.e. no diagnosed diabetes + elevated adiposity OR mildly impaired fasting	At risk	Age 60-79 years, CAIDE risk score ≥ 6 , cognitive performance at the mean level or slightly lower than expected for age according to local population norms (based on MoCA and CERAD), free of dementia or substantial cognitive impairment

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				glucose) are further randomized to metformin 2000mg/day, metformin 1000mg/day or placebo Vs. • Self-guided lifestyle intervention (based on healthy lifestyle advice (covering diet, physical activity, cognitive training, and cardiovascular/metabolic risk monitoring) received during individual consultations)		
TaiPEI NCT05407857 (Taiwan)	380	2 years	Cognitive function / composite z-score	• Remote multi-modal intervention (covering nutrition, physical activity and cognitive programs) using wearable devices, blue-tooth equipment, apps, feedback technology and artificial intelligence based remote comprehensive training programs • On-site multi-modal intervention (covering nutrition, physical activity and cognitive programs) Vs. • Education	At risk	Age >60, free for dementia, Modified Rankin Scale 0-1, ≥ 6 years of education, CAIDE risk score >8, MCI or SCD diagnosis in past 6 months
ACTIONcR NCT04962061 (Canada)	318	46 weeks/12 months	Cognitive function / global cognitive function, processing speed, executive function, episodic memory (MoCA, computerized tests)	• Home- or centre-based multidomain intervention (cognitive training + aerobic and resistance exercises) • Aerobic and resistance exercises Vs. • Stretching and toning control	General population	Age 60 years and older, no cognitive impairment (MMSE ≥25), inactive (<150 min physical activity/week)

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
SYN2 NCT05375513 (Canada)	550	48 weeks	Cognitive function / global cognition (ADAS-Cog)	<ul style="list-style-type: none"> • Remotely-delivered personalized multidomain intervention coached 1-to-1 (PMI@Home; bi-weekly coaching sessions) (including physical exercise, cognitive training, diet, sleep, vascular risk factors control) Vs. • Brain Health PRO educational program (including content relating to physical exercise, cognitive training, diet, sleep, vascular risk factors control) 	MCI	Age 60-85 years, MCI, ≥ 2 additional dementia risk factors (low physical activity, poor diet, insomnia or CAIDE score ≥ 6), with internet access, free of dementia
NCT05163067 (China)	200	7 years follow-up (intervention duration not specified)	Cognitive function / global cognition, executive function, language, memory visuospatial function (MoCA, MMSE, CDR, Verbal Fluency, Digit Span, TMT-A and B, Boston Naming Test, CVLT, Rey-Osterrieth Complex Figure)	<ul style="list-style-type: none"> • Combined aerobic exercise and cognitive training program (cycling + cognitive game simultaneously) Vs. • Standard health counselling 	At risk	Age 50-80 years, free of dementia, genetic risk factors (SNP model)
NCT05163626 (China)	200	7 years follow-up (intervention duration not specified)	Cognitive function / global cognition, executive function, language, memory visuospatial function (MoCA, MMSE, CDR, Verbal Fluency, Digit Span, TMT-A and B,	<ul style="list-style-type: none"> • Combined aerobic exercise and cognitive training program (cycling + cognitive game simultaneously) Vs. • Standard health counselling 	At risk	Age 50-80 years, free of dementia, low levels of blood biomarker risk factors (GAP43<1983pg/ml, synaptotagmin 1<431pg/ml, neurogranin<1433pg/ml, SNAP25<448pg/ml)

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
			Boston Naming Test, CVLT, Rey-Osterrieth Complex Figure)			
NCT04999813 (China)	600	3 years (intervention duration not specified)	Cognitive function / global cognition (MoCA, MMSE)	<ul style="list-style-type: none"> Comprehensive cerebrovascular intensive intervention (individualized cerebrovascular risk factor assessment, health education including guidance on medication, diet, exercise and weight loss) Vs. <ul style="list-style-type: none"> Routine management 	At risk General population	Age 50-70 years, healthy volunteers or Vascular Cognitive Impairment No Dementia
SUPERBRAIN NCT05023057 (Korea)	300	24 weeks	Cognitive function / global cognition (RBANS)	<ul style="list-style-type: none"> Multidomain intervention (monitoring and management of metabolic and vascular risk factors; cognitive training and social activity; physical exercise; nutritional guidance; motivational training) via tablet Vs. <ul style="list-style-type: none"> Health education and usual care 	MCI	Age 60-79 years, at least one modifiable dementia risk factor, MCI, free of dementia
SINGER NCT05007353 (Singapore)	1200	2 years	Cognitive function / global cognition (modified NTB)	<ul style="list-style-type: none"> Structured Lifestyle Intervention (physical exercise, diet, cognitive training, intellectual/social stimulation, management of vascular risk factors) Vs. <ul style="list-style-type: none"> self-guided general health information intervention 	At risk	Age 60-77 years, CAIDE score >6, cognitive performance at the mean level or slightly lower than expected for age (MoCA ≥18, ≤27), free of dementia
NCT05296551 (USA)	30	8 weeks	Cognitive function / cognitive fluidity (NIH)	<ul style="list-style-type: none"> Cognitive-motor dual-task (complex cognitive task) 	General population	Age 60-95 years, generally healthy, free of neurologic disorders affecting cognition

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
			Toolbox Cognitive Battery)	<ul style="list-style-type: none"> • Cognitive-motor dual-task (simple cognitive task) Vs. <ul style="list-style-type: none"> • Motor task 		
NCT05027789 (USA)	225	18 months (intervention duration not specified)	Cognitive function / episodic memory, attention, working memory, executive function, prospective memory (Logical memory, FCSRT, Digit Span, TMT, Digit Symbol, Verbal Fluency, Royal Prince Alfred Prospective Memory Test)	<ul style="list-style-type: none"> • Structured intervention (combined structured training in compensation and lifestyle modification: specific recommended behaviour targets + iPad application for recording activity and receiving reminders) Vs. <ul style="list-style-type: none"> • Education information sessions about memory support strategies and healthy lifestyles 	At risk	Age 65-90 years, cognitively normal with Subjective Cognitive Concerns, not a regular exerciser, free of dementia and cognitive impairment
NCT05483790 (China)	112	6 weeks	Cognitive function / global cognition (MoCA, MMSE)	<ul style="list-style-type: none"> • Multidomain intervention (cognitive training, physical exercise, healthy lifestyle intervention, and computerized cognitive training) delivered by general practitioners and community health workers in individual and group sessions Vs. <ul style="list-style-type: none"> • Regular health advice 	General population	Age 55-75 years, >6 years education, MCI or normal cognition, free of dementia
FINGER-NL NCT05256199 (Netherlands)	1206	2 years	Cognitive function / global cognition (NTB)	<ul style="list-style-type: none"> • Personalized multidomain lifestyle intervention (physical activity, cognitive training, cardiovascular risk factor management, dietary counselling, Souvenaid, sleep 	General population	Age 60-79 years, ≥3 self-reported risk factors for cognitive decline (at least 2 modifiable risk factors and 1 non-modifiable risk factor), free of dementia and MCI, TICSm ≥24

Ongoing multidomain trials						
Trial name/1st author/trial registry number (Country)	N	Length of intervention / follow-up (if different)	Type of primary cognitive endpoint	Details of intervention	Type of study population	Main eligibility criteria
				counselling, stress management, and social activities) Vs. • General lifestyle-related health information		
IRCT20151122025191N3 (Iran)	196	6 months	Cognitive function / global cognition (Addenbrooke's Cognitive Examination-II, CANTAB)	• Multidomain intervention (vascular risk factor management, psychiatric disorder management, physical activity, nutrition, cognitive training) Vs. • Regular health advice + training pamphlet on risk factors for cognitive decline	At risk	Age 55-74 years, ≥ 1 modifiable dementia risk factor, no neurocognitive disorder
PCOT NCT05106036 (USA)	4000	4 year	Cognitive function / global cognition (TICS-m)	• Intensive blood pressure intervention (combination of care with clinical decision support, practice facilitators and Pharm Ds to lower home BP to $< 130/80$ mmHg) Vs. • Usual care	At risk	Age 70 and older, BP $> 130/80$ mmHg, free of AD and significant neurological disease

References for supplementary tables 3-12

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