2016

Primary and secondary prevention interventions for cognitive decline and dementia

Overview of reviews

folkehelseinstituttet

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Responsible	Camilla Stoltenberg, direktør
Authors	Gerd M Flodgren, project leader, *researcher, the Knowledge Centre* Rigmor C Berg, *Head of Unit, for Social Welfare Research at the Knowledge Centre*
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Key messages

Dementia is a syndrome characterised by deterioration in memory, thinking, behaviour, and the ability to perform everyday activities, which ultimately may lead to total dependence and death. Since the world's population is steadily growing older, the number of people with dementia is also increasing. It is therefore of utmost importance to identify effective strategies to prevent or delay its onset.

The key findings of this overview of reviews are based on evidence from eight systematic reviews. The results for the single interventions targeting cognitively healthy people suggest that compared to control:

- Antihypertensive drugs may lead to a slight decrease in incidence of dementia in people with hypertension (low certainty of evidence).
- Statin therapy probably leads to little or no difference on incidence of dementia in people with, or at risk of, cardiovascular disease (moderate certainty).
- Omega-3 Fatty Acids (FAs) probably lead to little or no effect on cognitive test scores (moderate to high certainty).
- Computerised cognitive training probably leads to a slight improvement in cognitive test scores directly after the training (moderate certainty).
- Aerobic exercise may lead to little or no effect on cognitive test scores (low certainty).

The results for the interventions targeting people with mild cognitive impairment suggest that compared to control:

- Cholinesterase inhibitors probably lead to a slight decrease in dementia incidence, but to significantly more adverse events (moderate certainty).
- Vitamin E probably leads to little or no difference in incidence of Alzheimer's dementia (moderate certainty).
- Omega-3 FAs probably lead to little or no difference in cognitive test scores (moderate to high certainty).

We did not find any reviews that evaluated the effects of interventions targeting more than one risk factor, and we can therefore not say anything about the combined effects of these interventions.

Title:
Primary and secondary prevention interventions for cognitive decline and dementia

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Type of publication:

Overview of reviews

Doesn't answer everything:

- No interventions targeting people with dementia.
- No health economic evaluation.

Who is responsible for this publication?
The Norwegian Institute of Public Health completed this assignment which was commissioned by the National Association of Public Health.

When were the literature searched?
Literature searches were conducted in January 2016.

Peer referees:
Øyvind Kirkevold, professor Seksjon for sykepleie Avdeling for helse, omsorg og sykepleie, Norges Teknisk-Naturvitenskaplige Universitet.

Veslemøy Egede-Nissen, førstelektor, Institutt for sykepleie og helsefremmende arbeid, Høgskolen i Oslo og Akershus

Executive summary

Background

Dementia is a chronic syndrome characterised by deterioration in memory, thinking, behaviour, and the ability to perform everyday activities, which often leads to total dependence and death. The world's population is steadily growing older, and as dementia is more prevalent in people over 70, and increases with increasing age, the number of people with dementia is also increasing. In 2012, around 71, 000 people in Norway had a dementia diagnosis, which represents 1.6% of the total population.

Objectives

The aim of this overview of reviews was to answer the following two questions: 1) What is the documented effectiveness of interventions to prevent cognitive decline or incidence of dementia in cognitively healthy people (primary prevention), 2) What is the documented effectiveness of interventions to prevent (further) cognitive decline or progression to dementia in people with mild cognitive impairment (MCI) or other early symptoms or signs of dementia (secondary prevention)?

Methods

We conducted an overview of reviews in accordance with the Knowledge Centre's handbook. We searched in eight databases up to February 2016 for reviews evaluating the effects of interventions to prevent or delay cognitive decline or dementia in people with or without MCI. Two people independently screened all titles and abstracts, reviewed full texts, assessed review quality, and graded the certainty of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool. One author extracted data, and another checked that it was correct.

Results

We included eight high quality reviews published between 2009 and 2016. Five of the reviews involved primary prevention interventions for cognitively healthy people. Three reviews included secondary prevention interventions for people with MCI or memory complaints. The reviews evaluated the effects of pharmacological therapies (3 reviews), dietary supplements (3 reviews), aerobic training (one review), and cognitive training (one review). The comparator in the latter two was either another active intervention or no intervention, and placebo in all the others.

Primary prevention interventions

Pharmacological therapies

Antihypertensive drugs. We included one review (4 trials; n=15,936) concerned with the effects of antihypertensive drugs on dementia incidence in older people with hypertension. The participants were recruited in Europe, North America, China, Australasia and Tunisia. The pooled result (Odds Ratio [OR]: 0.89 [0.74 to 1.07]) indicates that antihypertensive drugs may lead to a slight decrease in incidence of dementia, as compared to placebo, at 1.8 to 4.5 years follow up.

Cholesterol lowering drugs (Statins). We included one review (2 trials; n=26,340) concerned with the effects of statins on incidence of dementia in cognitively healthy older people with evidence of, or at high risk of, cerebrovascular disease. The studies were conducted in the UK, Ireland, and the Netherlands. The result of one trial (OR: 1.00 [0.61 to 1.65], n=20,536) indicates that statin therapy may lead to little or no difference in incidence of dementia, as compared to placebo. The other trial (n= 5,804) reported no difference in cognitive test scores between groups at mean 3.2 years follow up.

Dietary supplements

Omega-3 Fatty Acids (FAs). We included one review (3 trials; n= 4,080) which evaluated the effects of Omega-3 FAs on cognitive decline in cognitively healthy participants. The pooled results (Standardised Mean Difference [SMD] [4 tests]: 0.06 higher to 0.04 lower scores; Mean Difference [MD] [2 tests]: 0.12 higher to 0.07 lower scores) suggest that Omega-3 FA supplementation probably leads to little or no difference in overall cognitive function, as compared to placebo, at 6 to 40 months follow up.

Aerobic exercise

We included one review (12 trials; n= 754) which evaluated the effects of supervised aerobic exercise on cognitive function in cognitively healthy older people. The studies were conducted in the USA, Canada and France. The pooled results suggest that aerobic exercise may lead to little or no effect on cognitive test scores (SMD: range 0.09 lower to 0.30 higher scores; MD [2 tests]: 0.10 to 0.16 as compared to no intervention at 8 to 24 weeks follow up).

Cognitive training

We included one review (52 trials; n=4,885) which evaluated the effects of computerised cognitive training (CCT) on cognitive decline in cognitively healthy people. The participants were from the USA, Europe, Canada, Australia, Israel, China, Taiwan, South Korea, and Japan. The pooled result of this review (Hedge's g: 0.22 [0.15 to 0.29]) suggests that CCT probably leads to a small improvement in cognitive test scores directly after the training.

Secondary prevention interventions

Pharmacological therapies

Cholinesterase inhibitors. We included one review (9 trials; n=5,149) concerned with the effects of cholinesterase inhibitors for the prevention of dementia in people with MCI. The studies were conducted in USA, Canada, Singapore, and Germany. The pooled

results suggest that cholinesterase inhibitors may lead to a slight decrease in progression to dementia (Relative Risk [RR]: 0.84 [0.70 to 1.02]), at 3 years, but to more adverse events than placebo (RR: 1.09 [1.02 to 1.16]).

Dietary supplements

Vitamin E. We included one review (1 trial; n=769) of the effects of vitamin E on dementia incidence in people with MCI. The results of this single trial, conducted in USA and Canada, suggest that Vitamin E supplementation possible has little effect on incidence of AD (Hazard Ratio: 1.02 [0.74 to 1.41]) at 36 months, as compared to placebo.

Omega-3 FAs. We included one review (4 trials; n= 676) of the effects of Omega-3 FAs on cognitive decline in people with MCI. The studies were conducted in the Netherlands, England, Wales, Japan, Israel, and the USA. The pooled results show that Omega-3 FAs probably lead to little or no difference in cognitive function (MD: 0.16 higher to 0.05 lower scores) at median 14.5 to 24 weeks, as compared to placebo.

Discussion

We included eight high quality reviews (86 original studies) concerned with the effects of interventions aimed at preventing cognitive decline and dementia. Results from four of these reviews suggest that statin therapy, Omega-3 FAs and vitamin E supplements probably lead to little or no difference in cognitive function or incidence of dementia. The results for cholinesterase inhibitors and antihypertensive drugs, suggest that these drugs may lead to a slight decrease in incidence of dementia, but that cholinesterase inhibitors probably lead to more adverse events than placebo. CCT probably leads to slightly improved cognitive function directly after the training, while aerobic exercise may lead to little or no difference in cognitive function.

We did not identify any eligible high quality reviews concerned with the effects of healthy life styles (other than aerobic exercise), e.g. change to a healthy diet, decreased alcohol use, etc., or other risk factors, e.g. depression, lack of social engagement, or low educational attainment. We found no reviews assessing the effects of interventions targeting multiple risk factors to prevent cognitive decline or dementia.

We unfortunately still have little knowledge from systematic reviews of effective preventive interventions, addressing single or multiple risk factors for dementia.

Conclusions

We found no convincing evidence for the effectiveness of the interventions included in this overview of reviews in preventing cognitive decline or dementia. Wide confidence intervals and few events in some of the analyses warrant caution when interpreting the results. As progression to dementia is partly determined by a number of modifiable factors related to lifestyle, environment, depression, educational level, and degree of social interaction, it is possible that preventive interventions may be more effective if they take into account the multifaceted aetiology behind the disease, i.e. interventions that targets multiple risk factors.

Hovedfunn (Norsk)

Demens er en sykdom kjennetegnet ved svekket hukommelse, tenkning, atferd og evne til å utføre daglige aktiviteter, som til slutt ofte fører til total avhengighet og død. Siden verdens befolkning stadig blir eldre forventes antall personer med demens å øke dramatisk. Det er derfor viktig å identifisere effektive strategier for å forebygge eller utsette sykdomsdebuten.

De viktigste funnene i denne oversikten over oversikter er basert på evidens fra åtte oversikter. For enkelt-tiltak rettet mot kognitivt friske eldre personer tyder resultatene på at sammenlignet med kontroll:

- Blodtrykkssenkende legemidler fører muligens til en liten reduksjon i forekomst av demens hos eldre personer med høyt blodtrykk (lav tillit til effektestimatene).
- Kolesterolsenkende legemidler (statiner) fører trolig til liten eller ingen forskjell i forekomst av demens hos eldre personer med hjerte- og karsykdommer (moderat tillit).
- Omega-3 fettsyretilskudd fører til liten eller ingen forskjell i kognitive testresultater (moderat til høy tillit).
- Datastyrt kognitiv trening fører trolig til en liten bedring i kognitive testresultater direkte etter treningen (moderat tillit).
- Aerob trening fører muligens til liten eller ingen forskjell i kognitive testresultater (lav tillit).

For tiltak rettet mot personer med mild kognitiv svikt, tyder resultatene på at sammenlignet med kontroll:

- Kolinesterasehemmere fører trolig til en liten reduksjon i forekomst av demens, men fører til signifikant flere bivirkninger (moderat tillit).
- Vitamin E fører trolig til liten eller ingen generell forskjell i forekomst av Alzheimers demens (moderat tillit).
- Omega-3 fettsyretilskudd fører trolig til liten eller ingen forskjell i kognitive testresultater (moderat til høy tillit).

Vi fant ingen oversikter som evaluerte effekten av tiltak rettet mot mer enn én risikofaktor, og vi kan det derfor ikke si noe om effekten av å kombinere disse tiltakene.

Tittel:
Primær- og sekundærforebyggende tiltak for kognitiv svikt og demens

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Publikasjonstype:
Oversikt over oversikter

Svarer ikke på alt:
• Ingen tiltak rettet mot personer med demens diagnose.
• Ingen helseøkonomisk evaluering

Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Nasjonalforeningen for Folkehelsen

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Når ble litteratursøket gjennomført:
Søk etter studier ble avsluttet i januar 2016.

Eksterne fagfeller:
Øyvind Kirkevold, Professor Seksjon for sykepleie Avdeling for helse, omsorg og sykepleie, Norges Teknisk-Naturvitenskaplige Universitet

Veslemøy Egede-Nissen, førstelektor, Institutt for sykepleiere og helsefremmende arbeid, Høgskolen i Oslo og Akershus

Sammendrag (Norsk)

Bakgrunn

Demens er et tilstand karakterisert ved svekkelse av hukommelsen, tenkning, adferd og evnen til å utføre daglige aktiviteter, som til slutt fører til total avhengighet og død. Siden verdens befolkning stadig blir eldre, og demens er mer utbredt hos personer over 70, forventes antallet personer med demens også å øke. I 2012 hadde omkring 71 000 personer i Norge en demensdiagnose, hvilket representerer 1,6 prosent av den totale befolkningen.

Problemstillinger

Målet med denne oversikt over oversikter var å besvare følgende to spørsmål: 1) Hva er den dokumenterte effekten av forebyggende tiltak for å forebygge kognitiv svikt og demens (primærforebygging)? 2) Hva er den dokumenterte effekten av tiltak for å forebygge (ytterligere) kognitiv svikt og progresjon til demens hos personer med mild kognitiv svikt eller andre tidlige symptomer eller tegn på demens (sekundærforebygging)?

Metoder

Vi gjennomførte en oversikt over oversikter i henhold til Kunnskapssenterets håndbok. Vi søkte i åtte databaser opp til januar 2016 for oversikter som evaluerte effekten av tiltak for å hindre eller forsinke kognitiv svikt, Alzheimers sykdom eller andre former for demens hos personer med eller uten mild kognitiv svikt. Uavhengig av hverandre gjennomgikk to personer alle titler og abstrakt, vurderte relevante oversikter i full tekst, vurderte den metodiske kvaliteten og bedømte tillit til effektestimatene ved hjelp av GRADE (Grading of Recommendations Assessment, Development and Evaluation). En forfatter hentet ut data, og en forfatter kontrollerte riktigheten av data.

Resultat

Vi inkluderte åtte oversikter av høy kvalitet publisert mellom 2009 og 2016. Fem av oversiktene omhandlet primærforebyggende tiltak rettet mot kognitivt friske personer. Tre oversikter omhandlet sekundærforebyggende tiltak rettet mot personer med mild kognitiv svikt. Oversiktene evaluerte effekten av farmakologiske tiltak (3 oversikter), kosttilskudd (3 oversikter), aerob trening (1 oversikt), og kognitiv trening (1 oversikt).

De to sistnevnte sammenlignet med enten en annen aktiv tiltak eller ingen tiltak, og alle de andre sammenlignet med placebo.

Primærforebyggende tiltak

Farmakologisk behandling

Blodtrykkssenkende legemidler. Vi inkluderte én oversikt (4 studier; n= 15 936) om effekten av blodtrykkssenkende midler på demens hos eldre personer med hypertensjon. Deltakerne var rekruttert fra Europa, Nord-Amerika, Kina, Australasia og Tunisia. Det samlede resultatet fra denne oversikten (Odds ratio [OR]: 0,89 [0,74 til 1,07]) tyder på at blodtrykkssenkende midler muligens fører til en liten reduksjon i forekomst av demens, sammenlignet med placebo ved 1,8 til 4,5 års oppfølging.

Kolesterolsenkende legemidler (statiner). Vi inkluderte én oversikt (2 studier; n=26 340) om effekten av statiner på forekomst av demens hos kognitivt friske eldre personer med høy risiko for, eller dokumentert cerebrovaskulær sykdom. Studiene ble utført i Storbritannia, Irland og Nederland. Resultatene fra en studie (OR 1,00 [0,61 til 1,65]; n= 20 536), tyder på at statiner trolig fører til liten eller ingen forskjell i forekomst av demens, sammenlignet med placebo. Den andre inkluderte studien (n= 5 804) rapporterte ingen forskjeller mellom gruppene i kognitive testresultater ved gjennomsnittlig 3,2 års oppfølging.

Kosttilskudd

Omega-3 Fettsyrer (FAs). Vi inkluderte én oversikt (3 studier; n=4 080) om effekten av Omega-3 FAs på kognitiv svikt hos kognitivt friske personer. De samlede resultatene (Standardisert gjennomsnittsforskjell [SMD] [4 tester]: 0,06 høyere til 0,04 lavere skåre; Gjennomsnittsforskjell [MD] [2 tester]: 0,12 høyere til 0,07 lavere skåre) tyder på at Omega-3 FAs fører til liten eller ingen effekt på kognisjon ved 6 til 40 måneders oppfølging.

Aerob trening

Vi inkluderte én oversikt (12 studier; n= 754) om effekten av aerob trening på kognitiv funksjon hos kognitivt friske eldre personer. Studiene var utført i USA, Canada og Frankrike. Aerob trening fører muligens til liten eller ingen forskjell i kognitive testresultater (SMD [8 tester]: 0,09 lavere til 0,30 høyere skåre; MD [2 tester]: 0,10 til 0,16, sammenlignet med ingen tiltak ved 8 til 24 ukers oppfølging).

Kognitiv trening

Vi inkluderte én oversikt (52 studier; n= 4 885) om effekten av ulike typer av datastyrt kognitiv trening (CCT) for forebygging av aldersrelatert kognitiv svikt hos kognitivt friske personer. De samlede resultatene fra denne oversikten (Hedge's g: 0,22 [0,15 til 0,29)) tyder på at CCT trolig fører til en liten forbedring i kognitiv funksjon direkte etter treningen.

Sekundærforebyggende tiltak

Farmakologisk behandling

Kolinesterasehemmere. Vi inkluderte én oversikt (9 studier; n= 5 149) om effekten av kolinesterasehemmere på forekomst av demens hos personer med mild kognitiv svikt. Studiene var gjennomført i USA, Canada, Singapore, Tyskland og i flere ikke-navngitte land. De samlede resultatene viser at kolinesterasehemmere trolig har en liten effekt på

progresjon til demens (data fra 3 studier; Risk ratio [RR]: 0,84 [0,70 til 1,02]) ved 3 års oppfølging, men har flere skadevirkninger enn placebo (RR: 1,09 [1,02 til 1,16]).

Kosttilskudd

Vitamin E. Vi inkluderte én oversikt (1 studie; n= 769) om effekten av vitamin E på forekomst av demens hos personer med mild kognitiv svikt. Resultatene fra denne enkeltstudien, utført i USA og Canada, tyder på at vitamin E har liten effekt på forekomst av mulig eller trolig Alzheimer (Hazard ratio: 1,02 [0,74 til 1,41]) ved 36 måneders oppfølging, sammenlignet med placebo.

Omega-3 Fettsyrer (FAs). Vi inkluderte én oversikt (4 studier; n= 676) om effekten av Omega-3 FAs på kognitiv svikt hos personer med mild kognitivt svikt. Studiene ble gjennomført i Nederland, England, Wales, Japan, Israel og USA. De samlede resultatene viser at Omega-3 FAs trolig har liten eller ingen effekt på kognitiv test skåre (MD 0,16 høyere til 0,05 lavere skåre) ved en median oppfølgingstid på 14,5 til 24 uker oppfølging, sammenlignet med placebo.

Diskusjon

Vi inkluderte åtte oversikter av høy metodisk kvalitet (86 originale studier) som oppsummerte effekten av tiltak for å forebygge kognitiv svikt og demens.

Resultater fra fire av disse oversiktene tyder på at kolesterolsenkende legemidler, Omega-3 fettsyrer og vitamin E tilskudd trolig fører til liten eller ingen forskjell i kognitiv funksjon eller forekomst av demens. Resultatene for kolinesterasehemmere og blodtrykkssenkende medisiner tyder på at disse medisinene kan føre til en svak nedgang i forekomsten av demens, men at kolinesterasehemmere sannsynligvis fører til flere bivirkninger enn placebo. CCT fører trolig til litt bedre kognitiv funksjon rett etter trening, mens aerob trening muligens fører til liten eller ingen forskjell i kognitiv funksjon.

Vi fant ingen oversikter av høy metodisk kvalitet som omhandlet effekten av endring til en sunn livsstil, annet enn aerob trening, f.eks. sunt kosthold, røykeslutt, eller oversikter av tiltak rettet mot andre risikofaktorer, f.eks. depresjon, lavt utdanningsnivå eller mangel på sosial tilknytning. Vi fant heller ingen oversikter om sammensatte tiltak rettet mot flere risiko faktorer for å forebygge kognitiv svikt eller demens.

Vi har dessverre fortsatt lite kunnskap fra systematiske oversikter om effektive tiltak, både når det gjelder én og flere risikofaktorer, for å forebygge kognitiv svikt eller demens.

Konklusjon

Ingen av de primær- eller sekundærforebyggende tiltakene oppsummert i de inkluderte oversiktene viser overbevisende effekt på forebygging av kognitiv svikt, AD og andre former for demens. Brede konfidensintervaller og få hendelser i noen av analysene tilsier at man må vise varsomhet ved tolkning av resultatene. Progresjon til demens er knyttet til en rekke modifiserbare faktorer, slik som livsstil, miljø, depresjon, utdanningsnivå og sosial tilknytning. Derfor er det mulig at forebyggende tiltak kan ha bedre effekt hvis de tar hensyn til den sammensatte etiologien bak sykdommen, dvs. hvis tiltak rettes mot flere risikofaktorer samtidig.

Preface

The Knowledge Centre at the National Institute of Public Health was in the autumn 2013 commissioned by the National Association of Public Health to conduct an overview of reviews evaluating the effectiveness of interventions aimed at preventing or delaying the onset of dementia in cognitively healthy people and in people with mild cognitive impairment without a dementia diagnosis.

In this overview of reviews we summarise and evaluate the evidence from eight systematic reviews (SRs) of the effect of various primary and secondary interventions (i.e. pharmacological therapy, dietary supplements, cognitive training and aerobic exercise) on cognitive function and progression to dementia in patients without a dementia diagnosis.

The Knowledge Centre follows a common approach in summarising research, documented in the manual "How we summarise research." It means that we may use standard formulations when we describe the methods, results and discussion of the findings.

Contributors to the project:
Project leader and researcher: Gerd M Flodgren, the Knowledge Centre,
Head of unit and researcher: Rigmor C Berg, the Knowledge Centre,
Internal contributors:
Rigmor C Berg served as project leader during the first phases of the project. She developed the project protocol, and led the work related to screening and quality assessment of literature. Gerd M Flodgren thereafter took on the role as project leader, and led data extraction, analysis, and write up of the report for publication. Rigmor C Berg commented on early versions of the report and approved the final version. We wish to acknowledge Kristin Thuve Dahm and Therese Dalsbø who contributed at the initial stage (i.e. to screening, review selection/quality assessment for the initial search), research librarian Gyri Hval Straumann who performed the systematic search, and research librarian Ingrid Harboe for peer reviewing the search strategy. We also wish to acknowledge Kjetil Brurberg for helpful comments on the report, and Gunn Vist, Liv Merete Reinar, who peer reviewed the report.
External contributors:
We also wish to acknowledge the external peer referees: Øyvind Kirkevold, Professor ved Seksjon for sykepleie Avdeling for helse, omsorg og sykepleie, Norges Teknisk-Naturvitenskaplige Universitet, and førstelektor Veslemøy Egede-Nissen, ved Institutt for sykepleiere og helsefremmende arbeid, Høgskolen i Oslo og Akershus.

Declaration of interest:
Neither the authors nor the external peer referees state any conflicts of interest.

The aim of this report is to support well-informed evidence-based decisions in health care that lead to improved quality of services. We suggest that when meeting with the individual patient, the results of this overview should be considered in conjunction with other relevant factors, patient needs and clinical experience.

Signe Flottorp Head of Department	Rigmor C Berg Head of Unit	Gerd M Flodgren Project leader

Objectives

The aim of this project was to conduct an overview of reviews that answers the following questions:

1) What is the documented effectiveness of interventions to prevent cognitive decline and incidence of dementia in cognitively healthy people (primary prevention)?
2) What is the documented effectiveness of interventions to prevent (further) cognitive decline and progression to dementia in people with mild cognitive impairment or other early symptoms or signs of dementia (secondary prevention)?

Background

Description of the condition

Dementia is a syndrome in which there is deterioration in memory, thinking, behaviour, and the ability to perform everyday activities. It is considered one of the major causes of disability and dependency in the world (1). Dementia mainly affects people over 70 years of age, but is not a part of normal ageing. The cause of dementia is death of brain cells, which in turn may be caused by various conditions. The most common cause is Alzheimer's disease, a neurodegenerative disease, which may account for as much as 60-70% of all dementia cases (1). Other types of dementia are vascular dementia, Lewy body dementia, and frontotemporal dementia. Other less common dementia causes are substance abuse, head injury, metabolic disease, vitamin deficiency and other diseases (2). The most common dementia types are described in more detail below. A glossary is found in Appendix 1.

Different types of dementia

Alzheimer's disease

Alzheimer's disease (AD) is characterised by a complex series of brain changes that develop over many years. It involves so called amyloid plaques and neurofibrillary tangles which develop in brain structures that help to encode memories, and in areas that are used in thinking and making decisions (3, 4). These evolving changes result in a slow decline in memory, thinking, and reasoning skills, that often leads to total dependency and death (3). It has been suggested that the cause of the pathophysiological brain changes is multifactorial, i.e. a combination of genetic, environmental, and lifestyle factors (3). Clinically it is only possible to make a probable AD diagnosis, and a definite diagnosis can only be achieved post mortem. Research is being conducted into the pathophysiology of AD, in order to find sensitive biomarkers to provide better diagnostic tools and criteria for early identification of AD (4).

Vascular dementia

Vascular dementia (VAD) is the second most common type of dementia after AD, and accounts for around 15% of dementia cases (5). It is generally agreed that the aetiology behind VAD involves various cardiovascular conditions causing damage to the blood vessels of the brain (e.g. stroke, high blood pressure; hardening of the arteries; diabetes) (6). There is however no consensus on exactly how the cerebrovascular pathological changes translate into cognitive impairment or dementia, and there is also no

agreed scheme for staging or diagnosing VAD (5). The cognitive changes in VAD varies more than in AD, but commonly include deficits in attention, information processing, and executive function (5). This effectively means that tools used to diagnose AD may not be effective in diagnosing VAD.

Lewy body dementia

Lewy body dementia (LBD) is an umbrella term that includes clinically diagnosed dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), which, according to many researchers, share the same pathology. While DLB usually develops concomitantly with or before any signs of Parkinsonism, PDD develops in patients with an already well established PD. The pathological changes, which are characterised by abnormal clumps of a protein called alpha-synuclein (Lewy bodies) in neurons in the brain, which results in a progressive cognitive decline (7). Despite improved consensus criteria for the diagnosis of DLB , diagnostic accuracy is still moderate in research and poor in clinical settings, and DLB is often misdiagnosed as AD (7).

Frontotemporal dementia

Frontotemporal dementia (FTD), is a group of neurodegenerative diseases characterised by deficits in behaviour, executive function, or language, and may often be mistaken for a psychiatric disorder (8). FTD, which is particularly common in people younger than 65 years, may be caused by a number of different neuropathological conditions, all of which are characterised by the selective degeneration of the frontal and temporal cortices of the brain. Improved tools for clinical imaging, and molecular characterisation have made it easier to diagnose the different subtypes of FTD, and also to differentiate FTD from psychiatric disorders (8).

Mixed type dementia

There are different types of mixed dementia, but in the most common form the abnormal plaques associated with AD exist together with blood vessel problems linked to VAD. Brain changes typical for AD may also coexist with Lewy bodies and sometimes all three conditions may co-exist. There is some evidence from autopsy studies suggesting that mixed dementia may be more common than what was previously thought (9). On the other hand, recent results from a cross-sectional study suggest low prevalence of mixed dementia in late-onset AD (10).

How many people are affected by dementia?

According to recent figures from the World Health Organisation (WHO), 47.5 million people around the world are afflicted by dementia, and every year there are approximately 7.7 million new cases (11). The estimated age standardised dementia prevalence for people more than 60 years old lies between 5 and 7 percent in most countries (12). In 2012 it was estimated that 1.6 percent of people in Norway lived with dementia, which is similar to the EU average of 1.5 percent (13). How many people that at present are undiagnosed and who live with the pre-stages of AD or other dementias in the general population is unknown. In Norway there are research indicating that only about half of people with dementia living in nursing homes have a diagnosis (14) and in home care the proportion may be even lower (15) .

What are the risk factors for dementia?

Old age is the strongest non-modifiable risk factor for the development of dementia (16). Other risk factors include female sex, genes, and familial disposition. Since there is to date no curative treatment for dementia, it is only natural that the modifiable risk factors are of great interest. It has been suggested that risk factors for vascular and mixed type dementia in particular, but also for AD, may be the same as for cardiovascular disease (17, 18), i.e. hypertension, high cholesterol, diabetes, inflammation, recurrent infections, and factors related to an unhealthy lifestyle, e.g. physical inactivity, smoking, excessive alcohol consumption, unhealthy diet, and obesity. Other risk factors are depression, low educational attainment, low socioeconomic status, and lack of social interaction (19, 20).

Mild cognitive impairment (MCI) is often thought of as a pre-stage to AD and other dementias. MCI is characterised by a cognitive deterioration, including memory problems, but which is not severe enough to hamper a person's day to day activities, and thus do not meet the dementia criteria (21). A review of the literature suggests a prevalence of MCI between 16 and 20 percent in people over the age of 60, according to the newer criteria (22). MCI does not always progress to dementia. In a recent systematic review most included studies reported progression rates between 20 to 40% (10-15% per year) (22). MCI due to AD is only one of many suggested subtypes. Amnestic MCI, is a subtype that primarily affects the memory. It may sometimes be difficult to differentiate normal age-related cognitive decline from different types of MCI, and MCI from dementia (23). Until fairly recently there has been little consensus about which tools and criteria to use for diagnosing MCI. In two recent papers (23, 24), consensus criteria for diagnosing MCI has been put forward. Results from a longitudinal cohort study of people with Parkinson's disease (25) suggest that the prognostic accuracy of MCI may be increased, if neuropsychological tests are repeatedly administered over time. Cognitive impairment no dementia (CIND) is a term that also describes people with below normal cognitive functioning who do not meet dementia criteria, but the definition is broader than that of MCI (22).

How the interventions may work

Since it at present is not possible to cure dementia, it is natural that focus of anti-dementia strategies, in addition to finding a cure, is on preventing its onset. AD is a slowly progressing condition, and early pathophysiological changes may be present many years or even decades before the actual diagnosis (26). If people at risk for developing AD and dementia can be identified at early pre-clinical stages, a window for early interventions opens up (27). To accomplish this, further research regarding the pathophysiological processes behind AD, and the identification of AD sensitive biomarkers, is needed to determine which factors best predict the risk of progression from "normal" cognition to mild cognitive impairment and AD dementia (27).

There are, as mentioned earlier, several modifiable risk factors for dementia, of which cardiovascular and lifestyle modifications have received great interest.
Thus, many dementia prevention strategies focus on cardiovascular risk-factors, e.g. statins for high cholesterol, antihypertensive drugs for high blood pressure, and cholinesterase inhibitors for inflammation. Below, we describe some of the theories behind why these, and other interventions, are considered for the prevention of cognitive decline and dementia.

Pharmacological treatment

Blood pressure lowering interventions

A number of longitudinal studies have consistently showed a relationship between mid-life hypertension and the development of cognitive impairment later in life, especially if untreated. For the relationship between late-life hypertension and dementia or cognitive impairment however, the results are inconsistent (28). In addition to pharmacological treatment, hypertension may also be reduced by interventions including salt restriction, weight reduction, physical exercise, and reduced alcohol consumption (29).

Cholesterol lowering drugs (statins)

Increased serum cholesterol level has been suggested to contribute to the pathological processes leading to AD. Statins are cholesterol lowering drugs of proven benefit in vascular disease (30, 31). Results from recent systematic reviews, including meta-analyses, mostly of observational data, suggest inconsistent effects of statins on incidence of dementia (32). These results should be interpreted with caution due to the high heterogeneity found in the meta-analyses. There are known adverse effects of statin use, but it is debated how frequently occurring these events are among users (33).

Cholinesterase inhibitors

Patients with AD have reduced cerebral production of choline acetyl transferase in the brain, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function (34). Cholinesterase inhibitors, which increase cholinergic transmission by inhibiting cholinesterase, have been shown to be of some benefit in patients with AD as well as other non-AD dementias, even though the effects in most cases have been modest (35). People with amnestic mild cognitive impairment are also believed to have a central cholinergic deficit (36). It has therefore been suggested that cholinesterase inhibitors could be used to delay or even prevent the progression from amnestic MCI to AD.

Dietary patterns and dietary supplements

Mediterranean diet

It has been suggested that various dietary patterns with differing food and nutrient compositions, may elicit different effects on the ageing brain. The traditional Mediterranean diet (MD) is characterised by high consumption of vegetables, fruits, olive oil, legumes, fish, wholegrain cereals, nuts and seeds, and moderate red wine consumption. It is low in processed foods, dairy products, red meat, and vegetable oils (37). A recent review of the literature (38) including mostly cohort- and observational studies, suggests

that MD may be effective in reducing cognitive decline in older age. The authors however, question the feasibility of introducing this type of dietary intervention in Western countries due to cultural differences.

Omega-3 Fatty Acids

Fatty acids (FAs) are among the most crucial molecules for the brain's ability to perform, and there is evidence for a relationship between inadequate dietary intake of fatty acids and impaired brain performance and diseases (39). A number of possible mechanisms for a protective role of Omega-3 FAs in dementia have been put forward, but results from trials investigating the effects of Omega-3 FAs on cognition in people with and without cognitive impairment have been mixed (40).

Vitamin E

Vitamin E is a dietary compound known for its ability to protect cells from the negative effects of free radicals. Evidence that free radicals may be involved in the pathological processes of AD (and other cognitive impairments) has led to interest in the use of vitamin E in the treatment of MCI and AD. There is also some evidence suggesting lower levels of Vitamin E in plasma of people with AD and in MCI (41), but whether the lower vitamin E level is a cause or an effect of poor dietary intake is debated (42).

Physical exercise

Evidence from a meta-analysis (43), and a more recent longitudinal study (44), suggests that the higher the amount of regular exercise, the lower the risk for developing AD. The evidence for the possible cellular and molecular mechanisms suggested to lie behind the neuroprotective effect of aerobic exercise, is from animal studies. The suggested mechanisms include increased cerebral blood flow which in turn triggers different neurobiological events that may increase the levels of different growth factors that are of importance to the neuroplasticity of the brain, and the antioxidant enzyme levels (45)

Cognitive training, education, and social engagement

The cognitive reserve hypothesis aims to explain why those with higher IQ, education, and more socially active people who participate in leisure activities exhibit less severe clinical or cognitive changes when afflicted by age-related or AD pathology (46, 47). The hypothesis proposes that differences between individuals in how tasks are processed by our brains provide a reserve against brain neuropathology. This reserve may allow for more flexible usage of the brain, greater neural efficiency and capacity, and greater ability to compensate for degenerated brain areas through the recruitment of additional brain regions, and thus improved brain function. It has been suggested that even cognitive training interventions delivered late in life may have a protective effect against AD and age related cognitive decline (48).

This overview of reviews is limited to effects of interventions on cognitively healthy older people, and people with cognitive impairment. People with diagnosed AD or other types of dementia are not included.

Why is it important to do this overview of reviews?

The prevalence of AD and other types of dementia is continuously increasing as the population in the world is steadily ageing, and therefore also the societal costs of caring for people with dementia are increasing (12). As there to date is no cure for dementia, there is a great need to identify effective interventions to delay or prevent dementia at an early stage of the disease process. In this overview of reviews we summarise the evidence from systematic reviews of the effectiveness of interventions to delay or prevent the onset of dementia in cognitively healthy people and in people with mild cognitive impairment. If effective interventions can be identified, a lot can be saved in terms of personal suffering, healthcare use and costs for the society as a whole. Also, helping older people to stay cognitive healthy, would enable this large and growing group of people to live an active and independent life, and to contribute to the society long after retirement.

Methods

We conducted an overview of reviews evaluating the effectiveness of interventions aimed at preventing or delaying cognitive decline and/or the onset of dementia. We included reviews of interventions that targeted cognitively healthy people (primary prevention) and people with cognitive impairment (secondary prevention). We excluded reviews/studies of interventions targeting people with a dementia diagnosis. This overview of reviews was conducted in accordance with the guidance for summarising evidence described in the Knowledge Centre's handbook (49).

Objectives

To summarise and critically appraise the existing evidence from systematic reviews of the effectiveness of interventions to prevent cognitive decline and dementia. Specifically, we aimed to answer the following questions:

1. What is the documented effectiveness of interventions to prevent cognitive decline and incidence of dementia in cognitively healthy people (primary prevention)?
2. What is the documented effectiveness of interventions to prevent (further) cognitive decline and dementia in people with mild cognitive impairment or other early symptoms or signs of dementia (secondary prevention)?

Inclusion criteria

We used the following criteria when considering reviews for inclusion:

Population	• Cognitively healthy older people • People with mild cognitive impairment
Intervention	We included systematic reviews of studies evaluating the effectiveness of any intervention aimed at delaying or preventing the onset of dementia including the following: • pharmacological therapy • psychosocial • dietary/nutritional supplements • lifestyle modification e.g. changes related to unhealthy diet, physical inactivity, use of alcohol or tobacco

Comparison	Usual care, no intervention or other intervention.
Outcomes	Development of dementia and symptoms of mild cognitive impairment. Symptoms included, but were not limited to, cognition, daily function, neuropsychiatric symptoms of dementia (e.g. agitation, depression and anxiety).
Study design	We considered systematic reviews of high quality, in any language, and published 2009 or later for inclusion.

Other inclusion criteria and specifications:
We considered a review as being systematic if it contained a description of 1) a robust search strategy, 2) criteria for inclusion and 3) assessment of the quality of included studies. We assessed the methodological quality of possibly eligible studies with the Knowledge Centre's checklist for systematic reviews, and included only reviews of high methodological quality. In addition, we included only finalised systematic reviews that we could find in full text. In cases where there was overlap between reviews (the same included individual studies, approximately the same research questions asked), we used data from the most recently updated review (or the larger and more detailed review) and excluded the other reviews.

Exclusion criteria

We applied the following exclusion criteria:

• Systematic reviews concerning measures directed towards individuals with dementia diagnosis.
• Systematic reviews concerning measures directed towards relatives of dementia sufferers.
• Systematic reviews concerning preventive complementary/alternative measures against dementia (e.g. Acupuncture, aromatherapy), and alternative measures that are not interventions described in the inclusion criteria.
• Systematic reviews of low or moderate methodological quality.
• Primary studies and other studies that do not summarise the effect of preventive measures against dementia.
• Abstracts and other publication formats that are not available in full text or missing details of a completed systematic review.

Literature search

We searched the following databases for systematic reviews up to February 2016:

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R)
- EMBASE (Ovid)
- PsycINFO (Ovid)
- Cinahl

- The Cochrane Database of Systematic Reviews (CDSR)
- CRD
- Web of Science
- Pubmed

The database search strategy was designed by and searches executed by research librarian Gyri Hval Straumann. The search strategy was peer-reviewed by research librarian Ingrid Harboe. The search was adapted to each database. We used a combination of subject terms, text words, and when available in the databases, filters for systematic reviews. The complete search strategy is available in Appendix 2. We supplemented the database search by searching literature lists of relevant reviews and included studies.

Selection of reviews

Two reviewers independently read all records resulting from the searches. We used pre-designed inclusion/exclusion forms for each screening level: (i) the review title/abstract, (ii) the complete full text of the review, and (iii) the review's methodological quality (see details below). We resolved disagreements through discussion and subsequent consensus. If there was complete overlap in terms of included studies between two or more of the reviews, we reported the results from the most recent review and/or the review with the largest number of included studies or the most detailed description. It was not necessary to contact the authors of any reviews to aid the decision process. We list the reviews considered in full-text, but subsequently excluded, in Appendix 3 along with the reasons for exclusion.

Quality assessment as part of the selection process:
Two reviewers independently assessed the methodological quality of each possible eligible systematic review using the Knowledge Centre's checklist for systematic reviews (49). The checklist evaluates the methods used in a review against 10 criteria to determine the degree to which the review methods are unbiased. A review that adequately met "all or most of the criteria" was considered to be of high quality, or if any of the criteria were not met, it had to be judged very unlikely that this would affect the review's conclusions. We included only systematic reviews of high quality and excluded reviews of moderate or low quality. We describe the results of the quality assessment, as well as the checklist items in Appendix 4.

Data extraction

All data were reviewed and extracted by one reviewer (GF) into a standardised data extraction form, which was then checked for accuracy by another reviewer (RB). The following data were extracted from each review: citation, aim of the review, theory used/evidence base of intervention, number of relevant and non-relevant included studies, study design of original studies, total number of participants, baseline characteristics of participants (age, gender, cognitive status, educational level, and ethnicity),

country, type and components of intervention, duration of intervention and follow up, comparators, methods used to assess outcomes (e.g. tools to assess cognitive status, or to diagnose dementia), effect sizes reported (and measures of dispersion), statistical methods used and adjustments for confounding factors in multivariate models, losses to follow up, conflict of interest of review authors and of authors of original studies (if available), and type of review (Cochrane or non-Cochrane review).

Data synthesis

We present the results separately for primary prevention interventions targeting cognitively healthy people, and secondary prevention interventions targeting people with cognitive impairment and/or memory complaints.

We organised the data within each of the two groups according to: i) type of intervention being evaluated (pharmacological interventions, dietary interventions, cognitive training and aerobic exercise), and ii) type of outcomes (incidence of dementia, cognitive test scores, adverse effects, and other clinical outcomes). We report the results for the main outcomes in text and in tables. If a combined measure of performance on a battery of cognitive tests was reported by the review authors, we used this summary estimate when reporting the results. If no summary of effect estimate was provided, we reported the range of effects. We conducted no overarching meta-analysis of the result reported in the included reviews, as they all evaluated different types of interventions.

Grading of the evidence

Two review authors (GF and RB) used the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation) developed by the GRADE working group (50) to determine the certainty of the estimates of effects of interventions reported in the included reviews, i.e. to what degree we could trust the results. We considered the compiled documentation for each of the main outcomes (i.e. progression to dementia, performance of cognitive tests) using GRADE.

Evidence from randomised controlled trials start as high certainty evidence but may be downgraded depending on five criteria in GRADE that are used to determine the certainty of the evidence: i) methodological study quality as assessed by review authors, ii) degree of inconsistency, iii) indirectness, iv) imprecision, and v) publication bias. Upgrading of results from observational studies is possible according to GRADE if there is a large effect estimate, or a dose-response gradient, or if all possible confounders would only diminish the observed effect and that therefore the actual effect most likely is larger than what is suggested by the data.

In accordance with the GRADE tool, we graded the certainty of the evidence as high, moderate, low, and very low. These grades of evidence are defined by the GRADE Working Group in the following way:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Ethics

In this overview of reviews we assessed whether and how authors of included reviews addressed issues pertaining to equity, benefits and harms, and financial disclosures reported in the original studies. In addition, we also took notes on any reporting of patient involvement in decisions regarding the trial design.

Results

Description of included reviews

Search results

The literature searches and searching other sources yielded 4,349 unique citations (see Figure 1). Of these we excluded 4,247 irrelevant citations on the basis of title and abstract. We retrieved and evaluated 102 reviews in full text. Forty-one of the 102 reviews were promoted to further evaluation of methodological quality (28, 40, 42, 51-87), and the others were either excluded with reasons (see Appendix 3), or listed under ongoing studies (see Appendix 5; 73-79). We judged 10 of the 41 reviews to be of high methodological quality and eligible for inclusion in this overview of reviews (28, 40, 42, 51, 57, 65-67, 71-73, 78, 85). After further scrutiny we found that two of the reviews (52, 57), which evaluated the effects of cholinesterase inhibitors, overlapped in terms of included studies with the review by Russ and colleagues (78). As the latter review was more detailed and included additional studies we decided to report the results from this review. Two other reviews (40, 71) that evaluated the effects of Omega 3 fatty acid supplements, had two out of three included studies targeting cognitively healthy people in common, and reported results for one unique study each. Since the unique study reported in one of the reviews (71) was small (49 participants) and of low quality, and the study in the other review (40) was large (2,911 participants), we decided to include the results for cognitively healthy people reported in the Sydenham review (40). We report the results for people with mild cognitive impairment (MCI) from the review by Mazereeuw and colleagues (71). See list of excluded reviews in Appendix 3.

Characteristics of included reviews

We identified eight high quality reviews (40, 42, 65, 71-73, 78, 85) that we included in this overview of reviews. All the reviews included randomised controlled trials only. Six were Cochrane reviews (40, 42, 72, 73, 78, 85), and two were non-Cochrane reviews (65, 71). For further details see table 1 and Appendix 6.

Populations

Five of the reviews included studies that targeted cognitively healthy people (40, 65, 72, 73, 85). Two reviews (42, 78) included studies of people with mild cognitive impairment (MCI). In one of the studies (42) people with MCI of amnestic type were included while the other study (78) included people with any type of MCI (however defined).

One review (71) included both cognitively healthy people and those with cognitive impairment. The latter group constituted people with memory complaints and objective cognitive decline.

Interventions

Three reviews focused on pharmacological interventions (72, 73, 78), and three evaluated the effects of dietary supplements (40, 42, 71). One review was concerned with the effects of cognitive training (65), and one with the effects of aerobic exercise (85). None of the included reviews evaluated the effects of other lifestyle changes, e.g. change to a healthy diet, reduced use of alcohol or tobacco, or interventions targeting other risk factors for dementia, e.g. depression, low level of education, or lack of social interaction.

Comparators

The comparator intervention was placebo in all but two reviews (65, 85), in which the active interventions (i.e. cognitive training and aerobic exercise) were compared with either another active intervention or no intervention.

Outcomes

Four of the included reviews (42, 72, 73, 78) reported on dementia incidence/progression to dementia. Three of these also reported cognitive test scores (72, 73, 78). The other four reviews reported only cognitive test scores (in total >350 different cognitive outcomes). One of the reviews, however, did not report any between-group comparisons for the cognitive tests scores (42). Four reviews (40, 72, 73, 78) reported adverse effects of interventions. Three reviews (72, 73, 85) reported other clinical outcomes (i.e. cholesterol level, blood pressure, and measures of aerobic capacity). One review (72) also reported activity level and instrumental activities of daily living.

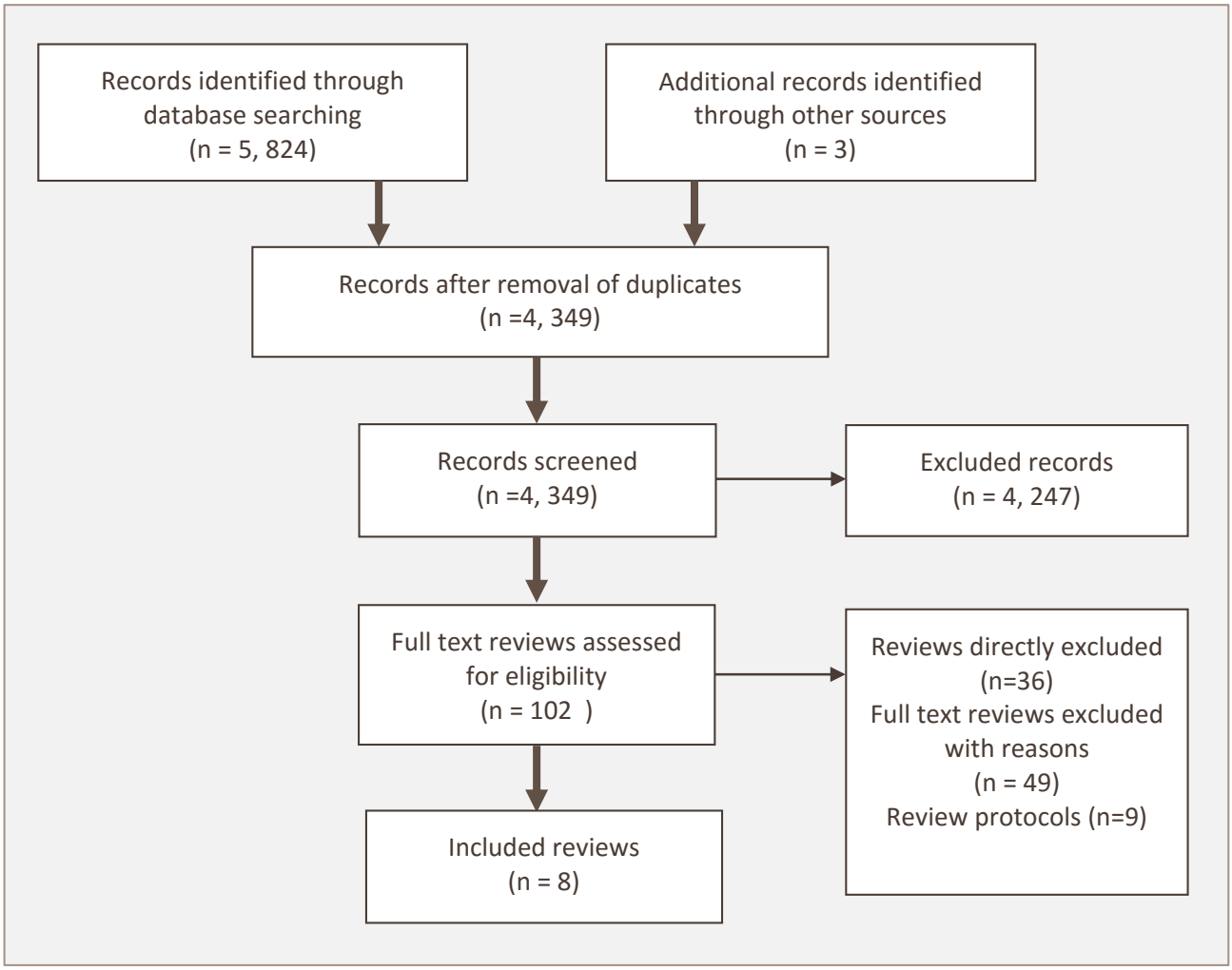

Figure 1
PRISMA study flow diagram (88) describing the review selection process.

Tools used by review authors to determine risk of bias and quality of the evidence

All five included Cochrane reviews used the Cochrane risk of bias tool (89) to assess the risk of bias of the included studies. In addition, one of the reviews (85) also used the CLEAR NPT tool for non-pharmacological interventions (90). One of the two non-Cochrane reviews used the PEDro scale (91) and the other non-Cochrane review used both the Cochrane tool and the PEDro scale (65). None of the included reviews used the GRADE tool (50) to assess the certainty of the included evidence for an effect, nor did they provide a summary of findings table.

Tools used in original studies to define participants as cognitively impaired

The original studies summarised in three of the included reviews (42, 71, 78) used different tests and criteria to determine the degree of cognitive impairment of participants at baseline. The most commonly used tests were Clinical Dementia Rating (CDR) scale (92), the modified Hachinski Ischemic Score (93) and the Mini Mental State Examination (MMSE) (94).

Tools used in original studies to assess effects on cognitive function

Around 400 different cognitive tests were used to assess the effects on cognitive function, of which the MMSE (94) was one of the most commonly used tests. Other tests were for example the ADAS-Cog, CDR Sum of boxes, and the Symbol Digit Modalities test. The number of different tests used by single studies ranged from one to more than 10. In one of the reviews (65) only the total number of tests (n=396) used in the 52 included studies was reported, but no information on the type and number of tests used in individual studies was provided. Little information was provided about the scaling and interpretation of the different tests (e.g. the desired direction of effect).

Tools used in original studies to determine effects on incidence AD and dementia

Four of the included reviews (42, 72, 73, 78) reported on incidence of dementia. Criteria that were used, with the verification of the diagnosis by a blinded expert panel, were the *Diagnostic and Statistical Manual of Mental Disorders* criteria (DSM-III R) (95) the *International Statistical Classification of Diseases and Related Health Problems* criteria (ICD 10) (96), and the *National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association* criteria (NINCSD-ADRDA) (26). These criteria were sometimes used together with the DSM-IV criteria (97).

Table 1. Description of the reviews (n=8) included in this overview of reviews.

Review	Search date	No of studies[1]	Population	Intervention
Farina 2012(42)	June 2012	3 (1)	Cognitively impaired	Vitamin E
Lampit 2014 (65)	July 2014	52 (52)	Cognitively healthy	Cognitive training
Mazereeuw 2012 (71)	September 2011	10 (7)[2]	Cognitively impaired (and cognitively healthy)	Omega 3 Fatty Acids
McGuinness 2009 (73)	February 2008	4 (4)	Cognitively healthy	Hypertensive drugs
McGuinness 2016 (72)	November 2015	2 (2)	Cognitively healthy	Cholesterol lowering drugs (statins)
Russ 2012 (78)	Not reported	8 (8)	Cognitively impaired	Cholinesterase inhibitors
Sydenham 2012 (40)	April 2012	3 (3)	Cognitively healthy	Omega 3 Fatty Acids
Young 2015 (85)	August 2013	12 (12)	Cognitively healthy	Aerobic exercise

1 From the included reviews we only used studies with populations and interventions that were relevant for our research question. The numbers within parenthesis give information on how many studies in the included review that met our inclusion criteria.

2 From this review only three studies targeting people with MCI was included in this overview of review, as the included studies targeting healthy people overlapped almost entirely with the Sydenham review.

The eight high quality systematic reviews included in total 86 unique original studies (range 1 to 52 studies) that were relevant for our research question.

We found no reviews concerned with the effects of lifestyle changes (other than aerobic exercise training), i.e. healthy eating, reduced alcohol consumption, smoking cessation, or interventions targeting other risk factors for dementia, like for example mid-life depression, low educational attainment. We also did not find any reviews concerned with multifaceted interventions to delay or prevent cognitive decline, AD or other types of dementia.

Primary prevention interventions

Six reviews (four Cochrane reviews (40, 72, 73, 85) and two non-Cochrane reviews (65, 71)), evaluated the effectiveness of interventions aimed at preventing cognitive decline and/or dementia in cognitively healthy people. The focus of three of the reviews (72, 73, 78) was on pharmacological interventions (i.e. antihypertensive drugs, cholesterol lowering drugs, and cholinesterase inhibitors). One focused on the effects of dietary supplements (40), one on the effects of aerobic exercise (85), and one review was concerned with the effects of cognitive training (65).

The characteristics of the included reviews are described below.

Pharmacological therapies

Antihypertensive drugs

One review by McGuinness et al from 2009 (73) evaluated the effects of antihypertensive drug therapy for the prevention of cognitive decline and incidence of dementia. The review included four RCTs of cognitively healthy older people with hypertension with no apparent prior cerebrovascular disease. All four trials met the inclusion criteria of our overview of reviews. The review authors judged the trials to be of high methodological quality. The included original studies were published between 1991 and 2008.

Participants

The average age of participants (n= 15, 936) was 75.4 years. Mean MMSE score at baseline ranged from 26 to 29 across studies. In one of the trials baseline MMSE score was not reported, only the MMSE cut-off for inclusion (>24). The average length of education in two of the studies was 11.7 and 12.3 years respectively, while in one study more than 50% of participants had either no education or primary school education only. One study did not report educational level. Mean blood pressure level at baseline was 171/86 mmHg across studies. The participants were recruited from a number of countries and geographic regions: Western and Eastern Europe, North America, China, and a smaller proportion of participants from Australasia and Tunisia. The majority were ambulatory patients, recruited in the community or in primary care settings.

Intervention

All four included studies reported a stepped care approach to hypertension treatment, and evaluated the effects of different first line drug therapies (calcium-channel blockers, thiazide diuretics, or angiotensin II type I receptor blockers). The second line drugs included diuretics, beta-blockers, centrally acting agents, and ACE inhibitors. For further details on the drug regimen please see the full text review (73). The mean duration of follow up ranged from 1.8 to 4.5 years across studies (median 2.8 years).

Comparison

The comparator intervention was placebo. It should however be noted that many of the participants in the control group were prescribed other non-study antihypertensive drugs during the study period as their blood pressure exceeded pre-set values. In one of the trials 84 percent of the control group participants and 75 percent of the treatment group were not on assigned therapy at study end. In another trial 44 percent of the placebo group participants as compared with 10 % of the intervention participants were not on assigned therapy at study end.

Outcomes

The primary outcomes in this review were incidence of dementia and change in cognitive test scores (one test; MMSE), for which pooled results were reported by the review authors. Secondary outcomes were blood pressure level, adverse effects requiring discontinuation of treatment, and quality of life. Pooled effect estimates were provided for the first two, while the quality of life data could not be analysed. Incidence of dementia was a secondary outcome in all trials included in the review.

Table 2. Characteristics of the review on antihypertensive drug therapy (McGuinness 2009).

No of studies	Population	Intervention	Comparison	Outcomes
4 trials	N=15,936 cognitively healthy hypertensive participants; mean age 75.4 years (range 70.3 to 83.6); mean BP 171/86 mmHg	Antihypertensive drug therapy[1,2] Follow up: range 1.8 to 4.5 years (median 2.8 years)	Placebo[3]	Incidence of dementia, change in cognitive test scores,[4] blood pressure level, incidence and severity of adverse effects requiring discontinuation of treatment[5]

1 The studies used different first-line drugs, and a number of different second-line drugs.
2 McGuinness and colleagues intended to include also non-pharmacological blood pressure lowering interventions, e.g. salt restriction, weight reduction, exercise, alcohol restriction, smoking cessation, but failed to find any eligible studies evaluating non-drug interventions for inclusion.
3 A large proportion of control group participants received other antihypertensive medication during the study.
4 Incidence of dementia and cognitive test scores were secondary outcomes in all four included studies. Only one test, the Mini Mental State examination (MMSE) were used to assess cognitive change. No information about the tests i.e. scaling or interpretation of the MMSE scores, was provided by the review authors.
5 Type of adverse effects that required discontinuation of treatment not further described.

Cholesterol lowering drugs

One review by McGuinness et al from 2016 (72) summarised the effects of statins (cholesterol lowering drugs) for the prevention of dementia and cognitive decline. The review included two trials involving cognitively healthy people with a history of, or at

high risk for cerebrovascular disease. Both trials were relevant for our research questions. The review authors judged the trials to be of high methodological quality. Both trials were published in 2002.

Participants

The age of participants (n=26,340) in the two trials ranged from 40 to 82 years. One of the trials recruited people with coronary heart disease, other occlusive arterial disease, and diabetes or hypertension (n=20,536 patients 40 to 80 years old, n=5,806 were at least 70 years old), and the other trial recruited people (n=5,804; age 70-82 years) with a history of, or at risk of vascular disease. One of the trials did not provide baseline measures of cognitive function, and the other trial reported a mean MMSE score of 28 across groups. Educational level or socioeconomic class were not reported in either study. Total cholesterol level ranged from mean 5.7 to 5.9 mMol/L at study entry. One of the trials was conducted in the UK, and the other in Scotland, Ireland, and the Netherlands. Most of the participants were ambulatory patients, recruited either in a community or in a primary care setting.

Intervention

Different types of statins were used in the two trials: in one trial participants received simvastatin 40 mg daily, and in the other the participants received pravastatin 40 mg daily. Mean follow up was 3.2 years in one study and 5 years in the other.

Comparison

The comparator intervention was placebo

Outcomes

The outcomes reported in the review were: incidence of dementia, change in cognitive test scores (4 tests; MMSE; Stroop Colour Word Test; Picture-Word Learning test; Letter Digit Coding test) or in interview assessed cognitive function (TICS-m), cholesterol level, and incidence and severity of adverse effects.

Table 3. Characteristics of the review on cholesterol lowering therapy (McGuinness 2016).

No of studies	Population	Intervention	Comparison	Outcomes
2 trials	N=26,340 cognitively healthy people with a history of, or risk factors for, vascular disease, age between 40 and 82 years	Cholesterol lowering drugs (Statins[1]) Follow up: 3.2 years and 5 years	Placebo	Incidence of dementia[2], change in cognitive test scores[2]; cholesterol level; incidence and severity of adverse effects

1 The two trials used different types of Statins (simvastatin and pravastatin)
2 Incidence of dementia was a secondary outcome in the trial reporting this outcome .No information was provided on what criteria that was used to diagnose dementia.
3 A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for all tests: Mini Mental State Examination (MMSE) Score: Score out of 30 (higher score better) (measures global cognitive function); Stroop Colour Word Test: Total number of seconds required to complete the third Stroop card containing 40 items (Measures attention); Picture-Word Learning Test 15 Picture Learning Test (measures immediate and delayed recall); Letter Digit Coding Test. Total number of correct entries completed in 60 seconds (measures processing speed); Modified Telephone Interview for Cognitive Status Score (Score out of 39) A TICS-m score below 22 out of 39 was pre-specified as indicative of some cognitive impairment..

Dietary supplements

Omega-3 FAs

One review by Sydenham et al from 2012 (40) evaluated the effects of Omega-3 FA supplements on cognitive decline in cognitively healthy people. The review included in total three trials that were relevant for our research question. The review authors judged the trials to be at low risk of bias. The trials were published between 2008 and 2011.

Population

The three trials recruited in total 4,080 cognitively healthy participants aged between 60 and 80 years. Performance on the MMSE was used to determine the eligibility of participants. The studies were conducted in the Netherlands, England, and Wales, and in one study the country of origin was unclear. In one of the studies the participants were recruited using a database with volunteers, in one study participants were drawn from patient lists of 20 general practices, and in the third study participants with previous myocardial infarction were recruited through cardiologists.

Intervention

In two studies intervention participants received gel capsules containing Omega-3 FAs. In one study, participants received margarine spread containing Omega-3 FAs. For details on doses please see the full text review. The follow up ranged from 6 to 40 months (median 24 months).

Comparison

The comparison intervention was matched placebo in all trials: capsuled with high-oleic sunflower oil (one study), with Omega-9 rich olive oil (one study), and placebo margarine in the third study.

Outcomes

This review aimed to investigate the effect of Omega-3 FAs on incidence of dementia but none of the included studies reported this outcome. The reported outcomes were cognitive test scores, adverse effects, and adherence. The authors categorised the cognitive tests into six sub-categories (MMSE, immediate and delayed recall, verbal fluency, and executive function) and pooled these separately.

Table 4. Characteristics of the review on the effects of Omega-3 FAs (Sydenham 2012).

No of studies	Population	Intervention	Comparison	Outcomes
3 trials[1]	N=4,080 cognitively healthy people aged 60 years or more	Omega 3 FAs (supplements or provided meals) Follow up: range 6 to 40 months	Placebo or usual diet	Cognitive tests score[s2], adverse effects, and adherence to supplementation

1 Two trials were included in both Mazareeuw 2012 and Sydenham 2012, and both reviews reported results from one unique study each. As the unique study reported in Mazereeuw 2012 was very small compared to the one reported in Sydenham 2012, it was excluded, and we here present the results reported in the review by Sydenham 2012.
2 A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided.

Physical exercise

Aerobic exercise

One Cochrane review by Young and colleagues from 2015 (85) evaluated the effects of aerobic exercise on cognitive function in cognitively healthy older people. The review included in total 11 trials (n=754), which all were relevant for our research question. The review authors judged the methodological quality of the included studies to be at high to moderate risk of bias, as assessed with the Cochrane risk of bias tool and the CLEAR NRT tool (mean score: 33; IQR: 29 to 37; the scale goes from 14 to 48 points, lower scores better). The trials were published between 1990 and 2012.

Participants

The 11 trials recruited in total 754 cognitively healthy participants, with a mean age ranging from 60 to 91 years across studies. The median number of participants in the included studies was 49 (IQR: 30 to 101 participants). The trials were conducted in the USA , Canada and France. Baseline aerobic and cognitive capacity of participants was not reported.

Intervention

The aerobic exercise was either brisk walking, jogging, or cycling, or a combination. The frequency and duration of supervised training ranged from 1 to 3 one-hour sessions per week, with a majority of studies providing 3X60 minutes training per week. The duration of follow up ranged from 8 to 24 weeks (median 16 weeks).

Comparison

The comparator was either no intervention, or an active intervention (a flexibility/balance programme, a strength training programme, or a social/cognitive programme). In a majority of studies the frequency and/or duration of sessions were not matched to those of the intervention programme.

Outcomes

The outcomes reported in this review were cognitive test scores (one to 14 tests across studies), measures of aerobic capacity (i.e. VO_2max, step tests, different walking tests or rate pressure product), and dropout rate. The cognitive tests were categorised into 11 subdomains and pooled.

Table 5. Characteristics of the review on the effects of aerobic exercise on cognition (Young 2015).

No of studies	Population	Intervention	Comparator	Outcomes
11 trials[1]	N= 754 cognitively healthy participants; mean age ranged from 61 to 91 years	Aerobic exercise (i.e. brisk walking, jogging or cycling) Follow up: range 8 to 24 weeks (median 16 weeks)	No intervention or other active intervention (i.e. strength training, flexibility/balance training, or social/cognitive training).	Cognitive tests scores[2], measures of aerobic capacity, and dropout rate.

1 One additional study reported a secondary analysis of a subgroup of participants from one of the included trials, but these results were not used in the review.
2 A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests:

Cognitive training

We included one non-Cochrane review (65) that evaluated the effectiveness of computerised cognitive training (CCT) in attenuating age-related cognitive decline in cognitively healthy older people. This review included in total 51 randomised studies (52 independent comparisons). The review authors judged the methodological quality of the included studies to be mixed: 34 of 51 studies were judged to be at high risk of bias, as assessed with the Cochrane's risk of bias tool. The mean PEDro score was 6.2/9 (SD 1.35), and according to this tool 35 studies were judged to be at high risk of bias. The trials were published between 1997 and 2013.

Participants

The trials recruited in total 4,885 participants, with mean ages ranging from 60.7 to 81.9 years across studies. According to the review authors the participants lacked any major cognitive, neurological, psychiatric, and/or sensory impairment. The MMSE scores at baseline ranged from >24 to 29.3 across studies that reported a baseline measure of cognitive function (39 of 51 studies). The median number of participants in the included studies was 44 (IQR: 30 to 67 participants). The participants were mainly from the USA and Europe, but also to a lesser extent from Canada. Australia, Israel, China, Taiwan Special Administrative Region, Republic of Korea, and Japan.

Intervention

The CCT programs were standardized, computerised tasks or video games. The total duration of the training varied from 4 to 60 hours, the number of sessions varied from 3 to 50 (of 15 to 120 minutes duration), and the intensity of intervention (frequency of sessions per week) ranged from one to seven times per week. Various electronic devices, e.g. personal computers, mobile devices, or gaming consoles, were used to deliver the training. The review authors categorized the CCT programs into 5 groups: multi-domain training (24 studies), speed of processing training (nine studies), working memory training (nine studies), attention training (six studies), and in four studies video-games were used. Fifteen studies used 'in-house' programs, and the remaining 36 studies used commercial cognitive training programs, or video-games. The intervention was delivered either as center-based group training (32 studies; 61.5%), or as unsupervised training in the participant's home (19 studies; 36.5%). No data on adherence to the intervention was provided.

Comparison

The comparison interventions were either active, i.e. another intervention (26 studies; 50%), or passive (no intervention). The active control conditions were not further described.

Outcomes

The primary outcome of this review was change in cognitive test scores from baseline to immediately post-training. No long-term effects were evaluated. In total, 396 cognitive outcomes were reported. No information was provided on what tests had been used in the different studies.

Table 6. Characteristics of the review on the effects of cognitive training (Lampit 2009).

No of studies	Population	Intervention	Comparator	Outcomes
51 trials (52 comparisons)	N=4,885 cognitively healthy participants; mean age ranged from 60 to 82 years	Computerized cognitive training (CCT);> 4 duration; home-based (unsupervised) or centre-based (group) training; 5 different types of CCT Follow up: 40 to 60 hours total duration (unclear number of weeks)	Active or passive interventions	Cognitive tests scores[1]

1 The names of the cognitive tests, details on the scaling and how to interpret the test scores were not provided in the review, neither was the number of tests used in the included studies.

Secondary prevention interventions

Three reviews (two Cochrane reviews (42, 78) and one non-Cochrane review (71)), evaluated the effects of secondary prevention interventions, i.e. pharmacological therapy (78), dietary supplements (71), to delay or prevent the onset of dementia in people with MCI or early symptoms and signs of dementia.

Pharmacological therapy

Cholinesterase inhibitors

One Cochrane review by Russ et al from 2012 (78) evaluated the effectiveness of cholinesterase inhibitors in preventing or delaying progression to dementia in people with MCI. The review included nine trials (8 published reports) which all were relevant for our research questions. The review authors judged all included studies to be "well conducted and robust RCTs". The trials were published between 2004 and 2012.

Participants

The eight included studies recruited in total 5,149 participants with MCI (anyway defined) with a mean age ranging from 45 to 90 years. Three of the studies were conducted in the USA, one in USA and Canada, one in Germany, one in Singapore, and in

two multisite studies the participants were from 16 and 14 countries respectively. The median number of participants per study was 769 (range 19 to 2,037 participants).

Intervention

Three different cholinesterase inhibitors were used in the included studies: donepezil (three studies), rivastigmine (two studies), and galantamine (four studies). One trial, which reported on two different dosages, was reported in two studies. In a majority of studies, the end-dose (after escalation from a lower dose), was 10-12 mg/day.

Comparator

The comparator intervention was placebo. In one study both intervention and control groups also received multivitamins. The median follow up was 76 weeks (range 16 weeks to 48 months).

Outcomes

The review reported on progression to dementia (primary outcome) and adverse effects of the drug therapy. Other outcomes were change in performance on cognitive tests (5 tests; MMSE, ADAS-Cog, CDR-sum of boxes, Symbol Digit Modalities, ADCS-ADL) and mortality. The review authors report the pooled effects of incidence of dementia at 3 years, and pooled effects of adverse events (any adverse event, serious adverse events, mortality, and other adverse events) that occurred during the study.

Table 7. Characteristics of the review on the effects of cholinesterase inhibitors (Russ 2012).

No of studies	Population	Intervention	Comparator	Outcomes
9 trials	N= 5,149 participants with MCI; age 45 to 90 years	Cholinesterase inhibitors[1](end-dose typically 10-12 mg/day) Follow up: range 16 weeks to 48 months (median 76 weeks)	Placebo	Progression to dementia, side effects, change in cognitive test scores[2] and mortality

1 Three different cholinesterase inhibitors were used in the included studies (Donepezil, Rivastigmine and Galantamine)
2 A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests:

Dietary supplements

Vitamin E

One Cochrane-review by Farina et al (42) evaluated the effectiveness of vitamin E supplementation in preventing progression to dementia in people with MCI. This review included three trials, of which one that recruited participants with MCI, was relevant for our overview of reviews. The review authors judged the trial to be at low risk of bias. The included study was published in 2005.

Population

In this multi-centre trial, people (n=516) with amnestic type of MCI and an average age of 73 years participated. The trial was conducted in the USA and in Canada.

Intervention

The included trial had three treatment groups but only data for the Vitamin E (alpha-tocopherol; 2000 IU/day) group and the placebo group were evaluated. Both intervention and control group participants also received multivitamins. The duration of follow up was 3 years.

Comparator

The comparator intervention was placebo.

Outcomes

The outcomes reported in the review were progression from MCI to possible or probable AD (primary outcome), adverse events and death.

Table 8. Characteristics of the review on the effects of vitamin E on AD incidence (Farina 2012).

No of studies	Population	Intervention	Comparator	Outcomes
3 trials (of which one was included in this overview of reviews)	N=516[1] participants with amnestic MCI; mean age 73 years, 46% females	Vitamin E (alpha-tocopherol; 2000 IU/day)+ multivitamins Follow up: 3 years	Placebo + multivitamins	Time to progression from MCI to possible or probable AD; cognitive test scores[2]

1 Total number of participants, including the third study arm (n= 769). The third study arm was not included in Farina 2012..

2 The authors of the original trial did not report any between group comparisons for any of the cognitive (secondary)outcomes. Nor did they provide information on the cognitive tests i.e. scaling and interpretation.

Omega 3 FAs

One review by Mazereeuw and colleagues from 2012 (71) evaluated the effects of Omega-3 FAs supplements on cognitive function in people with cognitive impairment but no dementia (CIND). The review included four trials, encompassing 650 participants with MCI or memory complaints, which were all eligible for inclusion in our overview of reviews. The review authors judged the methodological quality of the included studies to be high. The trials were published between 2006 and 2011.

Population

Participants (n=650) with CIND and/or memory complaints were recruited. Mean age of the participants ranged from 68.5 to 74.5 across studies. Two of the studies recruited people with CIND (in one study this was not confirmed with any cognitive tests). The other two studies recruited people with memory complaints. Mean MMSE score ranged from 27.6 to 28.2 across studies. In one study participants scored >25 on memory Complaint Questionnaire Scale). The studies were conducted in the Netherlands, England and Wales, Japan, Australia, Israel, and USA. The median number of participants in the included studies was 86 (range: 21 to 487).

Intervention

The intervention consisted in the provision of Omega-3 FA supplements to people with cognitive impairment. The duration of follow up ranged from 12.8 to 27 weeks (median 19.5 weeks).

Comparator

The comparator intervention was placebo.

Outcomes

The main outcomes were change in performance on a number of cognitive tests which were categorised into seven cognitive subdomains (MMSE, composite memory; immediate recall; delayed recall, recognition, attention and processing speed, working memory, and executive function).

Table 9. Characteristics of the review on the effects of Omega -3 FAs (Mazereeuw 2012).

No of studies	Population	Intervention	Comparator	Outcomes
4 trials	N= 650 participants with CIND; mean age 65.7 to 74.6; MMSE 27.6-28.2. One study did not report MMSE scores	Omega-3 FAs. Duration: 12.8 to 27 weeks (median 19.5 weeks) Follow up::range 12.8 to 27 weeks (median 19.5 weeks)	Placebo	Cognitive test scores[1].

1 A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests.

Certainty of the evidence

All studies in the included reviews were randomised controlled trials which are considered the highest level of evidence. In six of the included reviews, the authors judged the risk of bias of included studies to be low. In one review the authors judged the risk to be moderate to high (85), and in one review a majority of studies were judged to be at high risk (65), which resulted in downgrading of the evidence.

The certainty of the included evidence for the main outcomes (dementia and possible or probable AD) as assessed using the GRADE tool, was moderate in three of the reviews that reported this outcome (72, 78, 42), and low in one (73). For cognitive test scores (which were reported in all but one of the reviews) the certainty of the evidence ranged from low in one review, due to risk of bias and imprecision (85), to predominantly moderate to high certainty of evidence, in the other included reviews. In one review (78), however, the certainty of evidence for the effect on cognitive test scores ranged from very low to high. Regarding the results for adverse effects (three reviews reported pooled results) (72, 73, 78), the certainty of evidence was moderate to high. For further details see Appendix 7 Evidence profiles.

Effects of interventions

Primary prevention interventions

Pharmacological therapies

Antihypertensive drugs

Pooled results of incidence of dementia from the review by McGuinness and colleagues (73) (4 studies; n=15,427 participants), suggest a slight difference between participants who received antihypertensive drugs and those who received placebo (OR: 0.89 [0.74 to 1.07], p=0.21) at 1.8 to 4.5 years follow up. Below we report the range of effect sizes for cognitive test scores (MMSE), adverse effects, and change in blood pressure level across studies, rather than the pooled effect estimates reported by the review authors, in table 10 (all p<0.00001), as the heterogeneity was very high (I^2=97-98%). The mean difference for the change in MMSE scores (3 trials; n=10,640) ranged from 1.80 to 0.07; adverse effects (3 trials; n=12,091) ranged from OR 0.92 to 1.11. The mean decrease in blood pressure ranged from 3.2 to 15.0 mmHg and from 1.6 to 5.9 mmHg for systolic and diastolic blood pressure respectively.

In conclusion, low certainty of evidence suggest that antihypertensive drugs may lead to a slight decrease in incidence of dementia as compared with placebo. The results should be interpreted with caution, due to the wide CI, and large losses to follow up in some of the included studies.

Table 10. Summary of findings table of the effects of antihypertensive drugs on cognitive impairment and dementia incidence (McGuinness 2009).

Antihypertensive drugs vs. placebo for prevention of cognitive impairment and dementia in patients without prior cerebrovascular disease

Patient or population: cognitively healthy participants without prior cerebrovascular disease
Setting: Western and Eastern Europe, North America, China, Australasia and Tunisia
Intervention: antihypertensive drugs
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with antihypertensive drugs			
Dementia incidence[1]	**Study population**		**OR 0.89** (0.74 to 1.07)	15, 427 (4 RCT)	⊕⊕◯◯ LOW [2,3]
	34 per 1000	**30 per 1000** (25 to 36)			
Change in cognitive test score (MMSE)[4]	The mean cognitive test scores (MMSE) was **0**	The mean change in cognitive test scores from baseline (MMSE) in the intervention group was 0.42 higher (0.3 higher to 0.53 higher)	-	10, 640 (3 RCT)	⊕⊕◯◯ LOW [5]
	Study population				

Antihypertensive drugs vs. placebo for prevention of cognitive impairment and dementia in patients without prior cerebrovascular disease

Patient or population: cognitively healthy participants without prior cerebrovascular disease
Setting: Western and Eastern Europe, North America, China, Australasia and Tunisia
Intervention: antihypertensive drugs
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with antihypertensive drugs			
Adverse events[6]	186 per 1000	**187 per 1000** (174 to 202)	**OR 1.01** (0.92 to 1.11)	12, 091 (3 RCT)	⨁⨁◯◯ LOW [5,6]

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference
Note: The results on dementia incidence can be compared with the 80 per 1000 dementia incidence in Norway for people over the age of 80.

1. Follow up ranged from mean 2 to 4.5 years across three studies, and was average 1.8 years in one study.
2. Relatively wide CI.
3. Indirectness as many of the people in the control group also received non-study antihypertensive drugs.
4. MMSE: Mini Mental State Examination. Scaling and interpretation of scale not further described.
5. Very high heterogeneity (I^2=97-98%).*
6. Adverse events that required a discontinuation of treatment. No further description of the adverse events provided.

Cholesterol lowering drugs (statins)

The results from the review by McGuinness and colleagues from 2016 (72) indicate no difference in dementia incidence (1 study; n=20,536 participants) between participants receiving statins and those receiving placebo (OR: 1.00 (0.61 to 1.65)) at mean 5 years follow up (See Table 11). Further, the authors reported no between group differences in cognitive test scores (MMSE, SCWT, Picture word, Letter digit tests; range of mean differences: 0.8 higher to 0.01 lower than control), and no differences for telephone interview assessed cognitive status (TICS; mean difference 0.02). In addition, there were similar effects on adverse effects (2 trials; OR: 0.94 [0.83 to 1.05}). The LDL cholesterol level (2 trials; 1.2 mmol/L [-1.24 to -1.15]) was lower in the intervention group as compared to control.

Adherence to the drug therapy in the intervention group ranged from 82 to 94% across studies. Between 3 and 5% of intervention participants were on non-study statins alone and 2% on both, and between 10 and 17% of control patients received non-study statins. In one trial approximately 25% of the participants were lost to follow up, while in the other trial the losses to follow up were very small. In both trials analysis was by intention to treat.

In conclusion, there is moderate certainty of evidence indicating that statin therapy given to older people with, or at risk of, vascular disease, probably leads to little or no difference in incidence of dementia as compared to placebo. There were very few events (and wide CI), why the results should be interpreted with caution.

Table 11. Summary of findings table of the effects of cholesterol lowering therapy on incidence of dementia and cognitive decline (McGuinness 2016).

Cholesterol lowering therapy (statins) vs. placebo for the prevention of dementia and cognitive decline in cognitively healthy people

Patient or population: cognitively healthy people
Setting: UK, Ireland and the Netherlands
Intervention: statins (cholesterol lowering drugs)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with statins			
Dementia incidence; mean follow up: 5 years	**Study population**		**OR 1.00** (0.61 to 1.65)	20, 536 (1 RCT)	⊕⊕⊕◯ MODERATE[1]
	3 per 1000	**3 per 1000** (2 to 5)			
Cognitive test scores (MMSE); mean follow up: 3.2 years[1]	The mean cognitive test scores (MMSE) was **0**	The mean change in cognitive test scores (MMSE) in the intervention group was 0.06 higher (0.04 lower to 0.16 higher)	-	5, 804 (1 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test scores (Stroop, Picture world test, Letter Digit test)	The mean cognitive test scores was **0**	The mean change in cognitive test scores in the intervention group ranged from 0.8 higher to 0.01 lower	-	5, 804 (1 RCT)	⊕⊕⊕◯ MODERATE [2]
TICS-m[2] scores at mean 5 years (final visit)	The mean TICS-m scores at final visit was **0**	The mean TICS-m scores at final visit in the intervention group was 0.02 higher (0.12 lower to 0.16 higher)	-	20, 536 (1 RCT)	⊕⊕⊕⊕ HIGH
Adverse effect; at 3.2 to 5 years follow up	The mean adverse effects was **0**	The mean adverse effects in the intervention group was 0.94 higher (0.83 higher to 1.05 higher)	-	26, 340 (2 RCT)	⊕⊕⊕⊕ HIGH

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

1 We downgraded the evidence due to few events and wide CI.
2 Change from second baseline visit to last, on treatment for MMSE (Score out of 30 (higher score better), Stroop test (Total number of seconds required to complete the third Stroop card containing 40 items; lower is better), Picture word (15 Picture Learning Test; unclear scaling), and Letter digit tests scores (Total number of correct entries completed in 60 seconds, higher is better). Mean follow up 3.2 years. Moderate quality for Stroop test, but high for the other three tests.
3 TICS-m: The modified Telephone Interview of Cognitive Status. Score out of 39. No further information on interpretation of test.
4 Adverse effects requiring discontinuation of treatment i.e. Rhabdomyolysis; creatinine kinase levels >10 times upper limit of normal values, a liver aminotransferase levels>3 times upper limits of normal values.

Dietary supplements

Omega-3 FAs

The review by Sydenham and colleagues from 2012 (40) reported no differences for the pooled results (3 studies; n=4,080) of eight cognitive test scores (See Table 12) between participants receiving Omega-3 FAs and those receiving placebo at 6 to 40 months follow up. In addition there were little or no differences in adverse effects between groups.

Treatment compliance was reported to be high (81% and 99%) across treatment and placebo group.

In conclusion, high to moderate certainty of evidence suggest that Omega-3 FAs probably lead little or no difference in cognitive decline, as compared with placebo, when given to cognitively healthy older people.

Table 12. Summary of findings table of the effects of Omega-3 FAs on cognitive decline and dementia (Sydenham 2012).

Omega-3 FAs vs. placebo for prevention of cognitive decline and dementia in cognitively healthy older people

Patient or population: cognitively healthy older people
Setting: England and Wales
Intervention: omega-3 fatty acids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	**Risk with Omega-3 fatty acids**			
Cognitive test scores[1] (MMSE). Follow up: range 24 to 40 months	The mean cognitive test scores - was **0**	The mean MMSE scores in the intervention group was 0.07 lower (0.25 lower to 0.1 higher)	-	3, 221 (2 RCT)	⊕⊕⊕◯ MODERATE [2]
Cognitive test scores[1](Immediate recall, Delayed recall, Word recognition, Number of animals named). Follow up: range 6 to 24 months	The mean cognitive test scores was **0**	The mean cognitive test scores[3] in the intervention group was 0.06 standard deviations higher to 0.04 standard deviations lower	-	1, 043 (3 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test score[1] (Digit span forward and backward). Follow up: range 6 to 24 months	The mean cognitive test score was **0**	The mean cognitive test score[4] in the intervention group was 0.12 to 0.03 higher	-	1, 018 (3 RCT)	⊕⊕⊕⊕ HIGH

The risk in the* **intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

1. A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests.
2. High I^2=53%
3. We have reported the range of effects (SMD) since none of the individual test scores showed an effect of the intervention.
4. We have reported the range of effects (MD) for two tests here.

Aerobic training

The review by Young et al. from 2015 (85), reported no differences between groups for the individually pooled test scores for 10 cognitive categories (11 trials; n= 754) for the comparison aerobic exercise vs. no intervention (SDM [8 outcomes]: 0.09 lower to 0.30 higher; MD [2 outcomes], 0.10 to 0.16). See Table 13 below. The results for the comparison aerobic exercise versus any active intervention (SDM [10 outcomes], range: 0.26 lower to 0.38 higher; MD [1 outcome]: 0.15) (results not shown in Table 12). For all

outcomes the confidence interval included the point of no effect. For more details see evidence profile in Appendix 6.

In conclusion, aerobic exercise may lead to little or no effect on the performance on cognitive tests.

Table 13. Summary of findings table of the effects of aerobic exercise on cognitive decline (Young 2015).

Aerobic exercise vs. no intervention for the prevention of cognitive decline

Patient or population: cognitively healthy older people
Setting: USA, France and Canada
Intervention: Aerobic exercise
Comparison: no intervention

Outcomes[3]	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no intervention	**Risk with Aerobic exercise**			
Cognitive speed [1]	-	SMD 0.12 higher (0.16 lower to 0.41 higher)	-	260 (5 RCTs)	⨁⨁◯◯ LOW [2,3]
Verbal memory functions (immediate) [1]	-	SMD 0.09 higher (0.24 lower to 0.43 higher)	-	137 (2 RCTs)	⨁⨁◯◯ LOW [2,3]
Visual mamory functions (immediate) [1]	-	SMD 0.09 lower (0.57 lower to 0.40 higher)	-	65 (1 RCT)	⨁⨁◯◯ LOW [2,3]
Working memory [1]	The mean working memory was **0**	The mean working memory in the intervention group was 0,3 higher (0.54 lower to 1.15 higher)	-	137 (2 RCTs)	⨁⨁◯◯ LOW [2,3]
Memory functions (delayed) [1]	-	SMD 0.09 higher (0.23 lower to 0.41 higher)	-	152 (2 RCTs)	⨁⨁◯◯ LOW [2,3]
Executive functions [1]	-	SMD 0.18 higher (0.16 lower to 0.53 higher)	-	217 (3 RCTs)	⨁⨁◯◯ LOW [2,3]
Cognitive inhibition[1]	-	SMD 0.20 higher (0.06 lower to 0.47 higher)	-	217 (3 RCTs)	⨁⨁◯◯ LOW [2,3]
Visual attention [1]	-	SMD 0.05 higher (0.26 lower to 0.37 higher)	-	155 (3 RCTs)	⨁⨁◯◯ LOW [2,3]
Auditory attention[1]	The mean auditory attention was **0**	The mean auditory attention in the intervention group was 0,16 higher (0.01 lower to 1.33 higher)	-	65 (1 RCT)	⨁⨁◯◯ LOW [2,3]
Motor function [1]	The mean motor function was **0**	The mean motor function in the intervention group was 0,1 higher (7.87 lower to 8.08 higher)	-	65 (1 RCT)	⨁⨁◯◯ LOW [2,3]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

Table 13. Summary of findings table of the effects of aerobic exercise on cognitive decline (Young 2015).

Aerobic exercise vs. no intervention for the prevention of cognitive decline

Patient or population: cognitively healthy older people
Setting: USA, France and Canada
Intervention: Aerobic exercise
Comparison: no intervention

Outcomes[3]	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no intervention	Risk with Aerobic exercise			

1. A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests.
2. High to moderate risk of bias in at least one domain.
3. Fewer than 300 participants (imprecision).

Computerised cognitive training

The review by Lampit et al from 2014 (65), reported a small effect of computerised cognitive training (CCT) on cognitive test scores (52 studies; n=4,445 participants) in cognitively healthy older people (Hedge's g; 95% CI: 0.22 [0.15 to 0.29], p<0.001). There was low to moderate heterogeneity (I^2=29.92, p=0.03). Cognitive function was measured directly after the training, which varied in duration from 4 to 60 hours in total. See table 14.

In summary, there is moderate certainty of evidence of a small beneficial effect of CCT on cognitive test scores, directly after the training.

Table 14. Summary of findings table of the effects of computerised cognitive training on age-related cognitive decline (Lampit 2014).

Computerised cognitive training vs. active or passive intervention for prevention of age-related cognitive decline in cognitively healthy older people

Patient or population: cognitively healthy older people
Setting: USA, Europe, Canada, Australia, Israel, China, Taiwan, Republic of Korea and Japan
Intervention: Computerised cognitive training
Comparison: active or passive intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with active or passive intervention	Risk with Computerised cognitive training			
Cognitive test scores[1]	The mean cognitive test scores was **0**	The mean cognitive test scores in the intervention group was 0.22 higher (0.15 higher to 0.29 higher)	-	4, 885 (52 RCT)	⊕⊕⊕◯ MODERATE[2]

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

1. No information was provided on the type and number of cognitive tests used in the 51 included studies. No information on scaling and interpretation of test scores. Only short-term effects were evaluated.
2. Thirty-three of 51 included studies were at high risk of bias. Eighteen studies were at low risk.

Secondary prevention interventions

Pharmacological therapy

Cholinesterase inhibitors

The review by Russ et al from 2012 (78) reported a slight difference in progression to dementia (9 studies; n= 4,207) between groups receiving cholinesterase inhibitors and those receiving placebo at 3 years (RR:0.84 [0.70 to 1.02]). Further, the review authors report no effect of cholinesterase inhibitors on cognitive test scores, apart from a small and most likely clinically insignificant beneficial effect on a single test. There were significantly more adverse events in the cholinesterase inhibitor groups (RR: 1.09 [1.02 to 1.16]), but no more serious adverse events or deaths. Results for any adverse event were as follows: gastrointestinal side effects: diarrhea (RR 2.10 [1.30 to 3.39]), nausea (RR 2.97 [2.57 to 3.42]), vomiting (RR 4.42 [3.23 to 6.05]); muscle spasms or leg cramps (RR 7.52 [4.34 to 13.02]); abnormal dreams (RR 4.25 [2.57 to 7.04]); insomnia (RR 1.66 [1.36 to 2.02]); syncope or dizziness (RR 1.62 [1.36 to 1.93]); and headache (RR 1.34 [1.05 to 1.71]).

In summary, cholinesterase inhibitors probably lead to a slight decrease in incidence of dementia, as compared to placebo (moderate certainty). However, moderate certainty of evidence indicate higher incidence of any adverse events in the cholinesterase group, but a similar effect on serious adverse events. The results for incidence of dementia and serious adverse effects should both be interpreted with caution due to the wide CI. Evidence of mixed certainty suggest little or no effect of cholinesterase inhibitors on cognitive test scores.

Table 15. Summary of findings table of the effects of cholinesterase inhibitors on dementia incidence and cognitive decline (Russ 2012).

Cholinesterase inhibitors vs. placebo for prevention of dementia and cognitive decline in people with cognitive impairment no dementia (CIND)

Patient or population: people with mild cognitive impairment
Setting: USA, Canada, Singapore and a number of other countries
Intervention: Cholinesterase inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Cholinesterase inhibitors			
Conversion to dementia Follow up: mean 3 years	**Study population**		**RR 0.84** (0.70 to 1.02)	1, 530 (2 RCT)	⨁⨁⨁◯ MODERATE[1]
	237 per 1000	**199 per 1000** (166 to 241)			
Cognitive test scores (ADAS-Cog[1]). Follow up: mean 2 years	The mean cognitive test scores was **0**	The mean cognitive test scores in the intervention group was 0.78 lower (1.92 lower to 0.35 higher)	-	2, 675 (4 RCT)	⨁⨁◯◯ LOW [2,3]

Table 15. Summary of findings table of the effects of cholinesterase inhibitors on dementia incidence and cognitive decline (Russ 2012).

Cholinesterase inhibitors vs. placebo for prevention of dementia and cognitive decline in people with cognitive impairment no dementia (CIND)

Patient or population: people with mild cognitive impairment
Setting: USA, Canada, Singapore and a number of other countries
Intervention: Cholinesterase inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Cholinesterase inhibitors			
Cognitive test scores (CDR Sum of boxes[1]). Follow up: mean 1 years	The mean cognitive test scores was **0**	The mean cognitive test scores in the intervention group was 0.1 lower (0.11 lower to 0.09 lower)	-	1, 269 (2 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test scores- (Symbol digit modalities[1]). Follow up: mean 6 months	The mean cognitive test scores was **0**	The mean cognitive test scores in the intervention group was 0.17 higher (2.87 lower to 3.21 higher)	-	312 (2 RCT)	⊕◯◯◯ VERY LOW[2,3],
Cognitive test scores (MMSE); scale from 0 to 30. Follow up: mean 1 years	The mean cognitive test scores was **0**	The mean cognitive test scores in the intervention group was 0.24 higher (0.13 lower to 0.61 higher)	-	1, 269 (2 RCT)	⊕⊕◯◯ LOW [2,3]
Cognitive test scores [1](ADCS-ADL); scale from 0 to 78. Follow up: mean 1 years	The mean cognitive test scores was **0**	The mean cognitive test scores in the intervention group was 0.15 higher (0.27 lower to 0.57 higher)	-	2, 408 (3 RCT)	⊕⊕⊕◯ MODERATE[2]
Serious adverse events[4]	**Study population**		**RR 0.97** (0.86 to 1.10)	4, 207 (5 RCT)	⊕⊕⊕◯ MODERATE[3]
	190 per 1000	**185 per 1000** (164 to 209)			
Any adverse events[5]	**Study population**		**RR 1.09** (1.02 to 1.16)	4, 207 (5 RCT)	⊕⊕⊕◯ MODERATE[3]
	825 per 1000	**899 per 1000** (841 to 957)			

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests.
2. Wide CI.
3. I^2=79-98% and thus very high heterogeneity.
4. Serious adverse events (not further described) and death.
5. Any adverse events including gastrointestinal side effects (diarrhoea, vomiting and nausea), cardiac problems, muscle spasms or leg cramps, headache, syncope or dizziness, insomnia and abnormal dreams.

Dietary supplements

Vitamin E

The review by Farina et al from 2012 (42) reported little or no difference in the progression to possible or probable AD between the Vitamin E and the placebo group. At study endpoint (36 months), 76 out of 257 participants (29.6%) in the vitamin E group and 73 out of 259 participants (28.2%) in the placebo group had progressed to AD (HR: 1.02: 95% CI 0.74 to 1.41, p=0.91) (see Table 16). No between-group comparisons were reported for the cognitive test scores. Sixty-six participants from the treatment group and 72 from the placebo group dropped out during the study, with the main reasons being death, adverse effects, and withdrawal of consent. No information was provided regarding the distribution of the reasons for discontinuing treatment across groups, or on adverse effects of the intervention.

In summary, there is moderate certainty of evidence that vitamin E probably leads to little or no difference in incidence of possible or probable AD, as compared to placebo. However, due to the wide CI, the results should be interpreted with caution.

Table 16. Summary of findings table of the effects of vitamin E on progression to AD (Farina 2012)

Vitamin E vs. placebo for prevention of Alzheimer's disease in people with MCI

Population: people with mild cognitive impairment
Setting: USA and Canada
Intervention: Vitamin E
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Vitamin E			
Possible or probable Alzheimer's disease. Follow up: mean 3 years	**Study population**		**HR 1.02** (0.74 to 1.41)	516 (1 RCT)	⨁⨁⨁◯ MODERATE [1,2]
	282 per 1000	**287 per 1000** (217 to 373)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; HR: hazard ratio

1. Only one study. Relatively small groups.
2. Wide CI overlapping no effect.

* As noted by the review authors, measures were taken at 6, 12, 18, 24, 30 and 36 months, but results were only reported for 12 and 36 months, and for the remainder only changes from baseline were provided.

Omega-3 FAs

The pooled results from the review by Mazereeuw et al from 2011 (68) suggest little or no effects of Omega-3 FAs on cognitive test scores (4 studies; n=650) at median 14.5 to 24 weeks follow up. Only for two of the seven cognitive subdomains was there a beneficial effect of the intervention: immediate recall (Hedge's g (95% CI): 0.16 (0.01 to 0.32)), and attention and processing speed (Hedge's g (95% CI): 0.32 (0.03 to 0.61). See table 17. There were no differences in dropout rate or adverse events between groups.

In summary, evidence, mainly of high certainty, suggest that Omega-3 FAs probably lead to little or no difference in cognitive test scores, as compared to placebo.

Table 17. Summary of findings table on the effects of Omeaga-3 FAs on cognitive test scores (Mazereeuw 2012).

Omega-3 FAs vs. placebo for improved cognitive function in people with CIND

Population: people with cognitive impairment no dementia (CIND)
Setting: the Netherlands, England, Wales, Japan, Australia, Israel, and USA
Intervention: omega-3 FAs
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Omega-3 fatty acids			
Cognitive test scores (Composite memory[1]). Follow up: median 14.5 weeks	The mean Composite memory score was **0**	The mean cognitive test scores in the intervention group was 0.1 higher (0.06 lower to 0.25 higher)	-	676 (4 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test scores (Immediate and delayed recall[1]). Follow up: median 19.5 weeks	The mean Immediate recall test score was **0**	The mean cognitive test scores in the intervention group was 0.16 to 0.03 higher	-	676 (4 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test scores (Recognition[1])	The mean Recognition test score was **0**	The mean cognitive test in the intervention group was 0.03 lower (0.18 lower to 0.13 higher)	-	655 (3 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test scores (Attention and processing speed[1])	The mean Attention and processing speed test scores were **0**	The mean cognitive test in the intervention group was 0.32 higher (0.03 higher to 0.61 higher)	-	193 (3 RCT)	⊕⊕⊕◯ MODERATE[2]
Cognitive test scores (Working memory and executive function[1])	The mean Working memory and executive function test scores was **0**	The mean cognitive test scores - in the intervention group was 0.04 higher (0.13 lower to 0.21 higher)	-	533 (2 RCT)	⊕⊕⊕⊕ HIGH
Cognitive test scores – (MMSE). Follow up: mean 24 weeks	The mean MMSE score was **0**	The mean cognitive test scores in the intervention group was 0.06 lower (0.23 lower to 0.12 higher)	-	483 (1 RCT)	⊕⊕⊕⊕ HIGH

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

1 A description of the cognitive tests i.e. scaling and how to interpret them (i.e. if higher or lower score would indicate an improvement) was not provided for the cognitive tests
2 Downgraded due to imprecision (wide CI).

Ethics

None of the included reviews discussed equity, or the lack of a discussion of equity issues, in the studies included in the reviews. Nor did they attempt to discuss the balance

between benefits and harms, taking into account the costs and cost-effectiveness of interventions. In a majority of the included reviews, possible financial interests and conflicts of interest related to the intervention under study were not discussed. For example, in the review by Lampit and colleagues (65), in which commercial and so called 'in-house' computer programs were used to deliver the cognitive training, no information on possible financial conflicts of interest was provided (i.e. if people conducting the trials were in any way associated with, or funded by, the people producing the CCT programs). None of the included reviews discussed any consumer involvement in trial design, or the lack of it.

Discussion

Main results

In this overview of reviews we included eight high quality reviews summarising the effects of interventions aimed at preventing cognitive decline, AD, and other dementias in cognitively healthy people (primary prevention), and in people with mild cognitive impairment (secondary prevention). Moderate to high certainty of evidence from four of these reviews suggests that statin therapy (72) and the dietary supplements evaluated (40, 42, 71) probably lead to little or no difference in cognitive decline and incidence of dementia as compared to placebo. Moderate certainty of evidence for cholinesterase inhibitors (78), and low certainty of evidence for antihypertensive drugs (73) indicate that these drugs may lead to slightly decreased incidence of dementia, as compared to placebo. Wide CIs and few events in some of the analyses warrant caution when interpreting the results. Moderate certainty of evidence from one review (65) suggests that computerised cognitive training (CCT) probably leads to a small improvement in cognitive test scores directly after the training, but the long-term effects are unknown. Low certainty of evidence from one review (85) indicate that aerobic training possibly leads to little or no difference in cognitive function. Three of the included reviews (42, 72, 73) reported similar rates of adverse events in intervention and control groups. One review (78) reported higher incidence of adverse event in the treatment (cholinesterase) group as compared to placebo, and for serious adverse events the intervention effect varied.

Certainty of the evidence

All original studies included in the reviews were randomised controlled trials, which constitute the highest level of evidence. The certainty of the evidence for the outcome dementia incidence, as assessed using the GRADE tool, was moderate in three of the four reviews that reported this outcome, and low in one review, Moderate certainty, means that the true effect is likely to be close to the estimate of the effect, but there is also a possibility (both for the interventions supported by low and moderate certainty of evidence) that the effects of the evaluated drugs and the dietary supplements may be substantially different. Some caution when interpreting the results on incidence of dementia, is in order, as the incidence rate was rather low (around 3 %), for some of the analyses and/or the CIs relatively wide. For the cognitive test scores the quality of evidence ranged from high to low (due to imprecision, inconsistency and/or high risk of bias for some of the cognitive outcomes).

Strengths and weaknesses

We conducted a comprehensive search for systematic reviews of interventions to delay or prevent cognitive decline and dementia, which was updated in February 2016. There were no language restrictions. We searched the reference lists of included reviews, and the reference lists of other relevant publications identified. The search strategy was developed by an experienced information scientist, who also conducted the search. In addition, two authors independently screened all the references for inclusion, which makes it less likely that we missed any relevant reviews. We also graded the certainty of the evidence in duplicate. We included only reviews that we judged to be of high quality, and they in turn included only RCTs. Six of the eight included reviews were Cochrane reviews. All reviews were published between 2009 and 2016.

There are some limitations with our overview of reviews. One is that we only included high quality systematic reviews, as it can be argued that the exclusion of moderate- to low quality reviews may have excluded data relevant for the present work. Another limitation is that we relied entirely on the description of the original papers provided in the included systematic reviews, when conducting our overview of reviews. A third limitation, related to the old search date in one of the included reviews (literature search in 2008), is that we may have missed to include more recently published studies on the effects of antihypertensive drugs.

A limitation with the available evidence is that there are no studies with longer follow up time than 5 years. It may be doubted that this is sufficient time for change to take place given the nature of the condition (i.e. dementia) and the effects of the interventions under study.

Even if some reviews included studies of people with dementia, which was a group of people not within the scope of our overview of reviews, this did not constitute a problem as long as results for each group (cognitively healthy, MCI and dementia) were reported separately. We had to exclude one review targeting people with Parkinson's disease (67), and four other reviews (58, 63, 66, 77) as cognitively healthy people and cognitively impaired people were not analysed separately. We could, if it is judged important, include a third mixed group, if we decide to update this overview of reviews.

Ethics

The number of people living with AD is expected to increase dramatically over the next decades. Most of this increase will be in low-and middle income countries, where the prevalence already is the highest (12). Despite this, issues pertaining to equity were not addressed in any of the included reviews. The majority of the included studies were from high income countries, while in some cases it was not clear where the studies had been conducted.

Introducing and implementing new interventions/treatments can be costly, and paying for a new treatment for one disease group may take away money from other treatment alternatives, or from other patient groups. Ensuring that an intervention is cost-effective, and that the beneficial effects exceeds harms, is therefore very important to prevent waste of healthcare resources (99). None of the included reviews reported or discussed the lack of data on costs and cost-effectiveness of the interventions evaluated in the original studies.

There are huge financial interests involved in drug interventions to prevent cognitive decline, AD, and dementia. It has been suggested that research that is funded by drug companies is more likely to yield positive outcomes than research with other type of funding. This bias can be introduced in a number of ways (100). It is therefore important to disclose the funding sources for included studies, and possible relationships between those conducting the research and the pharmaceutical companies (101). Only one of the reviews (78) reported the financial disclosures of the original studies, which all were supported by drug companies.

When designing a trial, it is important to ensure that outcomes that are of importance to the patients are measured (102). Quality of life is one example of an important patient-centred outcome, which was only reported in two of the included reviews (72, 73), function in activities of daily living is another. None of the reviews reported on patient involvement in the trial development, or discussed the lack of it. Involving patients in refining an intervention may lead to clinical trial endpoints that better comply with the needs and concerns of patients and caregivers (103).

Potential biases in the overview process

At least two people independently applied eligibility criteria and assessed the reviews for inclusion. One author extracted data into a standardised data extractions form, and another author checked the accuracy of the extracted data, which should reduce bias in the overview process. At least two authors assessed the scientific quality of reviews according to the tool used by the Knowledge Centre. However, excluding reviews of moderate to low quality may have induced bias.

Overall completeness and applicability of the evidence

Only four of the included reviews reported on AD (42) or incidence of other types of dementia (72, 73, 78), while all reviews reported on cognitive test scores. It can be questioned if cognitive test scores is a good proxy for progression to dementia. Quality of life was only reported in two reviews (72, 73), and ADL function in one review only (72). Adverse effects were reported in four reviews (42, 72, 73, 78).

Even though the pharmacological interventions (antihypertensive drugs and statins) evaluated in two of the included reviews (72, 73), showed beneficial effects on the targeted risk factors for dementia (i.e. blood pressure and cholesterol level respectively),

incidence of dementia and cognitive function did not change significantly. The confidence intervals (for incidence of dementia) were relatively wide in both studies, why the results should be interpreted with caution.

McGuinness and colleagues (73), aimed to include also non-pharmacological blood pressure lowering interventions (e.g. salt restriction, weight reduction, exercise, reduced alcohol intake), but could not identify any such studies for inclusion. Some of the included trials suffered from large losses to follow up, and a large proportion of control participants receiving non-study antihypertensive drugs. Another limitation with the review on antihypertensive drugs was that only a single test (MMSE) was used to assess the effects on cognitive function.

A limitation with the statin review (72) was the unclear methods used to diagnose dementia in some of the included studies, and that only people deemed to be at moderate to high risk of a cardiovascular disease were included.

A limitation with both the review on antihypertensive drugs and the review on statins, is that incidence of dementia was a secondary outcome in all included studies

In the review that evaluated the effect of aerobic exercise on cognitive function (85), not all of the included studies reported improved aerobic fitness as a result of the intervention, and none reported a beneficial effect on cognition. In a majority of studies, the frequency/duration of the comparator interventions, were not matched to those in the intervention group. In addition, neither cognitive function nor aerobic fitness at baseline were reported, which makes it difficult to fully appreciate the results. It may be doubted whether the follow up time was sufficient for change to take place (from 8 to 26 weeks), and whether the studies were sufficiently powered (median 49 participants). It may also be questioned whether the targeted population was optimal for this type of intervention to show an effect, as it included very old people up to 92 years of age. It is possible that interventions addressing life style related risk factors like physical inactivity, are more likely to be effective in conserving cognitive function if they are delivered earlier in life. There is of course then the problem with very long intervention times, as the optimal age for outcome assessment is later in life (104).

The one review (65), which summarised the effects of CCT on cognitive test scores from a number of small studies (median n=44 participants), did not report any long-term effects on performance on cognitive tests. In addition, the review authors did not provide any information on what type of cognitive tests that had been used in the included studies, nor did they provide any details on the active comparison intervention or the adherence to the intervention, which make interpretation of the results difficult.

We did not find any high quality reviews concerned with the effects of healthy life style changes on cognitive function and dementia incidence (apart from the review on aerobic exercise), e.g. conversion to a healthy diet, decreased alcohol intake, smoking cessation, weight loss etc. Three excluded reviews (including mostly cohort and cross-sectional studies) report some evidence of an effect of increased fruit and vegetable intake and/or adherence to a Mediterranean diet (69, 70, 75). We also did not find any high

quality reviews concerned with the effects of interventions targeting other risk factors for dementia like for example mid-life depression, lack of social interaction, or low educational attainment. One excluded review of low quality (105) reported on interventions to treat depression in people with MCI and dementia, and two excluded reviews (79, 80) of moderate quality were concerned with cognitive and physical leisure activities. It has been suggested that low educational attainment is the risk factor contributing most to the burden of dementia worldwide, and that physical inactivity is the risk factor that contributes the most to the disease burden in USA and Europe (17). There is therefore an urgent need to evaluate effective interventions targeting these, and other risk factors, in RCTs and large scale population based studies, with long follow up times.

Dementias are syndromes that most likely are of a multifactorial origin (16). It is possible that preventive interventions may be more effective if they take into account the multifaceted aetiology behind the disease, i.e. interventions that target multiple risk factors may be more effective. However, all of the reviews included in this overview of reviews, evaluated the effectiveness of a single item intervention, targeting only one risk factor. We are aware of four large European trials of so called multidimensional interventions (including for example diet, exercise, cognitive training, and vascular risk monitoring) for people at risk for dementia. Three of these trials are ongoing (106). Results from one of the trials, recently published (107), suggest beneficial effects of the multidimensional intervention on cognitive function.

Until fairly recently (23, 26) there has been little or no consensus on what criteria and tools to use for the diagnosis of MCI, AD and other types of dementia. In the original studies included in the reviews now under consideration, of which 54.6 percent were published before the publication of the consensus criteria and 45.4 percent after, different criteria were used to determine the onset of dementia and to diagnose MCI. In addition, more than 396 different cognitive tests were used to assess the effects of interventions on cognitive function. Most commonly the tests were not well described, i.e. information about the scaling, the desired direction of effect, and what would be considered a clinically important effect was not provided. In one review all studies used only the Mini Mental State Examination (MMSE) to assess cognitive function, while other studies used up to ten different tests or test batteries to assess cognition. A change in 2 points on the MMSE scale has been suggested to be a clinically significant effect (108). The change in the MMSE ranged from 0.07 lower to 0.42 higher across six of the included reviews. Results from a recent systematic review (109) do not support the use of the MMSE as a single administered stand-alone test to assess progression to dementia. The review authors instead suggest to use a set of tests administered over time. To facilitate future evaluations of the comparative effectiveness of interventions, researchers should attempt to come to a consensus on what test batteries to use for assessment of cognitive function, and to use published consensus criteria and methods for diagnosing MCI and dementia.

Agreements or disagreements with other overviews of reviews

We identified one overview of reviews of interventions to prevent cognitive decline and dementia (110). This overview was published in 2010 and with a literature search from 2009, and thus it is becoming outdated. In contrast to our overview of reviews it had wider inclusion criteria, and also looked at factors associated with risk reduction, and not only effects of interventions to delay or prevent cognitive decline and dementia. In some respect their eligibility criteria were stricter, as they included only original studies with a follow up of at least 6 months duration, while we applied no restrictions to the length of follow up. Our results of non-significant effects of vitamin E, antihypertensive drugs, and cholinesterase inhibitors on dementia incidence, as compared to placebo, are in agreement with the results reported in this other overview of reviews. It did not identify any studies evaluating the effectiveness of Omega-3 FAs for inclusion, therefore comparison with our result could not be made.

Applications for practice

Physicians, patients, and carers should be made aware of the lack of convincing evidence for an effect of Omega-3 FAs, antihypertensive drugs, and statins on dementia incidence and cognitive function, when delivered to cognitively healthy older people. This of course have no bearing on the effects of antihypertensive drugs and statins on other conditions (e.g. cardiovascular disease). The practitioner should also be made aware of the evidence of little or no effect of Omega-3 FAs, vitamin E, and cholinesterase inhibitors in preventing cognitive decline, AD or other types of dementia, in people with mild cognitive impairment. There is some evidence for a small effect of CCT on the performance in cognitive tests in cognitively healthy people, but further research of the long term effects is needed.

Need for further research

Further research is needed to identify effective interventions to prevent cognitive decline and dementia, while waiting for researchers to discover a curative treatment for dementia. To increase the certainty of the results of this review, trials with more precise effect estimates and narrower CIs are needed. Since so far only effects of single faceted interventions have been evaluated and summarised in reviews, interventions involving a combination of healthy lifestyle changes, e.g. conversion to a healthy diet, decreased alcohol consumption, smoking cessation, weight loss, cognitive training etc., are needed. Also studies evaluating the effectiveness of interventions targeting other risk factors for dementia, like for example interventions for early identification and treatment of mid-life depression, for increased social interaction, and interventions to encourage education in populations with low educational attainment. Physical inactivity and low educational attainment should be addressed in large scale studies, since these risk factors are estimated to contribute most to the burden of disease.

Researchers should aim to use consensus methods and criteria to diagnose MCI, AD and dementia, and for assessing cognitive function, to enable effect comparisons between studies. They should also aim to improve the reporting (describe the tests/scales used to assess cognitive function, give details on the intervention and the comparator intervention), so as to provide sufficient detail to enable replication. Preferably all studies should report incidence of dementia (as a primary outcome), and not only performance on cognitive tests.

Conclusion

Given the evidence from the included systematic reviews, there is at present still some uncertainty about the effectiveness of the evaluated interventions for prevention of cognitive decline and dementia. Only single item interventions have so far been evaluated. However, since the aetiology behind dementia most likely is multifactorial, interventions addressing more than one modifiable risk factor may be needed. There is an urgent need to evaluate interventions targeting important risk factors, using RCTs and large scale population based studies, with long follow up times.

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Appendices

1 Glossary

Term	Explanation
AD	Alzheimer's disease (AD) is a progressive, degenerative disorder that attacks the brain's nerve cells, or neurons, resulting in loss of memory, thinking and language skills, and behavioural changes.
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog).
ADCS-ADL	Activities of Daily Living Inventory. An inventory of informant based items to assess activities of daily living and instrumental activities of daily living, i.e. functional performance, of Alzheimer's disease (AD).
ADL	Activities of daily living (ADL) scale.
Aerobic training	Aerobic training in physical exercise of low to high intensity that depends primarily on the aerobic energy-generating process i.e. that there is sufficient amount of oxygen to meet the body's energy demands.
Alpha-tocopherol	α-Tocopherol is a form of vitamin E that is preferentially absorbed and accumulated in humans .
Amnestic MCI	Mild Cognitive Impairment that primarily affects memory.
Bias	A bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect. Biases can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be entirely due to bias). Even a particular source of bias may vary in direction: bias due to a particular design flaw (e.g. lack of allocation concealment) may lead to underestimation of an effect in one study but overestimation in another study. It is usually impossible to

	know to what extent biases have affected the results of a particular study, although there is good empirical evidence that particular flaws in the design, conduct and analysis of randomized clinical trials lead to bias.
CDR-Sum of Boxes	The Clinical Dementia Rating Scale Sum of Boxes.
CI	Confidence Interval
CIND	Cognitive impairment no dementia (CIND) describes individuals whose cognitive functioning falls below normal but who do not meet dementia criteria. A criteria less restrictive than MCI, as it does not exclude people based on the aetiology of their cognitive impairment.
Cognitive function	An intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering.
Delayed recall	The ability to remember something after a period of rest or distraction ranging anywhere from minutes to days.
Dementia	Dementia is a loss of mental ability severe enough to interfere with normal activities of daily living, lasting more than six months, not present since birth, and not associated with a loss or alteration of consciousness. There are different types of dementia, of which the most commonly occurring is Alzheimer's disease.
Dietary supplement	A dietary supplement provide nutrients that may otherwise not be consumed in sufficient quantities and include vitamins, minerals, fiber, fatty acids, or amino acids, among other substances.
Digit span forward and backward	Digit-span task is used to measure working memory's number storage capacity. Participants are presented with a series of digits (e.g., '8, 2, 4') and must immediately repeat them back. The length of the longest list a person can remember is that person's digit span. While the participant is asked to enter the digits in the given order in the forward digit-span task, in the backward digit-span task the participant needs to reverse the order of the numbers.
Executive function	Cognitive control and supervisory attentional system. An umbrella term for the management (regulation, control) of cognitive processes, including working memory, reasoning, flexibility, and problem solving as well as planning and execution.
Frontotemporal dementia	Frontotemporal lobar degeneration is an umbrella term for a diverse group of uncommon disorders that primarily affect the

	frontal and temporal lobes of the brain i.e. the areas generally associated with personality, behaviour and language.
GRADE	Grading of Recommendations, Assessment, Development and Evaluation. A tool that is used to assess the certainty of the evidence in a systematic review.
Hedge's g	Hedges' g pool variances on the assumption of equal population variances, using n - 1 for each sample instead of n (as in Cohen's d), which provides a better estimate, especially the smaller the sample sizes. Provides the difference between the two means.
Heterogeneity	Any kind of variability among studies in a systematic review may be termed heterogeneity. Variability in the participants, interventions and outcomes studied may be described as clinical heterogeneity, and variability in study design and risk of bias may be described as methodological heterogeneity. Variability in the intervention effects being evaluated in the different studies is known as statistical heterogeneity, and is a consequence of clinical or methodological diversity, or both, among the studies. Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect due to random error (chance) alone.
HR	Hazard ratio. The instantaneous hazard rate is the limit of the number of events per unit time divided by the number at risk, as the time interval approaches 0.
Hypertension	Hypertension, also known as high blood pressure or arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is persistently elevated.
Immediate recall	The ability to remember events occurring within the past few minutes.
Imprecision	Imprecision in general, is when studies include relatively few participants, and few events, and therefore have wide confidence intervals around the estimate of effect.
Indirectness	Indirectness of evidence is when evidence comes from research that either does not directly compare the interventions of interest with control, or when the intervention is not applied to the populations of interest or if a study measures outcomes that are not direct measures important to patients but proxy measures or process measures.
Inconsistency	Inconsistency of relative (rather than absolute) treatment effects in binary/dichotomous outcomes may be determined by

	looking at the (dis)similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity (I^2).
Letter digit substitution test	Digit symbol substitution test (DSST) is a neuropsychological-test sensitive to brain damage, dementia, age and depression. It consists of (e.g. nine) digit-symbol pairs (e.g. 1/-,2/⊥ ... 7/Λ,8/X,9/=) followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g. 90 or 120 sec) is measured.
Levy body dementias	LBD is an umbrella term for two related diagnoses. LBD refers to both Parkinson's disease dementia and dementia with Lewy bodies. The earliest symptoms of these two diseases differ, but reflect the same underlying biological changes in the brain. Over time, people with both diagnoses will develop very similar cognitive, physical, sleep, and behavioral symptoms.
MCI	Mild cognitive impairment. MCI causes cognitive changes that are serious enough to be noticed by the individuals experiencing them or to other people, but the changes are not severe enough to interfere with daily life or independent function.
MMSE	The Mini Mental State Examination (MMSE) is the most commonly used test for complaints of problems with memory or other mental abilities. It can be used by clinicians to help diagnose dementia and to help assess its progression and severity. It consists of a series of questions and tests, each of which scores points if answered correctly. The MMSE tests a number of different mental abilities, including a person's memory, attention and language.
Omega-3 Fatty Acids	Omega-3 fatty acids (FAs) are poly-saturated fatty acids (PUFAs) with a double-bond (C=C) at the third carbon atom from the end of the carbon chain. Omega-3 fatty acids ae important for normal metabolism.
OR	An odds ratio (OR) is a measure of association between an exposure and an outcome. It represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure (i.e. in the control group).
Primary prevention	Primary prevention seeks to prevent the onset of specific diseases via risk reduction: by altering behaviours or exposures that can lead to disease, or by enhancing resistance to the effects of exposure to a disease agent.

Processing speed	The pace at which a person take in information, make sense of it and begin to respond.
RR	Risk ratio or relative risk. Relative risk is the ratio of the risk of disease among those exposed to a risk factor to the risk among those not exposed.
SMD	The standardized mean difference is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure depression but they use different psychometric scales). In this circumstance it is necessary to standardize the results of the studies to a uniform scale before they can be combined. The standardized mean difference expresses the size of the intervention effect in each study relative to the variability observed in that study.
Secondary prevention	Secondary prevention includes procedures that detect and treat pre-clinical pathological changes and thereby control disease progression.
SD	The standard deviation (SD) is a measure used to quantify the amount of variation of a set of data values. If close to '0' it indicates that the data points tend to be very close to the mean of the data set, while a high standard deviation indicates that the data points are spread out over a wider range of values.
SDMT	The Symbol Digit Modalities test (SDMT) involves a simple substitution task. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures.
Statins	Statins (or HMG-CoA reductase inhibitors) are a class of cholesterol lowering drugs that inhibit the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol.
Stroop test	The Stroop effect is the finding that naming the colour of the first set of words is easier and quicker than the second. In psychology, the Stroop effect is a demonstration of interference in the reaction time of a task.
TICS-m	The Modified Telephone Interview for Cognitive Status.
VAD	Vascular dementia is caused by reduced blood supply to the brain due to diseased blood vessels. It is the second most common type of dementia after AD. There are several different types of VAD that differ in the cause of the damage and the part of the brain that is affected. The different types of VAD have some symptoms in common and some symptoms that differ. Their symptoms tend to progress in different ways.

Verbal fluency test	Verbal fluency tests are a kind of cognitive test in which participants are asked to say as many words as possible from a category (e.g. animals, fruits or words that begin with a specific letter) in a given time (usually 60 seconds).
Working memory	The part of short-term memory which is concerned with immediate conscious perceptual and linguistic processing.

2 Search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R)

#	Searches	Results
1	exp Dementia/	128933
2	Lewy Bodies/	1591
3	alzheim$.mp.	111287
4	binswanger$.mp.	555
5	cadasil.mp.	996
6	cerad.tw.	501
7	dement$.mp.	98538
8	(ftld or ftd$).tw.	3680
9	((fronto?temporal or cortico?basal or fronto temporal or cortico basal or frontal lobe) adj5 (degenerat$4 or dysfunction$)).tw.	4266
10	(kluver adj5 (bucy or busy)).mp.	249
11	((lew$2 adj5 bod$3) or dlbd).mp.	7187
12	(lobar adj5 atroph$3 adj5 (brain or cerebr$2)).tw.	17
13	(mesulam adj5 syndrome$).tw.	3
14	(pick$2 adj5 (disease$1 or complex)).mp.	3987
15	posterior cortic$ atroph$.tw.	236
16	((primary or progressive) adj5 aphasi$).tw.	1311
17	sdat.tw.	648
18	sivd.tw.	118
19	((subcortic$3 or sub?cortic$3) adj5 (encephalopath$3 or leukoencephalo-path$3)).tw.	988
20	(dement$ or alzheim$).jw.	11541
21	(mesulam or huntington*).tw.	13555
22	mesulam m.au.	86
23	amentia.tw.	72
24	or/1-23 [demens]	201139
25	Cognition/	70348
26	exp Cognition Disorders/	68645
27	exp Memory Disorders/	24068
28	((cognit$ or memor$ or mental$) adj5 (disabil$ or disabl$ or declin$ or defect$ or impair$ or los$ or deteriorat$)).tw.	93040
29	(memory adj (deficit or disorder$)).tw.	3200
30	((cognit$ or behavio?r$) adj5 symptom$).tw.	20537

31	(cognit$ adj2 (abnormal$ or disorder$)).tw.	5387
32	(mci$1 or cind$1).tw.	12363
33	or/25-32 [mild kognitiv svikt]	227065
34	Primary Prevention/ or Secondary Prevention/	16433
35	pc.fs.	1077475
36	prevent*.ti,ab.	1016676
37	(early adj3 (intervention* or therap* or treatment*)).ti,ab.	80321
38	or/34-37 [forebygging]	1855764
39	(24 or 33) and 38	34224
40	systematic review.kw.	1529
41	(((systematic* or literature or integrative) adj3 (overview or review* or search*)) or meta-analys*).ti,ab.	312951
42	meta-analysis.pt.	54768
43	or/40-42	324678
44	39 and 43	1198
45	limit 44 to yr="2009 -Current"	687

Embase 1974 to 2014 November 20

#	Searches	Results
1	exp dementia/	234963
2	exp primary progressive aphasia/	1783
3	Binswanger encephalopathy/	411
4	corticobasal degeneration/	1655
5	Lewy body/	5429
6	alzheim$.mp.	152189
7	binswanger$.mp.	845
8	cadasil.mp.	1640
9	cerad.tw.	861
10	cerad.tw.	861
11	dement$.mp.	127933
12	(ftld or ftd$).tw.	5250
13	((fronto?temporal or cortico?basal or fronto temporal or cortico basal or frontal lobe) adj5 (degenerat$4 or dysfunction$)).tw.	5337
14	(kluver adj5 (bucy or busy)).mp.	311
15	((lew$2 adj5 bod$3) or dlbd).mp.	10861
16	(lobar adj5 atroph$3 adj5 (brain or cerebr$2)).tw.	24
17	(mesulam adj5 syndrome$).tw.	2
18	(pick$2 adj5 (disease$1 or complex)).mp.	5211
19	posterior cortic$ atroph$.tw.	348

20	((primary or progressive) adj5 aphasi$).tw.	1799
21	sdat.tw.	745
22	sivd.tw.	128
23	((subcortic$3 or sub?cortic$3) adj5 (encephalopath$3 or leukoencephalo-path$3)).tw.	1202
24	(dement$ or alzheim$).jw.	23003
25	(mesulam or huntington*).tw.	15654
26	mesulam m.au.	85
27	amentia.tw.	81
28	or/1-27 [demens]	280278
29	cognition/	161153
30	cognitive defect/	99835
31	exp memory disorder/	52627
32	((cognit$ or memor$ or mental$) adj5 (disabil$ or disable$ or declin$ or defect$ or impair$ or los$ or deteriorat$)).tw.	119465
33	((cognit$ or behavio?r$) adj5 symptom$).tw.	27113
34	(memory adj (deficit or disorder$)).tw.	4021
35	(cognit$ adj2 (abnormal$ or disorder$)).tw.	7696
36	(mci$1 or cind$1).tw.	19492
37	or/29-36 [mild kognitiv svikt]	341074
38	primary prevention/	28363
39	prophylaxis/	71282
40	secondary prevention/	17234
41	pc.fs.	977503
42	prevent*.ti,ab.	1207917
43	(early adj3 (intervention* or therap* or treatment*)).ti,ab.	107582
44	or/38-43 [forebygging]	2005544
45	(28 or 37) and 44	51079
46	systematic review.kw.	8906
47	(((systematic* or literature or integrative) adj3 (overview or review* or search*)) or meta-analys*).ti,ab.	363376
48	“systematic review”/	81429
49	meta analysis/	84604
50	or/46-49 [SR]	404522
51	45 and 50	1960
52	limit 51 to yr="2009 -Current"	1161
53	limit 52 to embase	1157

PsycINFO 1806 to November Week 3 2014

#	Searches	Results

1	exp dementia/	54112
2	alzheimer's disease/	32737
3	corticobasal degeneration/	230
4	kluver bucy syndrome/	52
5	alzheim$.mp.	43337
6	binswanger$.mp.	425
7	cadasil.mp.	216
8	cerad.tw.	300
9	dement$.mp.	51846
10	(ftld or ftd$).tw.	1988
11	((fronto?temporal or cortico?basal or fronto temporal or cortico basal or frontal lobe) adj5 (degenerat$4 or dysfunction$)).tw.	2368
12	(kluver adj5 (bucy or busy)).mp.	127
13	((lew$2 adj5 bod$3) or dlbd).mp.	2583
14	(lobar adj5 atroph$3 adj5 (brain or cerebr$2)).tw.	5
15	(mesulam adj5 syndrome$).tw.	2
16	(pick$2 adj5 (disease$1 or complex)).mp.	651
17	posterior cortic$ atroph$.tw.	162
18	((primary or progressive) adj5 aphasi$).tw.	915
19	sdat.tw.	325
20	sivd.tw.	55
21	((subcortic$3 or sub?cortic$3) adj5 (encephalopath$3 or leukoencephalo-path$3)).tw.	231
22	(dement$ or alzheim$).jw.	9968
23	(mesulam or huntington*).tw.	3665
24	mesulam m.au.	3
25	amentia.tw.	194
26	or/1-25 [demens]	79799
27	cognition/	21672
28	cognitive impairment/	23622
29	exp memory disorders/	8217
30	((cognit$ or memor$ or mental$) adj5 (disabil$ or disable$ or declin$ or defect$ or impair$ or los$ or deteriorat$)).ti,ab.	65797
31	((cognit$ or behavio?r$) adj5 symptom$).ti,ab.	20101
32	(memory adj (deficit or disorder$)).tw.	2843
33	(cognit$ adj2 (abnormal$ or disorder$)).ti,ab.	4073
34	(mci$1 or cind$1).ti,ab.	4157
35	or/27-34 [mild kognitiv svikt]	118087
36	Prevention/	21979
37	preventive medicine/	1763

38	prevent*.ti,ab.	150008
39	early intervention/	8704
40	(early adj3 (intervention* or therap* or treatment*)).ti,ab.	18624
41	or/36-40 [forebygging]	169892
42	(26 or 35) and 41	9685
43	"literature review"/	21991
44	meta analysis/	3473
45	(((systematic* or literature or integrative) adj3 (overview or review* or search*)) or meta-analys*).ti,ab.	80629
46	or/43-45 [SR]	96129
47	42 and 46	429
48	limit 47 to yr="2009 -Current"	236

Cinahl

S48	S41 AND S45 Limiters - Exclude MEDLINE records; Published Date: 20100101-20141231	2
S47	S41 AND S45 Limiters - Published Date: 20090101-20141231	14
S46	S41 AND S45	16
S45	S42 AND S43 AND S44	3,411
S44	TI ((((systematic* or literature or integrative) N3 (review* or overview or search*)) or meta-analys*)) OR AB ((((systematic* or literature or integrative) N3 (review* or overview or search*)) or meta-analys*))	66,155
S43	(MH "Meta Analysis")	15,067
S42	(MH "Systematic Review")	19,946
S41	S34 AND S40	12,594
S40	S35 OR S36 OR S37 OR S38 OR S39	462,399
S3	(MH "Preventive Health Care+")	139,635
S38	(MH "Early Intervention")	5,908
S37	TI ((early N3 (intervention* or therap* or treatment*))) OR AB ((early N3 (intervention* or therap* or treatment*)))	14,242
S36	TI prevent* OR AB prevent*	136,404
S35	MW pc OR MJ pc	283,361

S34	S24 OR S33	90,993
S33	S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32	57,280
S32	TI (mci* or cind*) OR AB (mci* or cind*)	1,848
S31	TI ((cognit* N2 (abnormal* or disorder*))) OR AB ((cognit* N2 (abnormal* or disorder*)))	876
S30	TI (((cognit* or behavio?r*) N5 symptom*)) OR AB (((cognit* or behavio?r*) N5 symptom*))	2,665
S29	TI (((cognit* or memor* or mental*) N5 (disabil* or disable* or declin* or defect* or impair* or los* or deteriorat*)) or (memory W0 (deficit or disorder*))) OR AB (((cognit* or memor* or mental*) N5 (disabil* or disabel* or declin* or defect* or impair* or los* or deteriorat*)) or (memory W0 (deficit or disorder*)))	16,642
S28	(MH "Memory+")	12,749
S27	(MH "Memory Disorders+") Search modes - Boolean/Phrase Interface - EBSCOhost Research Databases	3,484
S26	(MH "Cognition Disorders+")	13,114
S25	(MH "Cognition+")	24,111
S24	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	43,984
S23	TI amentia OR AB amentia	1
S22	AU mesulam	40
S21	TI ((mesulam or huntington*)) OR AB ((mesulam or huntington*))	719
S20	SO dement* or alzheim*	5,022
S19	TI (((subcortic* or sub?cortic*) N5 (encephalopath* or leukoencephalopath*))) OR AB (((subcortic* or sub?cortic*) N5 (encephalopath* or leukoencephalopath*)))	102
S18	TI sivd OR AB sivd	19
S17	TI sdat OR AB sdat	17
S16	TI (((primary or progressive) N5 aphasi*)) OR AB (((primary or progressive) N5 aphasi*))	331

S15	TI posterior cortic* atroph* OR AB posterior cortic* atroph*	51
S14	TI ((pick* N5 (diseases or complex))) OR AB ((pick* N5 (diseases or complex)))	10
S13	TI (mesulam N5 syndrome*) OR AB (mesulam N5 syndrome*)	0
S12	TI ((lobar N5 atroph* N5 (brain or cerebr*))) OR AB ((lobar N5 atroph* N5 (brain or cerebr*)))	1
S11	TI (((lew* N5 (body or bodies)) or dlbd)) OR AB (((lew* N5 (body or bodies)) or dlbd))	615
S10	TI ((kluver N5 (bucy or busy))) OR AB ((kluver N5 (bucy or busy)))	6
S9	TI (((frontotemporal or corticobasal or fronto temporal or cortico basal or frontal lobe) N5 (degenerat* or dysfunction*))) OR AB (((frontotemporal or corticobasal or fronto temporal or cortico basal or frontal lobe) N5 (degenerat* or dysfunction*)))	398
S8	TI (ftld or ftd*) OR AB (ftld or ftd*)	380
S7	TI dement* OR AB dement*	21,186
S6	TI cerad OR AB cerad	78
S5	TI cadasil OR AB cadasil	120
S4	TI binswanger* OR AB binswanger*	26
S3	TI alzheim* OR AB alzheim*	12,136
S2	(MH "Aphasia+")	3,300
S1	(MH "Dementia+")	35,097

CDSR

#1	MeSH descriptor: [Dementia] explode all trees	3863
#2	MeSH descriptor: [Lewy Bodies] this term only	6
#3	alzheim*:ti,ab,kw	5076
#4	binswanger*:ti,ab,kw	6
#5	cadasil:ti,ab,kw	15
#6	cerad:ti,ab,kw	16
#7	dement*:ti,ab,kw	5327
#8	ftld or ftd*:ti,ab,kw	53
#9	((frontotemporal or corticobasal or fronto temporal or cortico basal or frontal lobe) near/5 (degenerat* or dysfunction$*)):ti,ab,kw	50
#10	(kluver near/5 (bucy or busy)):ti,ab,kw	1
#11	((lew* near/5 bod*) or dlbd):ti,ab,kw	128
#12	(lobar near/5 atroph* near/5 (brain or cerebr*)):ti,ab,kw	0
#13	mesulam near/5 syndrome*:ti,ab,kw	0
#14	pick* near/5 (disease* or complex):ti,ab,kw	38
#15	posterior next cortic* next atroph*:ti,ab,kw	1
#16	((primary or progressive) near/5 aphasi*):ti,ab,kw	11

#17	sdat:ti,ab,kw	42
#18	sivd:ti,ab,kw	5
#19	(subcortic* near/5 (encephalopath* or leukoencephalopath*)):ti,ab,kw	15
#20	mesulam or huntington*:ti,ab,kw	184
#21	amentia:ti,ab,kw	1
#22	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	8991
#23	MeSH descriptor: [Cognition] this term only	4956
#24	MeSH descriptor: [Cognition Disorders] explode all trees	2823
#25	MeSH descriptor: [Memory Disorders] explode all trees	909
#26	((cognit* or memor* or mental*) near/5 (disabil* or disable* or declin* or defect* or impair* or los* or deteriorat*)) or (memory next (deficit or disorder*)):ti,ab,kw	7836
#27	((cognit* or behavio*) near/5 symptom*):ti,ab,kw	2359
#28	(cognit* near/2 (abnormal* or disorder*)):ti,ab,kw	3315
#29	mci* or cind*:ti,ab,kw	2920
#30	#23 or #24 or #25 or #26 or #27 or #28 or #29	20294
#31	MeSH descriptor: [Primary Prevention] explode all trees	3506
#32	MeSH descriptor: [Secondary Prevention] explode all trees	257
#33	Any MeSH descriptor with qualifier(s): [Prevention & control - PC]	77444
#34	prevent*:ti,ab,kw	73266
#35	(early near/3 (intervention* or therap* or treatment*)):ti,ab,kw	8571
#36	#31 or #32 or #33 or #34 or #35	131591
#37	(#22 or #30) and #36 Publication Year from 2009 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Technology Assessments	410

CRD

Line	Search for	Hits
1	MeSH DESCRIPTOR Dementia EXPLODE ALL TREES	612
2	MeSH DESCRIPTOR Lewy Bodies EXPLODE ALL TREES	0
3	(alzheim*)	523
4	(binswanger*)	4
5	(cadasil)	1
6	(cerad)	6
7	(dement*)	825
8	(ftld or ftd*)	4
9	((frontotemporal or corticobasal or fronto temporal or cortico basal or frontal lobe) near5 (degenerat* or dysfunction$*))	4
10	(kluver near5 (bucy or busy))	0
11	((lew* near5 bod*) or dlbd)	19
12	(lobar near5 atroph* NEAR5 (brain or cerebr*))	0
13	(mesulam near5 syndrome*)	0

Line	Search for	Hits
14	(pick* near5 (disease* or complex))	5
15	(posterior next cortic* next atroph*)	0
16	((primary or progressive) near5 aphasi*)	0
17	(sdat)	2
18	(sivd)	2
19	(subcortic* near5 (encephalopath* or leukoencephalopath*))	1
20	(mesulam or huntington*)	24
21	(amentia)	0
22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1083
23	MeSH DESCRIPTOR Cognition EXPLODE ALL TREES	221
24	MeSH DESCRIPTOR Cognition Disorders EXPLODE ALL TREES	254
25	MeSH DESCRIPTOR Memory Disorders EXPLODE ALL TREES	36
26	((cognit* or memor* or mental*) near5 (disabil* ir disable* or declin* or defect* or impair* or los* or deteriorat*)) or ((memory near0 (deficit or disorder*))	1392
27	((cognit* or behavio*) near5 symptom*)	171
28	(cognit* near2 (abnormal* or disorder*))	297
29	(mci* or cind*)	327
30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	2122
31	MeSH DESCRIPTOR Primary Prevention EXPLODE ALL TREES	812
32	MeSH DESCRIPTOR Secondary Prevention EXPLODE ALL TREES	89
33	(prevent*)	16401
34	(early near3 (intervention* or therap* or treatment*))	0
35	#31 OR #32 OR #33 OR #34	16515
36	#22 OR #30	2756
37	#35 AND #36	649
38	* IN DARE, HTA FROM 2009 TO 2014	34131
39	#37 AND #38	186

Pubmed 241114

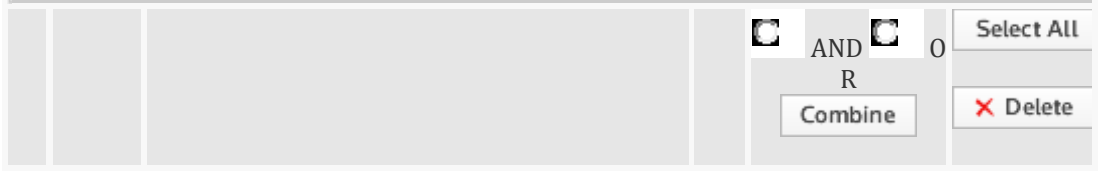
Search ((((((prevent* OR (early AND (intervention* OR therap* OR treatment*))))) AND ((((systematic* OR integrative OR literature) AND (review* OR overview* OR search*)) OR meta-analys* OR medline OR pubmed OR embase))) AND (((alzheim* OR dement* OR "lewy body" OR "lewy bodies" OR binswanger* OR cadasil OR cerda OR ftld OR ftd* OR ((frontotemporal OR corticobasal) AND (degenerat* OR dysfunction*)) OR (kluver AND (bucy OR busy)) OR dlbd OR (lobar AND atroph* AND (brain OR cerebral*)) OR mesulam* OR (pick* AND (disease* OR complex)) OR (posterior AND cortic* AND atroph*) OR aphasi* OR sdat OR sivd OR (subcortic* AND (encephalopath* OR leukoencephalopath*)) OR huntington* OR amentia)) OR ((((cognit* or

memor* or mental*) and (disable* or disabil* or declin* or defect* or impair* or los* or deteriorat*)) OR (memory disorder* or memory deficit) or ((cognit* or behavio*) AND symptom*) OR (cognit* AND (abnormal* or disorder*)) OR mci* OR cind*))))) AND publisher [sb]

Search History: Web of ScienceTM Core Collection

Set	Results	Save History / Create Alert / Open Saved History	Edit Sets	Combine Sets (AND / OR / Combine)	Delete Sets (Select All / Delete)
#7	1,686	#6 AND #5 *Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014*	Edit	Select to combine sets.	Select to delete this set.
#6	170,236	**TOPIC:** (((systematic* OR integrative OR literature) AND (review* OR overview* OR search*))) *Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014*	Edit	Select to combine sets.	Select to delete this set.
#5	26,796	#4 AND #3 *Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014*	Edit	Select to combine sets.	Select to delete this set.
#4	509,052	**TOPIC:** ((prevent* OR (early AND (intervention* OR therap* OR treatment*)))) *Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014*	Edit	Select to combine sets.	Select to delete this set.
#3	213,833	#2 OR #1 *Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014*	Edit	Select to combine sets.	Select to delete this set.
#2	151,467	**TOPIC:** ((((cognit* or memor* or mental*) and (disabil* or disable* or declin* or defect* or impair* or los* or deteriorat*)) OR (memory and (disorder* or deficit)) or ((cognit* or behavio*) AND symptom*) OR (cognit* AND (abnormal* or disorder*)) OR mci* OR cind*)) *Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014*	Edit	Select to combine sets.	Select to delete this set.
#1	94,246	**TOPIC:** ((alzheim* OR dement* or "lewy body" OR "lewy bodies" OR binswanger* OR cadasil OR cerad OR ftld OR ftd* or ((frontotemporal OR corticobasal) AND (degenerat* OR dysfunction*)) OR (kluvy AND (bucy OR busy)) OR dlbd OR (lobar AND atroph* AND (brain OR cerebral*)) OR mesulam* OR (pick* AND (disease* OR complex)) OR (posterior AND cortic* AND atroph*) OR aphasi* OR sdat OR sivd OR	Edit	Select to combine sets.	Select to delete this set.

(subcortic* AND (encephalopath* or leu-
koencephalopath*)) OR huntington* OR amen-
tia))
Indexes=SCI-EXPANDED, SSCI Timespan=2009-2014



3 Excluded reviews and reasons for exclusion

Table 18. Excluded reviews and reasons for exclusion.

First author (ref no.)	Reason for exclusion
Aarsland 2010 (111)	Not a systematic review (no assessment of studies' methodological quality)
Barnes 2012(112)	Not a population without dementia diagnosis
Blondell 2014 (53)	Not a systematic review of high methodological quality (moderate)
Cheng 2015 (54)	Not a systematic review of high quality (moderate)
Cooper 2013 (55)	Not a systematic review of high methodological quality (moderate)
Dangour 2010 (56)	Not a systematic review of high methodological quality (moderate)
Etgen 2012(113)	Not a systematic review (no assessment of studies' methodological quality)
Faucounau 2010 (114)	Not a systematic review (no assessment of studies' methodological quality)
Forbes 2015 (58)	Not a systematic review of highmethodological quality (low to moderate quality). Also cognitively healthy people and cognitively impaired people are not analysed separately.
Fotuhi 2009 (115)	Not a systematic review (no assessment of studies' methodological quality)
Franco-Martin 2013 (116)	Not a systematic review (no assessment of studies' methodological quality)
Gizachew 2012 (117)	Not a systematic review (no assessment of studies' methodological quality)
Jiao 2014 (63)	Mixed groups. Data from people with mild to moderate cognitive impairment, were not separately analysed.
Kim 2014 (118)	There is no full description of the systematic review (abstract only)
Kueider 2012 (119)	Not a systematic review (no assessment of studies' methodological quality)
Kuiper 2015 (64)	Not an intervention review
Law 2014 (66)	Mixed groups. Data from people with cognitive impairment and dementia were not separately analysed
Leung 2014 (67)	Not a population without dementia diagnosis
Li 2014 (68)	Not a systematic review of high mthodological quality (moderate).
Ligthart 2010 (120)	Not a systematic review (no assessment of studies' methodological quality)
Loef 2012 (69)	Not a systematic review of high methodological quality (moderate)
Lopez-Leon 2013 (121)	There is no full description of the systematic review (abstract only)

Lourida 2013 (70)	Not an intervention review
Maidment 2013 (122)	Not an intervention to prevent dementia
Martin 2011 (87)	Not a systematic review of high methodological quality (moderate to low quality)
Mauer 2014 (123)	Not a systematic review (no assessment of studies' methodological quality)
Muangpaisan 2010 (74)	Not a systematic review of high methodological quality (moderate)
Naqvi 2013 (124)	Not a systematic review (no assessment of studies' methodological quality)
Ooi Cheow 2011 (125)	Not a prevention intervention for dementia
Opie 2013 (75)	Not a systematic review of high methodological quality (moderate)
Ott 2015 (126)	Not a prevention intervention for dementia
Regan 2013 (76)	Not a systematic review of high methodological quality (low)
Rouch 2015 (77)	Not a systematic review of high methodological quality (moderate quality). Also, cognitively healthy and cognitively impaired (and people with dementia) are not reported separately
Ruiz Aragon 2010 (127)	Not a population without dementia diagnosis
Santos 2010 (128)	Not a systematic review (no assessment of studies' methodological quality)
Simon 2012 (129)	Not a systematic review (no assessment of studies' methodological quality)
Sofi 2011 (130)	Not a systematic review (no assessment of studies' methodological quality)
Stern 2010 (79)	Not a systematic review of high methodological quality (moderate)
Stern 2009 (80)	Not a systematic review of high methodological quality (moderate)
Swiger 2013 (81)	Not a systematic review of high methodological quality (moderate)
Tseng 2011 (82)	Not a systematic review of high methodological quality (moderate)
Valenzuela 2009 (83, 131)	Not a systematic review of high methodological quality (moderate)
Van der Schaft 2013 (132)	Not a systematic review (no assessment of studies' methodological quality)
Wald 2010 (133)	Not a systematic review (no assessment of studies' methodological quality)
Weih 2010 (134)	Not a systematic review (no assessment of studies' methodological quality)
Wong 2013 (32)	Not a systematic review (no assessment of studies' methodological quality)
Yang 2014 (135)	Not a population without dementia diagnosis
Zheng 2015 (86)	Not a systematic review of high methodological quality (moderate)

4 Assessment of methodological quality

We used the Knowledge Centre's checklist for systematic reviews for assessing the systematic reviews included in out overview of reviews.
The checklist consists of 9 questions which all answers with a 'yes', 'unclear' or 'no'.
1. Did the authors of the review clearly describe what methods they used to identify primary studies?
2. Was a comprehensive literature search conducted?
3. Did the review authors describe what criteria they used to assess the eligibility of studies for inclusion (study design, participants, intervention, and end-points)?
4. Did the authors attempt to prevent bias when selecting studies by using explicit eligibility criteria, and by independent eligibility assessment of studies by at least two people?
5. Was a set of criteria to assess intern validity of original studies described?
6. Was the validity of included studies assessed (either at inclusion of primary studies or in the analysis of primary studies) using relevant criteria?
7. Were the methods used when summarizing the results clearly described?
8. Were the results summarized in an appropriate way?
9. Are the authors' conclusions supported by the data and/or the analysis reported in the review?

Overall assessment of each review (Question 10. How will you rank the methodological quality of this review?) is it judged as being 'high', ' moderate' or 'unclear' on the basis of the following:

- High quality: Used if all or most of the checklist criteria are answered with a 'yes' (adequate). If some of the criteria are not fulfilled, it must be clear that this will not have an effect on the conclusion of the review.
- Moderate quality: Used if some of the checklist criteria are not fulfilled or not satisfactory described. The overall assessment indicates that the likelihood that this would have an effect on the review conclusions is very small.
- Unclear quality: Used if few or no criteria from the checklist are fulfilled, and/or not adequately described. Overall assessment indicates that it is likely that the review's conclusion may change due to this.

Table 19. Results of the assessment of the methodological quality of included reviews (n=8).

Review	1	2	3	4	5	6	7	8	9
Farina 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lampit 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Un-clear	Yes
Mazereeuw 2012	Yes	Yes	Yes	Un-clear	Yes	Yes	Yes	Yes	Yes
McGuinness 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McGuinness 2016	Yes	Yes	Yes	Yes	Yes	Un-clear	Yes	Yes	Yes
Russ 2012	Yes	Un-clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sydenham 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Young 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Un-clear	Yes

Note: None of the included reviews had used the GRADE tool to grade the certainty of the evidence, or reported their main results in a Summary of findings table.

5 Ongoing reviews

Table 20. Ongoing reviews and overviews of reviews.

Author Year	Protocol title
Abraham 2015 (136)	Vitamin and mineral supplementation for prevention of dementia or delaying cognitive decline in people with mild cognitive impairment
Forbes 2015 (137)	Exercise interventions for maintaining cognitive function in cognitively healthy people in late life
Forbes 2015 (138)	Exercise interventions for preventing dementia or delaying cognitive decline in people with mild cognitive impairment
Forbes 2015	Exercise interventions for maintaining cognitive function in cognitively healthy people in mid life
Harrison 2015 (139)	Dietary interventions for maintaining cognitive function in cognitively healthy people in mid life
Jordan 2015 (140)	Aspirin and anti-inflammatory drugs for the prevention of dementia
Krause 2015 (141)	Dietary interventions as a neuroprotective therapy for the delay of the onset of cognitive decline in older adults: an umbrella review protocol
Siervo 2015 (142)	Dietary interventions for maintaining cognitive function in cognitively healthy people in late life.
Tang 2015 (143)	Dietary interventions for prevention of dementia in people with mild cognitive impairment

6 Description of included reviews

Table 21. Description of included reviews (listed in alphabetical order; n=8).

Farina 2009 (42)	**Description of review**
Population:	People (n=569) with mild cognitive impairment from the USA and Canada
Intervention:	Vitamin E supplements (2000 IU per day) for 3 years
Comparator:	Placebo
Outcomes:	Time to progression to possible or probable AD
Included studies:	3 RCTs (Lloret 2009, Petersen 2005*, Sano 1996) * Included in this overview of reviews (one study out of 3).
Lampit 2014 (65)	**Description of review**
Population:	Cognitively healthy older people (n=4, 885) largely from the USA or Europe, but also from Canada, Australia, Israel, China, Taiwan Special Administrative Region, Republic of Korea, Japan and Australia
Intervention:	>4 hours computerized cognitive training
Comparator:	In 50% of studies the comparator was passive (no intervention) and in the remaining studies the control condition was another active intervention.
Outcomes:	Performance in neuropsychological tests (not further described).
Included studies:	52 trials (Ackerman 2010; Anderson 2013; Anguera 2013; Ball 2002; Barnes 2013; Basak 2008; Belchier study 1 2013; Belchior study 2 2013; Berry 2010; Boot 2013; Bottiroli 2009; Bozoki 2013; Brehmer 2012; Burki 2014; Buschkuehl 2008; Casutt 2014; Colzato 2011; Dahlin 2008; Dustman 1992; Edwards 2002; Edwards 2005, Edwards 2013; Garcia-Campuzano 2013; Goldstein 1997; Heinzel 2013; Lampit 2014; Lee 2012; Legault 2011; Li 2010; Lussier 2012; Mahncke 2006; Maillot 2012; Mayas 2014; McAvinue 2013; Miller 2013; Nouchi 2012; O'Brien 2013; Peng 2012; Peretz 2011; Rasmusson 1999; Richmond 2011; Sandberg 2014; Shatil 2013; Shatil 2014; Simpson 2012; Smith 2009; Stern 2011;Vance 2007; Van Muijden 2012; von Bastian 2013; Wang 2011, Wolinski 2011). All 52 trials were included in our overview of reviews.
Mazereeuw 2012 (71)	**Description of review**
Population:	Cognitively healthy people (n=1,218), and cognitively Impaired people (n=670), with no dementia diagnosis from the

	Netherlands, England, Wales, Japan, Australia, Israel and the USA
Intervention:	Omega-3 Fatty Acids
Comparator:	Placebo
Outcomes:	Change in cognitive test scores (Immediate recall; delayed recall, recognition, working memory and executive function, attention and processing speed).
Included studies:	10 trials (3 trials that included cognitively healthy people: Dangour 2010*; Johnson 2008*; Van de Rest 2008*; 4 RCTs that included people with CIND (Kotani 2006*; Sinn 2011*; Vakhapora 2010*; Yurko-Mauro 2010*) and three studies targeting people with AD (Chiu 2008; Freund-Levi 2006; Quinn 2010). Included in this overview (4 out of 10 trials, i.e. the trials of cognitively impaired people).
McGuinness 2016 (72)	**Description of review**
Population:	Cognitively healthy people (n=26,340) aged 40 to 82 years of whom 11,610 were aged 70 or older, and with evidence of cerebrovascular disease or at high risk of cerebrovascular disease from UK, Scotland, Ireland and the Netherlands
Intervention:	Cholesterol lowering drugs i.e. any member of the statin family. Dose: 40 mg per day.
Comparator:	Placebo
Outcomes:	Primary outcomes: objective diagnosis of dementia, AD or VAD according to standard criteria, change in cognitive test scores (MMSE, ADAS-cog or other accepted objective and standardized tests). Secondary outcomes: cholesterol level; incidence and severity of adverse effects, change in cognitive status in patients at risk of dementia on treatment with statins accounting for prior cholesterol level, APOE genotype and cognitive level, quality of life, change in Activities of Daily Living (ADL), and change in behaviour
Included studies:	2 RCTs (HPS 2002 and PROSPER 2002) of which both were relevant for this overview of reviews
McGuinness 2009 (73)	**Description of review**
Population:	Cognitively healthy people (n=15,936) with a diagnosis of hypertension and an average age of 75.4 years (range 60 to 89),

	from Europe (East and West), North America, China, and to a lesser extent from Australasia and Tunisia.
Intervention:	Antihypertensive drugs Note: The review authors aimed to include also studies evaluating non-pharmacological hypertension treatment in the review, but found only studies evaluating pharmacological therapy
Comparator:	Placebo
Outcomes:	Primary outcomes: Incidence of dementia (diagnosed according to standard diagnostic criteria or those appropriate at the time), change in cognitive test scores Secondary outcomes: Blood pressure level, incidence and severity of adverse effects, and quality of life
Included studies:	4 RCTs (HYVET 2008; SCOPE 2003; SHEP 1991, SystEur 1997) All studies were eligible for inclusion in our overview of reviews.
Russ 2012 (78)	**Description of review**
Population:	People with mild cognitive impairment (n=5,149) from the USA, Canada, Germany, Singapore, and from a number of countries that were not named
Intervention:	Cholinesterase inhibitors (of any dose but at least one months' duration)
Comparator:	Placebo
Outcomes:	Progression to dementia, either in general or specific subtypes, side effects, Secondary outcomes: change in cognitive test scores
Included studies:	8 RCTs (Doody 2009, Petersen 2005a; Salloway 2004; Feldman 2007, Koontz 2005; Narasimhalu 2010, Winblad 2008 (combined)). All 8 studies were included in this overview of reviews.
Sydenham 2012 (40)	**Description of review**
Population:	Cognitively healthy people (n=4,080), 60 years and older from the Netherlands, England and Wales. In one study the location was unknown.
Intervention:	Vitamin E supplements (capsules or enriched margarine)
Comparator:	Placebo or usual margarine

Outcomes:	Measures of cognitive function, adverse effects and adherence to therapy.
Included studies:	3 RCTs, of which one trial included two interventions (Dangour 2010; Geleijnse 2011; Van de Rest 2008 high and medium dose). All studies were relevant for this overview of reviews.
Young 2015 (85)	**Description of review**
Population:	Cognitively healthy people (N= 754); mean age ranged from 61 to 91 years across the studies which were from USA, France and Canada
Intervention:	Aerobic exercise training
Comparator:	No intervention or other active intervention
Outcomes:	Measures of cognitive function, adverse effects and drop-out. In addition, an objective measure of cardiorespiratory fitness was required.
Included studies:	11 RCTS (Bakken 2001, Blumenthal 1989, Emery 1990a, Fabre 2002, Kramer 2001, Langlois 2012, Legault 2011, Madden 1989 , Moul 1995, Oken 2006, Panton 1990, Whitehurst 1991) of which all were relevant for our overview of reviews.

7 GRADE evidence profiles

GRADE evidence profiles for the eight included reviews are found below organised in alphabetical order.

Author(s): Flodgren G, Berg R
Date: 11.12.15
Question: Vitamin E compared to placebo for prevention of Alzheimer's disease in people with mild cognitive impairment
Setting: USA and Canada
Bibliography: Farina N, Isaac MG, Clark AR, Rusted J, Tabet N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD002854. DOI:10.1002/14651858.CD002854.pub3.

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Vitamin E**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Possible or probable Alzheimer's disease (follow up: mean 3 years; assessed with: no information)											
1	randomised trials	not serious	not serious	not serious	serious [1,2]	none	76/257 (29.6%)	73/259 (28.2%)	**HR 1.02** (0.74 to 1.41)	**5 more per 1000** (from 65 fewer to 91 more)	⊕⊕⊕◯ MODERATE

HR – hazard ratio; CI: confidence interval

1. Only one study. Relatively small groups.
2. Wide CI overlapping no effec

Author(s): Flodgren G, Berg R
Date: 17.12.15
Question: Computerised cognitive training compared to active or passive intervention for prevention of age-related cognitive decline in cognitively healthy older people
Setting: the participants' homes (unsupervised training) and in other facilities (centre-based group training). Trials mainly from the USA or Europe, with the addition of studies from Canada, Australia, Israel, China, Taiwan Special Administrative region, Republic of Korea and Japan
Bibliography: Lampit A, Hallock H, Valenzuela M (2014) Computerized Cognitive Training in Cognitively Healthy Older Adults: A Systematic Review and Meta-Analysis of Effect Modifiers. PLoS Med 11(11): e1001756. doi:10.1371/journal.pmed.1001756

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Computerised cognitive training**	**Active or passive intervention**	**Relative (95% CI)**	**Absolute (95% CI)**	
Cognitive test scores (assessed with: no information)											
52	randomised trials	serious [1]	not serious	not serious	not serious	none	2527	2358	-	MD **0.22 higher** (0.15 higher to 0.29 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **MD:** Mean difference

1. Thirty-three of 52 studies at high risk of bias. Eighteen studies were at low risk.

Author(s): Flodgren G, Berg R
Date: 17.12.15
Question: Omega-3 fatty acids to improve cognitive function as compared to placebo for people with cognitive impairment no dementia (CIND)
Setting: the Netherlands, England, Wales, japan, Israel and the US
Bibliography: Mazereeuw G, Lanctot KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging 2012. Jul;33 (7):1482.e17-29.

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Omega-3 fatty acids**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Cognitive test scores - Composite memory (follow up: median 14.5 weeks; assessed with: unclear)											
4	randomised trials	not serious	not serious	not serious	not serious	none	349	327	-	MD **0.1 higher** (0.06 lower to 0.25 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores - Immediate recall (follow up: median 19.5 weeks; assessed with: unclear)											
4	randomised trials	not serious	not serious	not serious	not serious	none	349	327	-	MD **0.16 higher** (0.01 higher to 0.32 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores - Delayed recall (follow up: median 19.5 weeks; assessed with: unclear)											
4	randomised trials	not serious	not serious	not serious	not serious	none	349	327	-	MD **0.03 higher** (0.12 lower to 0.18 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores - Recognition (assessed with: unclear)											
3	randomised trials	not serious	not serious	not serious	not serious	none	337	318	-	MD **0.03 lower** (0.18 lower to 0.13 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores - Attention and processing speed (assessed with: unclear)											
3	randomised trials	not serious	not serious	not serious	not serious	none	107	86	-	MD **0.32 higher** (0.03 higher to 0.61 higher)	⊕⊕⊕⊕ HIGH

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Omega-3 fatty acids**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Cognitive test scores - Working memory and executive function (assessed with: unclear)											
2	randomised trials	not serious	not serious	not serious	not serious	none	277	256	-	MD **0.04 higher** (0.13 lower to 0.21 higher)	⨁⨁⨁⨁ HIGH
Cognitive test scores - MMSE (follow up: mean 24 weeks; assessed with: MMSE)											
1	randomised trials	not serious	not serious	not serious	not serious	none	242	241	-	MD **0.06 lower** (0.23 lower to 0.12 higher)	⨁⨁⨁⨁ HIGH

CI: Confidence interval; **MD:** Mean difference

Author(s): Flodgren G, Berg R
Date: 11.12.15
Question: Blood pressure lowering drugs compared to placebo for the prevention of dementia in cognitively healthy people with hypertension
Setting: Western and Eastern Europe, North America, China and to a lesser extent Australasia and Tunisia
Bibliography: McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD004034. DOI: 10.1002/14651858.CD004034.pub3.

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antihypertensive drugs**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Incidence of dementia (follow up: median 2.8 years; assessed with: DSM III-R, DSM-IV, ICD 10, MMSE)											
4	randomised trials	not serious	not serious	not serious	serious [1]	none	236/7767 (3.0%)	259/7660 (3.4%)	**OR 0.89** (0.74 to 1.07)	**4 fewer per 1000** (from 2 more to 9 fewer)	⊕⊕◯◯ **LOW**
Change in cognitive test scores from baseline (MMSE) (follow up: range 1.8 years to 4.5 years; Scale from: 0 to 30)											
3	randomised trials	not serious	serious [2]	not serious	not serious	none	5402	5238	-	MD **0.42 higher** (0.3 higher to 0.53 higher)	⊕⊕⊕◯ MODERATE
Adverse events (follow up: range 2 years to 4.5 years)											
3	randomised trials	not serious	Serious[2]	not serious	not serious	none	1138/6080 (18.7%)	1117/6011 (18.6%)	**OR 1.01** (0.92 to 1.11)	**2 more per 1000** (from 12 fewer to 16 more)	⊕⊕⊕◯ MODERATE

MD – mean difference, OR – odds ratio

1. Wide CI.
2. High heterogeneity: I^2=98%.

Author(s): Flodgren G, berg R
Date: 17.12.15
Question: Statins compared to placebo for prevention of dementia in cognitively healthy people
Setting: UK, Ireland and the Netherlands
Bibliography: McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No.: CD003160. DOI: 10.1002/14651858.CD003160.pub3

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Dementia incidence (follow up: range 3.2 years to 5 years)											
1	randomised trials	not serious	not serious	not serious	serious [1]	none	31/10269 (0.3%)	31/10267 (0.3%)	**OR 1.00** (0.61 to 1.65)	**0 fewer per 1000** (from 1 fewer to 2 more)	⊕⊕⊕◯[1] MODERATE
Change in cognitive test scores from baseline (MMSE) (follow up: range 3.2 years to 5 years)											
1	randomised trials	not serious	not serious	not serious	not serious	none	2891	2913	-	MD **0.06 higher** (0.04 lower to 0.16 higher)	⊕⊕⊕⊕ HIGH
Change in cognitive test scores from baseline (Stroop) (follow up: range 3.2 years to 5 years)											
1	randomised trials	not serious	not serious	not serious	serious [1]	none	2891	2913	-	MD **0.8 higher** (0.38 lower to 1.98 higher)	⊕⊕⊕◯[1] MODERATE
Change in cognitive test scores from baseline (Picture world) (follow up: range 3.2 years to 5 years)											
1	randomised trials	not serious	not serious	not serious	not serious	none	2891	2913	-	MD **0.02 higher** (0.12 lower to 0.16 higher)	⊕⊕⊕⊕ HIGH
Change in cognitive test scores from baseline (Letter digit test) (follow up: range 3.2 years to 5 years)											
1	randomised trials	not serious	not serious	not serious	not serious	none	2891	2913	-	MD **0.01 lower** (0.25 lower to 0.23 higher)	⊕⊕⊕⊕ HIGH

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	Placebo	Relative (95% CI)	Absolute (95% CI)	
Cognitive test scores- TICS-m at final visit (follow up: range 3.2 years to 5 years)											
1	randomised trials	not serious	not serious	not serious	not serious	none	10269	10267	-	MD **0.02 higher** (0.12 lower to 0.16 higher)	⨁⨁⨁⨁ HIGH
Adverse effects requiring discontinuation of treatment (follow up: range 3.2 years to 5 years)											
2	randomised trials	not serious	not serious	not serious	not serious	none	13160	13180	-	OR **0.94 higher** (0.83 higher to 1.05 higher)	⨁⨁⨁⨁ HIGH

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

1. Wide CI.

Author(s): Flodgren G, Berg R
Date: 11.12.15
Question: Cholinesterase inhibitors compared to placebo for people with mild cognitive impairment no dementia
Setting: USA, Canada, Singapore and a number of other countries
Bibliography: Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database Syst Rev [Internet]. 2012 [cited CDSR 211114; (9).

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cholinesterase inhibitors	Placebo	Relative (95% CI)	Absolute (95% CI)	
Conversion to dementia (follow up: mean 3 years; assessed with: NINCDS-ADRDA with or without DSM-IV, and without explicit criteria in one study)											
2	randomised trials	not serious	not serious [2]	not serious	serious	none	151/761 (19.8%)	182/769 (23.7%)	RR 0.84 (0.70 to 1.02)	38 fewer per 1000 (from 5 more to 71 fewer)	⊕⊕⊕◯ MODERATE
Cognitive test scores - ADAS-Cog (follow up: mean 2 years; assessed with: ADAS-Cog (modified))											
4	randomised trials	not serious	serious [1]	not serious	serious [2]	none	1321	1354	-	MD 0.78 lower (1.92 lower to 0.35 higher)	⊕⊕◯◯ LOW
Any adverse event											
5	randomised trials	not serious	serious [3]	not serious	not serious	none	1849/2101 (88.0%)	1737/2106 (82.5%)	RR 1.09 (1.02 to 1.16)	74 more per 1000 (from 16 more to 132 more)	⊕⊕⊕◯ MODERATE
Cognitive test scores - CDR Sum of boxes (follow up: mean 1 years)											
2	randomised trials	not serious	not serious	not serious	not serious	none	632	637	-	MD 0.1 lower (0.11 lower to 0.09 lower)	⊕⊕⊕⊕ HIGH
Cognitive test scores- Symbol digit modalities (follow up: mean 6 months)											
2	randomised trials	not serious	serious [4]	not serious	very serious [5]	none	155	157	-	MD 0.17 higher (2.87 lower to 3.21 higher)	⊕◯◯◯ VERY LOW
Cognitive test scores -Mini Mental State Examination (follow up: mean 1 years; Scale from: 0 to 30)											
2	randomised trials	not serious	serious [3]	not serious	serious [6]	none	632	637	-	MD 0.24 higher (0.13 lower to 0.61 higher)	⊕⊕◯◯ LOW
Cognitive test scores - ADCS-ADL (follow up: mean 1 years; Scale from: 0 to 78)											
3	randomised trials	not serious	not serious	not serious	serious [5]	none	1191	1217	-	MD 0.15 higher (0.27 lower to 0.57 higher)	⊕⊕⊕◯ MODERATE
Serious adverse events											

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cholinesterase inhibitors	Placebo	Relative (95% CI)	Absolute (95% CI)	
5	randomised trials	not serious	not serious	not serious	serious [2]	none	391/2101 (18.6%)	401/2106 (19.0%)	RR 0.97 (0.86 to 1.10)	6 fewer per 1000 (from 19 more to 27 fewer)	⊕⊕⊕◯ MODERATE

MD – mean difference, RR – risk ratio

1. High heterogeneity: I2=98%.
2. Wide CI overlapping no effect.
3. High heterogeneity: I^2=79%.
4. High heterogeneity: I^2=99%
5. Wide CI overlapping no effect.
6. Wide CI overlapping no effect.

Author(s): Flodgren G, Berg R
Date: 17.12.15
Question: Omega-3 fatty acids compared to placebo for prevention of cognitive decline and dementia in cognitively healthy older people
Setting: England and Wales
Bibliography: Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev 2012;6:CD005379. (NB! Also published in Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Sao Paulo Med J 2012;130(6):419.)

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Omega-3 fatty acids**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Cognitive test scores - MMSE (follow up: range 24 months to 40 months)											
2	randomised trials	not serious	serious [1]	not serious	not serious	none	990	2231	-	MD **0.07 lower** (0.25 lower to 0.1 higher)	⊕⊕⊕◯ MODERATE
Cognitive test scores -Immediate recall (follow up: range 6 months to 24 months)											
3	randomised trials	not serious	not serious	not serious	not serious	none	472	571	-	SMD **0.01 higher** (0.11 lower to 0.14 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores - Delayed recall (follow up: range 6 months to 24 months)											
3	randomised trials	not serious	not serious	not serious	not serious	none	472	571	-	SMD **0.04 lower** (0.16 lower to 0.09 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores - Word recognition (follow up: range 6 months to 24 months)											
3	randomised trials	not serious	not serious	not serious	not serious	none	472	571	-	SMD **0.04 higher** (0.08 lower to 0.16 higher)	⊕⊕⊕⊕ HIGH
Cognitive test scores- Number of animals named (follow up: range 6 months to 24 months)											

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-3 fatty acids	placebo	Relative (95% CI)	Absolute (95% CI)	
3	randomised trials	not serious	not serious	not serious	not serious	none	472	570	-	SMD **0.06 higher** (0.06 lower to 0.18 higher)	⨁⨁⨁⨁ HIGH
Cognitive test scores - Digit span forward (follow up: range 6 months to 24 months)											
3	randomised trials	not serious	not serious	not serious	not serious	none	458	560	-	MD **0.03 higher** (0.25 lower to 0.31 higher)	⨁⨁⨁⨁ HIGH
Cognitive test scores - Digit span backwards (follow up: range 6 months to 24 months)											
3	randomised trials	not serious	not serious	not serious	not serious	none	458	557	-	MD **0.12 higher** (0.12 lower to 0.36 higher)	⨁⨁⨁⨁ HIGH

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference

1. High I2.

Author(s): Flodgren GM, Berg R
Date: 27.04.16
Question: Aerobic exercise compared to active or passive control for cognitive decline
Setting: USA, France and Canada
Bibliography: Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD005381. DOI: 10.1002/14651858.CD005381.pub4.

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**primary and secondary prevention interventions**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**	
Cognitive test scortes											
6	randomised trials	serious [1]	not serious	not serious	serious [2]	none	389	-	-	SMD **0.12 SD higher** (0.08 lower to 0.33 higher)	⊕⊕◯◯ LOW
Verbal memory function (immediate)											
2	randomised trials	serious [1]	serious	not serious	serious [2]	none	299	-	-	SMD **0.08 SD higher** (0.38 lower to 0.55 higher)	⊕◯◯◯ VERY LOW
Visual memory functions (immediate)											
2	randomised trials	serious [1]	serious	not serious	serious [3]	none	89	-	-	SMD **0.26 SD lower** (0.97 lower to 0.44 higher)	⊕◯◯◯ VERY LOW
Woorking memory											
3	randomised trials	serious [1]	not serious	not serious	serious [2]	none	238	-	-	SMD **0.1 SD higher** (0.16 lower to 0.36 higher)	⊕⊕◯◯ LOW
Memory function (delayed)											

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**primary and secondary prevention interventions**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**	
3	randomised trials	serious [1]	not serious	not serious	serious [2]	none	249	-	-	SMD **0.1 SD higher** (0.16 lower to 0.35 higher)	⨁⨁◯◯ LOW
Executive functions											
6	randomised trials	serious [1]	serious [4]	not serious	serious [2]	none	367	-	-	SMD **0.38 SD higher** (0.14 lower to 0.9 higher)	⨁◯◯◯ VERY LOW
Perception											
3	randomised trials	serious [1]	not serious	not serious	serious [2]	none	178	-	-	SMD **0.01 SD lower** (0.5 lower to 0.48 higher)	⨁⨁◯◯ LOW
Cognitive inhibition											
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	314	-	-	SMD **0.06 SD lower** (0.28 lower to 0.17 higher)	⨁⨁◯◯ LOW
Visual attention											
3	randomised trials	serious [1]	not serious	not serious	serious [2]	none	265	-	-	SMD **0.22 SD higher** (0.03 lower to 0.46 higher)	⨁⨁◯◯ LOW
Auditory attention											

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**primary and secondary prevention interventions**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**	
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	251		-	MD **0.15 higher** (0.38 lower to 0.69 higher)	⨁⨁◯◯ LOW
Motor function											
2	randomised trials	serious [1]	not serious	not serious	serious [2]	none	189	-	-	SMD **0.08 SD higher** (0.2 lower to 0.37 higher)	⨁⨁◯◯ LOW

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

1. High to moderate risk of bias in one or more domains., 2. Fewer than 400 particpants., 3.No explanation was provided, 4. High heterogeneity I2=80%

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**primary and secondary prevention interventions**	**control**	**Relative (95% CI)**	**Absolute (95% CI)**	
4	randomised trials	serious [1]	not serious	not serious	serious [2]	none	251		-	MD **0.15 higher** (0.38 lower to 0.69 higher)	⨁⨁◯◯ LOW
Motor function											
2	randomised trials	serious [1]	not serious	not serious	serious [2]	none	189	-	-	SMD **0.08 SD higher** (0.2 lower to 0.37 higher)	⨁⨁◯◯ LOW

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

1. High to moderate risk of bias in one or more domains., 2. Fewer than 400 particpants., 3.No explanation was provided, 4. High heterogeneity I2=80%

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Utgitt av Folkehelseinstituttet
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Postboks 4404 Nydalen
NO-0403 Oslo
Telefon: 21 07 70 00
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