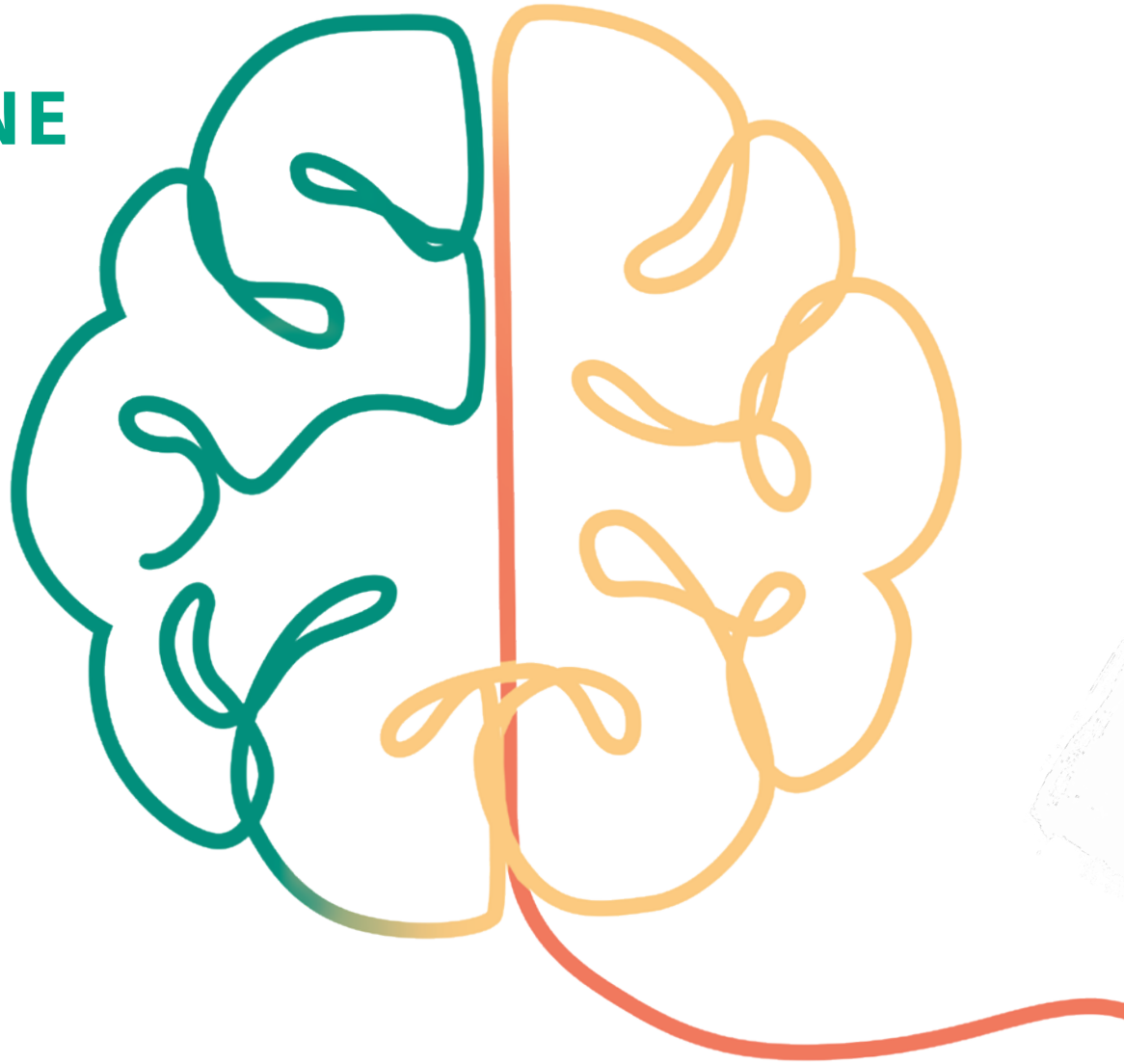
RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES

EVIDENCE PROFILES

Physical activity interventions
Tobacco cessation interventions
Nutritional interventions
Interventions for alcohol use disorder
Cognitive interventions
Social activity
Weight management
Management of hypertension
Management of diabetes
Management of dyslipidaemia
Management of depression
Management of hearing loss



World Health Organization

Risk reduction guidelines for cognitive decline and dementia

Evidence profile:
Physical activity and cognitive decline or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment, are physical activity interventions more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

As the number of older adults increases worldwide, a rise in dementia and Alzheimer's disease (AD) has also been reported,[1] causing health, economic and social burdens.[2,3] In 2015, it has been estimated that there were 46.8 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050.[1] AD/dementia has been linked to modifiable, lifestyle-related and cardiovascular risk factors[1-4] and since the management of cardiovascular diseases is still suboptimal in many countries, especially among older adults and no cure is available for AD, management of cardiovascular risks could be crucial in halting the rapid increase in the prevalence of dementia, as some projection models suggested.[5,6]

Regular physical exercise during the life course is associated with significant health benefits. Physical activity is associated with lower risk for cardiovascular diseases[7] and premature death[8,9]. Physical activity also promotes mobility and functional independence[10,11] and may also provide psychological and social benefits[12].

Physically active lifestyle is linked also to brain health. In large observational studies with follow-up periods extending up to decades physically active persons seem to be less likely to develop cognitive decline, all-cause dementia, vascular dementia and Alzheimer's disease when compared to inactive persons[13-16]. Especially highest levels of physical exercise seem to be most protective[14,15]. Physical activity seems to have beneficial effects on brain structures[17], which may underlie the found associations[17]. Other potential mechanisms underlying the found associations are most likely indirect, such as effects of physical exercise on other modifiable cardiovascular risk factors, such as hypertension, insulin resistance and cholesterol.

The current knowledge of beneficial effects of physical activity on dementia prevention lies mainly on observational evidence, and physical activity interventions aiming to prevent cognitive decline have been less successful. There is very limited evidence that physical activity which improves cardiovascular fitness could have beneficial effects on cognition especially among people without any cognitive deficits[18]. However, physical activity-induced improvements in certain cognitive domains have been observed among persons with mild cognitive impairment[19,20]. Also multidomain interventions promoting physical activity and simultaneously targeting other dementia-related risk factors have shown promising results especially among persons at high risk for cognitive decline[21].

This review of systematic reviews was carried out to search, identify, and synthesise the evidence currently available on the efficacy of physical activity interventions (aerobic, resistance training or multicomponent physical activity) aimed at reducing the risk of dementia and/or cognitive impairment.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment, are physical activity interventions more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

- ✓ P: Adults with normal cognition or mild cognitive impairment
- ✓ I: Physical activity interventions (aerobic, resistance training or multicomponent physical activity)
- ✓ C: Care as usual or no intervention
- ✓ O: *Critical*
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Dementia

  Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Date of search: 02nd May 2018

Search starting time: 31st December 2015

Full search terms

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Exercise OR exercise therapy OR Acute Exercise OR Aerobic Exercise OR Exercise Training OR Exercise, Aerobic OR Exercise, Isometric OR Exercise, Physical OR Isometric Exercise OR Physical Activity OR resistance training)

Simplified search terms

(dementia OR MCI OR cognition OR Quality Of Life OR ADL OR Adverse Effects OR Drop-out) AND (exercise OR physical activity)

*Searches were conducted in the following databases**:

- Cochrane
- Pubmed
- NICE Guidelines
- Embase
- PsycInfo
- Global Health Library (Including WHOLIS, PAHO, AIM, LILACS)
- Database of impact evaluations
- AFROLIB
- ArabPsycNet
- HERDIN NeON
- HrCak
- IndMED
- KoreaMed
- AJOL

* Please note that the EurasiaHealth database did not return any meaningful answer to the search.

List of systemic reviews identified by the search process

Included in GRADE[1] tables:

Comparison: Aerobic exercise intervention vs usual care or no intervention in adults with normal cognition

Barha CK et al. Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. Front Neuroendocrinol. 2017 Jul;46:71-85. doi: 10.1016/j.yfrne.2017.04.002.

Comparison: Training exercise intervention vs usual care or no intervention in adults with normal cognition

Barha CK et al. Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. Front Neuroendocrinol. 2017 Jul;46:71-85. doi: 10.1016/j.yfrne.2017.04.002.

Comparison: Multimodal exercise intervention vs usual care or no intervention in adults with normal cognition

Barreto PS et al. Exercise training for preventing dementia, mild cognitive impairment, and clinically meaningful cognitive decline: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2017 Dec 5. doi: 10.1093/gerona/glx234

Northey JM et al. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysisBr J Sports Med. 2018 Feb;52(3):154-160. doi: 10.1136/bjsports-2016-096587.

Comparison: Aerobic exercise intervention vs usual care or no intervention in adults with mild cognitive impairment (MCI)

Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002

Comparison: Training exercise intervention vs usual care or no intervention in adults with mild cognitive impairment (MCI)

Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002

Comparison: Multimodal exercise intervention vs usual care or no intervention in adults with mild cognitive impairment (MCI)

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[1] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO Table

Serial Number	Intervention vs Comparison & Population	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Aerobic exercise vs care as usual or no intervention or active control in individuals with normal cognition	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Barha CK et al. Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. Front Neuroendocrinol. 2017 Jul;46:71-85. doi: 10.1016/j.yfrne.2017.04.002.	Most recent (2017) and only available systematic review (moderate quality) assessing the effect of aerobic exercise on cognitive function in adults with normal cognition.
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Drop-out Rates	No relevant systematic review available	N/A
2	Resistance exercise vs care as usual or no intervention or active control in individuals with normal cognition	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Barha CK et al. Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. Front Neuroendocrinol. 2017 Jul;46:71-85. doi: 10.1016/j.yfrne.2017.04.002.	Most recent (2017) and only available systematic review (moderate quality) assessing the effect of resistance training on cognitive function in adults with normal cognition.
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Drop-out Rates	No relevant systematic review available	N/A
3	Multimodal exercise vs care as usual or no intervention no intervention or active	Incidence of dementia	Barreto PS et al. Exercise training for preventing dementia, mild cognitive impairment, and clinically meaningful cognitive decline: a systematic review and	Most recent (2017) and only available systematic review (moderate quality) assessing the effect of multimodal physical

	control in individuals with normal cognition		meta-analysis. J Gerontol A Biol Sci Med Sci. 2017 Dec 5. doi: 10.1093/gerona/glx234	activity on dementia onset in adults with normal cognition.
		MCI	Barreto PS et al. Exercise training for preventing dementia, mild cognitive impairment, and clinically meaningful cognitive decline: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2017 Dec 5. doi: 10.1093/gerona/glx234	Most recent (2017) and only available systematic review (moderate quality) assessing the effect of multimodal physical activity on the onset of MCI in adults with normal cognition
		Cognitive function	Northey JM et al. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysisBr J Sports Med. 2018 Feb;52(3):154-160. doi: 10.1136/bjsports-2016-096587.	Most recent (2018) and only available systematic review (moderate quality) assessing the effect of multimodal physical activity on cognition in adults with normal cognition
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Drop-out Rates	Barreto PS et al. Exercise training for preventing dementia, mild cognitive impairment, and clinically meaningful cognitive decline: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2017 Dec 5. doi: 10.1093/gerona/glx234	Most recent (2017) and only available systematic review (moderate quality) reporting on drop-out in multimodal physical activity interventions in adults with normal cognition.
4	Aerobic exercise vs care as usual or no intervention no intervention or active control in individuals with MCI	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002	Most recent (2018) and only available systematic review (moderate quality) assessing the effect of aerobic exercise on cognitive function in adults with MCI.

		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
5	Resistance training vs care as usual or no intervention no intervention or active control in individuals with MCI	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002	Most recent (2018) and only available systematic review (moderate quality) assessing the effect of resistance training on cognitive function in adults with MCI.
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Drop-out Rates	No relevant systematic review available	N/A
6	Multimodal exercise vs care as usual or no intervention no intervention or active control in individuals with MCI	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002	Most recent (2018) and only available systematic review (moderate quality) assessing the effect of multimodal physical activity on cognitive function in adults with MCI.
		Quality of Life	Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002	Most recent (2018) and only available systematic review (moderate quality) assessing the effect of multimodal physical activity interventions on quality of life in adults with MCI.
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A

		Drop-out Rates	Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002	Most recent (2018) and only available systematic review (Moderate quality) reporting on attrition of multimodal physical activity interventions in adults with MCI.

Narrative descriptions of the studies that went into the analysis

GRADE tables 1-3: Physical activity interventions in adults with normal cognition

Grade tables 1-3 present the evidence from three systematic reviews that assessed the efficacy of aerobic exercise[22], resistance training[22] and multimodal[23,24] interventions in preventing/delaying dementia and/or cognitive decline in people with normal cognition. Although Barha et al. (2017)[22] assessed the effects of all three types of physical activity interventions (aerobic exercise, resistance training and multimodal exercise) on cognition, a more recent systematic review of equal quality by Northey et al. (2018)[24] investigating the effects of multimodal exercise on cognition was selected.

Barha et al.[22] conducted a systematic review and meta-analysis to assess if different types of exercise interventions can improve domain-specific cognition in older adults with normal cognition. Two reviewers (C B and RF) conducted the extensive literature search and study evaluation independently. A total of 41 randomised controlled trials (RCTs) were included in the narrative qualitative synthesis and 39 in the meta-analysis. The interventions were classified into three categories: aerobic training, resistance training and multimodal training. The control groups varied from active balance and tone group to sedentary groups (36 studies) to multimodal control groups (1 study) and not reported (2 studies). The outcomes included domain-specific cognition (global, executive function, episodic memory, visuospatial function, word fluency and processing speed). Each cognitive domain was measured with a range of tests (e.g. global cognition with MMSE; executive function with set shifting, Stroop test; episodic memory with logical memory, immediate and delayed recall; visuospatial function with useful field of view, reaction time, clock drawing; word fluency with words by letter and category; processing speed with cancellation test, simple/choice reaction time test). The number of the participants, who were middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders, ranged from 18–666. The mean follow-up time of the 41 RCTs was 30 weeks.

The authors found that aerobic exercise had greater cognitive benefits than resistance training for all cognitive domains. Beneficial effects of aerobic exercise were observed for global cognition: standardized mean difference (SMD 0.85, 95% CI: 0.24 – 1.47, p=0.007); executive function (SMD 2.06, 1.58 – 2.55, p<0.000); visuospatial function (SMD 0.64, 0.14 – 1.15, p=0.013); word fluency (SMD 0.35, 95% CI: 0.2 – 0.5, p<0.000); processing speed (SMD 0.47, 0.24 – 0.7, p<0.000). The gains in the episodic memory (SMD 0.04, 95% CI: -0.36 – 0.45, p= 0.827) were not significant (GRADE table 1).

Resistance training improved executive function (SMD 0.64, 95% CI: 0.41 – 0.87, p<0.000) and visuospatial function (SMD 0.55, 95%CI: 0.14–0.95, p=0.009). No improvement was seen for episodic memory (SMD 0.07, 95% CI: 0.08 – 0.22, p=0.337) and word fluency (SMD 0.83, 95% CI: 0.87–2.53, p=0.339) and there was negative effect for global cognition (SMD -1.81, 95% CI: 2.88 –0.75, p=0.001). No study assessing impact of resistance training on processing speed was available (GRADE table 2). The authors also conducted tests for heterogeneity among the studies (Q statistic and Higgins I^2); and noted how longer interventions may have greater impact on cognitive function.

Barreto et al.[23] conducted a systematic review to assess effects of multimodal exercise on dementia onset, mild cognitive impairment (MCI) onset and cognitive decline. Two reviewers conducted literature search independently. Cochrane Collaboration's tool for evaluating risk of bias was applied to the included studies. A total of 5 randomised controlled trials (RCTs) were included in the review with total participants (n=2878) and age range (65–80 years). The mean follow-up was 12 months. Control group varied from placebo to sham exercise to social group.

For dementia onset, 3 studies with participants (n=1966) were included. These studies had high heterogeneity (I^2=63.1%). The incidence of dementia was 3.7% (n=949) for exercisers and 6.1% (n=1017) for controls. Multimodal exercise was not found to reduce the risk of dementia onset (Risk ratio (RR)= 0.56 95% CI: 0.23 – 1.36, p=0.20). In a sensitivity analysis, the authors found a significant effect of exercise for reducing the risk of dementia onset by 35%. However, this must be interpreted with caution since and should not be assumed as a definitive finding. It remains undecided that exercise can decrease the risk of incident dementia (GRADE table3). For MCI onset, only one

study was available with participants (n=1635) and a follow-up duration of 2 years. The incidence of dementia was 10.2% (n=686) for exercisers and 9.1% (n=682) for controls. Multimodal exercise was not found to reduce the risk of MCI onset (Risk ratio (RR)=1.12, 95% CI: 0.81 – 1.55, p=0.49). Drop-out rates were also reported individually for 5 studies and were not included into any meta-analysis. Mean drop-out rates for the exercise group were 21.4% and for the control group 14.2% (GRADE table 3).[23]

Northey et al.[24] conducted a systematic review to assess effects of exercise upon cognition in adults with normal cognition. Since this review was of similar quality as the review used for the dementia and MCI outcomes[23], but more recent, it was chosen to gather the evidence on the cognitive function outcomes. After an extensive literature search, two authors (NJ and SD) independently extracted the data and assessed the risk of bias of included RCTs according to the Cochrane Collaboration Guidelines[25]. GRADE guidelines[26] were also applied independently by two authors (NJ and SD) to evaluate the overall quality of evidence for the comparison of cognitive function between exercise and control groups. To study effects of multimodal exercise upon cognition, the review included nine RCTs with total participants (n=716) of age >50 years. Cognition was assessed across following domains: global, attention, executive function, memory and working memory. In order to assess heterogeneity, Q-statistic was applied ($p < 0.01$) showing significant heterogeneity across included studies. Publication bias was identified through an evaluation of funnel plot asymmetry and the effect size was not large enough to downgrade the evidence.

Benefits of multimodal exercise were reported for attention (SMD 0.27, 95% CI: 0.41–0.41), executive function (SMD 0.34, 95% CI 0.2– 0.47), memory (SMD 0.36, 95% CI: 0.22 –0.5), working memory (SMD 0.29, 0.12 –0.45) except for global cognition (SMD 0.16, 95% CI: 0.14 – 0.47) (GRADE table 3). The authors provide positive evidence for both aerobic and resistance training (i.e. multicomponent training), in compliance with exercise recommendations for age group (>50 years) to improve cognitive functions.

Overall risk of bias in included studies varied from not-serious to serious risk of bias. Methodological inconsistences in the studies with high risk of bias were mainly due to sequence generation, random allocation, allocation concealment, incomplete outcome data, and attrition (GRADE tables 1-3).

GRADE tables 4, 5, and 6: Physical activity Interventions in adults with mild cognitive impairment (MCI)

Song et al.[20] conducted a systematic review assessing the effects of aerobic exercise, resistance training, and multimodal exercise on cognition in individuals with MCI. Literature search, and quality assessment of the included RCTs was carried out by two authors independently (SD and LY). A total of eleven RCTs (n=881, age range 50–94 years) were included in the systematic review. Control group varied from placebo, to stretching, to health education, to social recreational activities. The review included studies with a single component (aerobic exercise or resistance training) as well as multimodal interventions, and the results were reported on domain-specific cognitive function (global function, executive function, and memory).

In the analysis of aerobic exercise intervention (GRADE table 4), only one of the two studies that reported on global cognition showed a significant improvement of global cognition following aerobic exercise intervention (SMD 0.58 95% CI:0.18–0.98)[27]. For the effect on executive functioning Three aerobic exercise studies were pooled, with no significant effect being detected (SMD 0.03; 95% CI −0.26 to 0.32). Similar results were reported for memory, both as immediate (SMD 0.01; 95% CI −0.22 to 0.24) and delayed recall (SMD 0.01; 95% CI -0.21 to 0.23).

When interventions specifically focused on training exercise were analysed (GRADE table 5), a small to moderate improvement on global cognition was reported (SMD 0.41; 95% Cl 0.01 to 0.80). However, executive function improved only in one of the three studies included in the pooled analysis, the one characterised by the longest and intensive intervention[28]. Furthermore, resistance training did not seem to improve either immediate (SMD 0.12; 95% Cl -0.24 to 0.48) nor delayed (SMD 0.19; 95% Cl -0.17 to 0.55) recall as measures of memory.

The main analysis of the systematic review focused on multidomain exercise interventions (GRADE table 6). For global cognition, beneficial effects were reported after pooling data from seven studies (SMD 0.30 95%CI: 0.10–0.49, p=0.02). For executive functioning, no significant beneficial effects were reported (SMD 0.12 95%CI: 0.04–0.29, p=0.14), after combining data from nine studies. For memory, no significant beneficial effects were reported after pooling data from eight studies (SMD 0.04 95%CI: -0.06–0.15, p=0.43). The authors also reported effects of multimodal exercise intervention on health-related quality of life assessed using questionnaires in two RCTs[29,30]. No meta-analysis was conducted but no significant beneficial effect on health-related quality of life was reported. Drop-out rates of 20.8% and 25% were also reported by same RCTs.

The included RCTs mostly had serious risk of bias due to concerns in allocation concealment, and selection in several studies included in the analysis. Although publication bias was not formally investigated the search was limited only to a small number of databases and no other source was included. Heterogeneity was investigated across studies for each analysis, using I^2 statistics, which revealed no significant results.

Since these types of intervention studies in this population are limited and are subject to various methodological flaws, more RCTs with rigorous study designs are needed. Future studies are recommended specifying (1) recruitment methods; (2) systematic recruitment of participants to ensure sample representativeness; (3) appropriate controls to enhance internal validity of the findings; (4) clear description of numbers and reasons for withdrawals and drop-outs; (5) approaches to improve adherence; (6) outcomes evaluating the transferability of cognitive gains to psychological well-being and quality of life; (7) comparison group- and individual-based exercises on cognitive and psychological outcomes; (8) long-term follow-ups. These would allow researchers to detect the effects of physical exercise on delaying the progression to dementia among such cohort.

Additional Evidence

The evidence (low to high quality), obtained from the systematic search presented here above, points towards a beneficial effect of physical activity in reducing the risk of dementia and cognitive decline in particular, especially for aerobic exercise and in people with normal cognition. Observational evidence also confirms this conclusion.

In 2016, Lafortune et al.[31] conducted a quick systematic review on mid-life behavioral risk factors (including physical activity, diet, smoking, alcohol, weight change, as well as leisure, cognitive activity, and social networks) associated with healthy ageing, dementia, disability and frailty in later life. Concerning the association between mid-life physical activity and cognition/dementia, ten longitudinal cohort studies were included in the qualitative synthesis. The review reported consistent evidence of the association between mid-life physical activity and lower risk of dementia as well as better cognitive functioning, in older life.

The following year after, a systematic review and meta-analysis[32] of longitudinal studies investigating the potential protective role of physical activity against cognitive decline, all-cause dementia, Alzheimer's disease (AD) and vascular dementia was published by Guure and colleagues. 25 studies for all cause dementia with follow-up of at least 12 months and up to 28, were included. The overall sample size was n=117410. The meta-analysis reported a protective effect for high level of physical activity on all-cause dementia (OR 0.79, CI 0.69–0.88), cognitive decline (OR 0.67, CI 0.55–0.78), AD (OR 0.62, CI 0.49–0.75), and a non-protective effect for vascular dementia (OR 0.92, CI 0.62–1.30).

A second systematic review with meta-analysis[33] of cohort studies was conducted to assess the dose-response relationship between physical activity and dementia (all-cause, AD and vascular dementia). The systematic review included a total of 16 studies and for all-cause dementia, the sample size was n= 37436, and the follow-up ranged from 3–31.6 years. The meta-analysis reported higher levels of physical activity to be associated with lower risk of all-cause dementia (RR 0.73, CI 0.62–0.87), and AD (RR 0.74, CI 0.58–0.94). The review identified a linear relationship between dementia/AD and leisure-time physical activity, in the range 0–2000 kcal/week or 0–45 metabolic

equivalent of task hours (MET-h)/week. For every 500 kcal or 10 MET-h increase per week, an approximate decrease of 10% and 13% in the risk of all-cause dementia and AD was reported, respectively.

Finally, Engeroff and colleagues[34] conducted a systematic review assessing the association between physical activity in adult life (18+ years) cognitive functions in late adulthood (60+ years). 14 longitudinal studies and nine cross-sectional studies were included. The review concluded that leisure-time physical activity in early, mid, and late adulthood was associated with better cognitive functioning (including global cognition, executive function, and memory) in older age. Limitations were identified concerning the impact of physical activity in early adulthood and the effect of adherence to current WHO recommendations oh physical activity, due to the fact that only two longitudinal studies have used cut-offs comparable to these recommendations.

Other relevant guidelines

WHO recommendations on physical activity for health 2010[42]. http://www.who.int/dietphysicalactivity/publications/9789241599979/en/

GRADE Tables

GRADE table 1

Author(s): Ruth Stephen, Mariagnese Barbera, Jenni Kulmala
Date: 13th June 2018
Question: Aerobic exercise intervention compared to no intervention for reducing risk of dementia and /or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders
Bibliography: Barha CK et al. Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. Front Neuroendocrinol. 2017 Jul;46:71-85. doi: 10.1016/j.yfrne.2017.04.002.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aerobic exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Global cognition (follow up: mean 41.5 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
4	randomised trials	serious [a]	not serious	not serious	not serious	none	N/A [b]	N/A [b]	-	SMD **0.85 SD higher** (0.24 higher to 1.47 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Executive functioning (follow up: mean 26 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
14	randomised trials	serious [c]	not serious	not serious	not serious	none	N/A [d]	N/A [d]	-	SMD **2.06 SD higher** (1.58 higher to 2.55 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Episodic memory (follow up: mean 37 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aerobic exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
7	randomised trials	serious [c]	not serious	not serious	not serious	none	N/A [e]	N/A [e]	-	SMD **0.04 SD higher** (0.36 lower to 0.45 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Visuospatial function (follow up: mean 32.5 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
9	randomised trials	serious [c]	not serious	not serious	not serious	none	N/A [f]	N/A [f]	-	SMD **0.64 SD higher** (0.14 higher to 1.15 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Word fluency (follow up: mean 34 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
7	randomised trials	serious [c]	not serious	not serious	not serious	none	N/A [g]	N/A [g]	-	SMD **0.35 SD higher** (0.2 higher to 0.5 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Processing speed (follow up: mean 21 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
3	randomised trials	serious [c]	not serious	not serious	serious [h]	none	N/A [h]	N/A [h]	-	SMD **0.47 SD higher** (0.24 higher to 0.7 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Downgraded due to 2 of the studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence, and attrition.

b. Total 869 participants for global cognition, but no numbers reported per arm (intervention or control)

c. Downgraded due to majority of the studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence, and attrition.
d. Total 446 participants for executive functioning, but no numbers reported per arm (intervention or control)
e. Total 1145 participants for episodic memory, but no numbers reported per arm (intervention or control)
f. Total 1179 participants for visuospatial function, but no numbers reported per arm (intervention or control)
g. Total 1043 participants for word fluency, but no numbers reported per arm (intervention or control)
h. Total 242 participants for processing speed, but no numbers reported per arm (intervention or control)

GRADE table 2

Author(s): Ruth Stephen, Mariagnese Barbera, Jenni Kulmala
Date: 13th June 2018
Question: Resistance training intervention compared to no intervention for reducing the risk of dementia and/or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenrative/clinical disorders
Bibliography: Barha CK et al. Sex differences in exercise efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials in older humans. Front Neuroendocrinol. 2017 Jul;46:71-85. doi: 10.1016/j.yfrne.2017.04.002.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Resistance training intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Global Cognition (follow up: mean 48 weeks; assessed with: measured with a range of tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
3	randomised trials	not serious	serious [a]	serious [b]	not serious [c]	none	N/A [d]	N/A [d]	-	SMD **1.81 SD lower** (2.88 lower to 0.75 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Executive functioning (follow up: mean 30.5; assessed with: measured with a range of tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
7	randomised trials	serious [e]	not serious	not serious	not serious	none	N/A [f]	N/A [f]	-	SMD **0.64 SD higher** (0.41 higher to 0.87 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Episodic memory (follow up: mean 44.5 weeks; assessed with: a range of tests ; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
4	randomised trials	serious [g]	not serious	not serious	not serious	none	N/A [h]	N/A [h]	-	SMD **0.07 SD higher** (0.08 lower to 0.22 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Visuospatial function (follow up: mean 64 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Resistance training intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	not serious	none	N/A [i]	N/A [i]	-	SMD **0.55 SD higher** (0.14 higher to 0.95 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Word fluency (follow up: mean 60 weeks; assessed with: a range of different tests; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
2	randomised trials	not serious	not serious	not serious	not serious	none	N/A [j]	N/A [j]	-	SMD **0.83 SD higher** (0.87 lower to 2.53 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Although heterogeneity was not formally assessed, of the three studies included (Alves et al., Ansai et al., Komulainen et al.), only one (Alves et al.) showed a significant negative correlation between resistance training and global cognition. The remaining studies reported no correlation. The effect was therefore only driven by one single study, which also had the smallest number of participants in both the control and the intervention arms: 14 participants/arm *versus* 23/arm (Ansai et al.) and ~230 (Komulainen et al.).

b. One study (Alves et al.) was conducted only on women and another study (Ansai et al.) was conducted on oldest old (80+) participants.

c. In all the three studies included (Alves et al., Ansai et al., Komulainen et al.), the intervention on resistance training was only one component of different types of multimodal interventions, therefore only small subgroups of participants were included in the meta-analysis of the systematic review. The authors of the systematic review reported only the total number of participants included in the meta-analysis but did not clarify the specific number per study and per arm (intervention and control).

d.Total 757 participants for global functioning, but no numbers reported per arm (intervention or control).

e. Downgraded due to three studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence.

f. Total 626 participants for executive functioning, but no numbers reported per arm (intervention or control).

g. Downgraded due to two studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence.

h. Total 904 participants for episodic memory, but no numbers reported per arm (intervention or control).

i. Total 728 participants for visuospatial function, but no numbers reported per arm (intervention or control).

j. Total 735 participants for word fluency, but no numbers reported per arm (intervention or control).

References:

Alves et al. PLoS One. 2013 Oct 3;8(10):e76301

Ansai et al. Geriatr Gerontol Int. 2015 Sep;15(9):1127-34.

Komulainen et al. European Geriatric Medicine. 2010;1:266–272

GRADE table 3

Author(s): Ruth Stephen, Mariagnese Barbera, Jenni Kulmala
Date: 13th June 2018
Question: Multimodal exercise compared to usual care or active control for reducing risk of dementia and/or cognitive decline in adults with normal cognition
Setting: Older adults without dementia; Community dwelling older people >50 years (no limitations on baseline cognitive status)
Bibliography: FOR INCIDENCE OF DEMENTIA & MCI, Drop-out (1) Barreto PS et al. Exercise training for preventing dementia, mild cognitive impairment, and clinically meaningful cognitive decline: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2017 Dec 5. doi: 10.1093/gerona/glx234 FOR COGNITION (2) Northey JM et al. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis Br J Sports Med. 2018 Feb;52(3):154-160. doi: 10.1136/bjsports-2016-096587.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multimodal exercise**	**usual care or active control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Incidence of Dementia (follow up: mean 12 months; assessed with: new diagnosis of dementia)												
3	randomised trials	not serious	serious [a]	not serious	not serious	publication bias strongly suspected [b]	35/949 (3.7%)	62/1017 (6.1%)	**RR 0.56** (0.23 to 1.36)	**27 fewer per 1,000** (from 22 more to 47 fewer)	⊕⊕◯◯ LOW	CRITICAL
MCI (follow up: mean 24 months; assessed with: new diagnosis)												
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	70/686 (10.2%)	62/682 (9.1%)	**RR 1.12** (0.81 to 1.55)	**11 more per 1,000** (from 17 fewer to 50 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Global cognition (assessed with: MMSE; Scale from: 0 to 30; Higher SMD=better cognitive performance)												
N/A [e]	randomised trials	serious [c]	serious [d]	not serious	not serious	none	N/A[e]	N/A[e]	-	**SMD 0.16 SD higher** (0.14 lower to 0.47 higher)	⊕⊕◯◯ LOW	CRITICAL
Attention (assessed with: a range of different tests; Scale from: N/A to N/A Higher SMD=better cognitive performance)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multimodal exercise**	**usual care or active control**	**Relative (95% CI)**	**Absolute (95% CI)**		
N/A[e]	randomised trials	serious [c]	serious [d]	not serious	not serious	none	N/A[e]	N/A[e]	-	SMD **0.27 SD higher** (0.41 higher to 0.41 higher)	⨁⨁◯◯ LOW	CRITICAL
Executive functioning (assessed with: a range of different tests; Scale from: N/A to N/A Higher SMD=better cognitive performance)												
N/A[e]	randomised trials	serious [c]	serious [d]	not serious	not serious	none	N/A[e]	N/A[e]	-	SMD **0.34 SD higher** (0.2 higher to 0.47 higher)	⨁⨁◯◯ LOW	CRITICAL
Memory (assessed with: a range of different tests; Scale from: N/A to N/A Higher SMD=better cognitive performance)												
N/A[e]	randomised trials	serious [c]	serious [d]	not serious	not serious	none	N/A[e]	N/A[e]	-	SMD **0.36 SD higher** (0.22 higher to 0.5 higher)	⨁⨁◯◯ LOW	CRITICAL
Working memory (assessed with: a range of different test; Scale from: N/A to N/A Higher SMD=better cognitive performance)												
N/A[e]	randomised trials	serious [c]	serious [d]	not serious	not serious	none	N/A[e]	N/A[e]	-	SMD **0.29 SD higher** (0.12 higher to 0.45 higher)	⨁⨁◯◯ LOW	CRITICAL
Drop-out (follow up: mean 12 months; assessed with: Percentages)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multimodal exercise**	**usual care or active control**	**Relative (95% CI)**	**Absolute (95% CI)**		
5	randomised trials	serious [f]	serious [d]	not serious	not serious	publication bias strongly suspected [b]	Drop-out rates of the 5 studies included were reported individually and not included into any meta-analysis: CONTROL GROUP mean =14.2 range = 6.7% to 28%; INTERVENTION GROUP mean= 21.4%, range= 9.2% to 46.2%				⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded due significant heterogeneity (I2=63).

b. Downgraded due to no adequate investigation of the publication bias, partially incomplete search strategies and no detailed description of reason for exclusion in the systematic review.

c. Downgraded due to studies judged at high risk of bias allocation concealment, sequence generation, and incomplete outcome data.

d. Downgraded due to significant heterogeneity across studies. Q-statistic was applied to assess heterogeneity, p-value obtained was <0.01, showing significant heterogeneity across studies.

e. A total of 36 studies were included overall in the quantitative synthesis. However, not all the studies were included into the analysis of each cognitive domain and, for each cognitive outcome, the review provided only a number of size effect and no other information necessary to identify the exact studies considered included into the analysis of each cognitive domain.

f. Downgraded due to studies judged at high risk of bias for blinding of the participants, allocation concealment.

GRADE table 4

Author(s): Ruth Stephen, Mariagnese Barbera, Jenni Kulmala
Date: 13th June 2018
Question: Aerobic exercise intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Bibliography: Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aerobic exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Global Cognition (assessed with: a range of measurements Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	65	67	Out of the two studies included, only one reported a significant improvement of global cognition following aerobic exercise intervention (SMD 0.58 95% CI:0.18–0.98)[1]		⊕◯◯◯ VERY LOW	CRITICAL
Executive functioning (follow up: mean 6.5 months; assessed with: Verbal fluency, Stroop test; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
3	randomised trials	serious [d]	not serious	not serious	not serious	publication bias strongly suspected [c]	115	100	-	SMD **0.03 SD higher** (0.26 lower to 0.32 higher)	⊕⊕◯◯ LOW	CRITICAL
Memory (follow up: mean 6 months; assessed with: Immediate recall; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
4	randomised trials	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [c]	170	170	-	SMD **0.01 SD higher** (0.22 lower to 0.24 higher)	⊕⊕◯◯ LOW	CRITICAL
Memory (follow up: mean 6 months; assessed with: Delayed recall; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aerobic exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomised trials	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [c]	170	170	-	SMD **0.01 SD higher** (0.21 lower to 0.23 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Downgraded due to allocation, and selection bias in the studies included.

b. Downgraded due to low sample size.

c. No formal analysis for publication bias was conducted, the search was carried out on a limited number of databases and no other source was included.

d. Downgraded due to presence of allocation, and selection bias in two studies included in the analysis.

Reference:

1. Lautenschlager, N., Cox, K., Flicker, L., Foster, J., Bockxmeer, F., Xiao, J., Almeida, O., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. J. Am. Med. Assoc. 300 (9), 1027–1037.

GRADE table 5

Author(s): Ruth Stephen, Mariagnese Barbera, Jenni Kulmala
Date: 13th June 2018
Question: Resistance training intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Bibliography: Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aerobic exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Global Cognition (assessed with: a range of measurements Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	49	53	-	SMD **0.41 SD higher** (0.01 higher to 0.80 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Executive functioning (follow up: mean 6.5 months; assessed with: Verbal fluency, Stroop test; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
3	randomised trials	serious [d]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	60	67	Out of the three studies considered, significant improvement in executive functioning was identified only in the one with the longest follow up.[1]		⨁◯◯◯ VERY LOW	CRITICAL
Memory (follow up: mean 6 months; assessed with: Immediate recall; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	77	81	-	SMD **0.12 SD higher** (0.24 lower to 0.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Memory (follow up: mean 6 months; assessed with: Delayed recall; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aerobic exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	77	81	-	SMD **0.19 SD higher** (0.17 lower to 0.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Downgraded due to allocation, and selection bias in the studies included.

b. Downgraded due to low sample size.

c. No formal analysis for publication bias was conducted, the search was carried out on a limited number of databases and no other source was included.

d. Downgraded due to presence of allocation, and selection bias in two studies included in the analysis.

Reference:

1. Nagamatsu, L.S., Chan, A., Davis, J.C., Beattie, B.L., Graf, P., Voss, M.W., Liu-Ambrose, T., 2013. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. J. Aging Res.

GRADE table 6

Author(s): Ruth Stephen, Mariagnese Barbera, Jenni Kulmala
Date: 13th June 2018
Question: Multimodal exercise intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Bibliography: Song D et al. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis doi: 10.1016/j.ijnurstu.2018.01.002

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multimodal exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Global Cognition (assessed with: a range of measurements Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
7	randomised trials	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	327	301	-	SMD **0.30 SD higher** (0.10 lower to 0.49 higher)	⊕⊕◯◯ LOW	CRITICAL
Executive functioning (follow up: mean 6.5 months; assessed with: Verbal fluency, Stroop test; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
8	randomised trials	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	450	400	-	SMD **0.12 SD higher** (0.04 lower to 0.29 higher)	⊕⊕◯◯ LOW	CRITICAL
Memory (follow up: mean 6 months; assessed with: Immediate recall/Delayed recall; Scale from: N/A to N/A: Higher SMD=better cognitive performance)												
8	randomised trials	serious [a]	not serious	not serious	not serious	publication bias strongly suspected [b]	280	287	-	SMD **0.04 SD higher** (0.06 lower to 0.15 higher)	⊕⊕◯◯ LOW	CRITICAL
Health related quality of life (follow up: mean 15 months; assessed with: Questionnaires)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multimodal exercise intervention**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	No significant difference was observed in health-related quality of life				⊕⊕⊕◯ MODERATE	IMPORTANT
Drop-out (assessed with: number reported)												
2	randomised trials	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [b]	Drop-out rates of two included studies: 25% and 20.8%				⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Downgraded due to allocation, and selection bias in some of the studies included.

b. No formal analysis for publication bias was conducted, the search was carried out on a limited number of databases and no other source was included.

c. Downgraded due to presence of allocation and selection blinding bias in one study included in the analysis.

Part 2: From evidence to decisions

Summary of Findings

Table 1

Aerobic exercise intervention compared to no intervention for reducing risk of dementia and /or cognitive decline in adults with normal cognition

Patient or population: reducing risk of dementia and /or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Aerobic exercise intervention				
Global cognition (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 41.5 weeks	-	SMD **0.85 SD higher** (0.24 higher to 1.47 higher)	-	(4 RCTs)	⨁⨁⨁◯ MODERATE [a,b]	Aerobic exercise seems to have a significant beneficial effect on global cognition
Executive functioning (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 26 weeks	-	SMD **2.06 SD higher** (1.58 higher to 2.55 higher)	-	(14 RCTs)	⨁⨁⨁◯ MODERATE [c,d]	Aerobic exercise seems to have significant beneficial effect on executive functioning

Aerobic exercise intervention compared to no intervention for reducing risk of dementia and /or cognitive decline in adults with normal cognition

Patient or population: reducing risk of dementia and /or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Aerobic exercise intervention				
Episodic memory (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 37 weeks	-	SMD **0.04 SD higher** (0.36 lower to 0.45 higher)	-	(7 RCTs)	⨁⨁⨁◯ MODERATE [c,e]	Aerobic exercise does not seem to have a beneficial effect on episodic memory
Visuospatial function (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 32.5 weeks	-	SMD **0.64 SD higher** (0.14 higher to 1.15 higher)	-	(9 RCTs)	⨁⨁⨁◯ MODERATE [c,f]	Aerobic exercise seems to have a significant beneficial effect on visuospatial function
Word fluency (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 34 weeks	-	SMD **0.35 SD higher** (0.2 higher to 0.5 higher)	-	(7 RCTs)	⨁⨁⨁◯ MODERATE [c,g]	Aerobic exercise seems to have a significant beneficial effect on word fluency

Aerobic exercise intervention compared to no intervention for reducing risk of dementia and /or cognitive decline in adults with normal cognition

Patient or population: reducing risk of dementia and /or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Aerobic exercise intervention				
Processing speed (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 21 weeks	-	SMD **0.47 SD higher** (0.24 higher to 0.7 higher)	-	(3 RCTs)	⨁⨁◯◯ LOW [c,h]	Aerobic exercise seems to have a significant beneficial effect processing speed

***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).
Higher SMD = better cognitive performance.
CI: Confidence interval; **SMD:** Standardised mean difference

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

Explanations
a. Downgraded due to 2 of the studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence, and attrition.
b. Total 869 participants for global cognition, but no numbers reported per arm (intervention or control)
c. Downgraded due to majority of the studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence, and attrition.
d. Total 446 participants for executive functioning, but no numbers reported per arm (intervention or control)
e. Total 1145 participants for episodic memory, but no numbers reported per arm (intervention or control)
f. Total 1179 participants for visuospatial function, but no numbers reported per arm (intervention or control)
g. Total 1043 participants for word fluency, but no numbers reported per arm (intervention or control)
h. Total 242 participants for processing speed, but no numbers reported per arm (intervention or control)

Table 2

Resistance training intervention compared to no intervention for reducing the risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing the risk of dementia and/or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders
Intervention: Resistance training intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Resistance training intervention				
Global Cognition (Cognition) assessed with: measured with a range of tests Scale from: N/A to N/A follow up: mean 48 weeks	-	SMD **1.81 SD lower** (2.88 lower to 0.75 lower)	-	(3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	Resistance training seem to decrease global cognition compared to controls
Executive functioning (Cognition) assessed with: measured with a range of tests Scale from: N/A to N/A follow up: mean 30.5	-	SMD **0.64 SD higher** (0.41 higher to 0.87 higher)	-	(7 RCTs)	⨁⨁⨁◯ MODERATE [e,f]	Resistance training seems to have a beneficial effect on executive functioning
Episodic memory (Cognition) assessed with: a range of tests Scale from: N/A to N/A follow up: mean 44.5 weeks	-	SMD **0.07 SD higher** (0.08 lower to 0.22 higher)	-	(4 RCTs)	⨁⨁⨁◯ MODERATE [g,h]	Resistance training does not seem to have a beneficial effect on episodic memory

Resistance training intervention compared to no intervention for reducing the risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing the risk of dementia and/or cognitive decline in adults with normal cognition
Setting: Middle-aged older adults (45 years and older) without any neurodegenerative/clinical disorders
Intervention: Resistance training intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Resistance training intervention				
Visuospatial function (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 64 weeks	-	SMD **0.55 SD higher** (0.14 higher to 0.95 higher)	-	(2 RCTs)	⨁⨁⨁⨁ HIGH [i]	Resistance training seems to have a beneficial effect on visuospatial function
Word fluency (Cognition) assessed with: a range of different tests Scale from: N/A to N/A follow up: mean 60 weeks	-	SMD **0.83 SD higher** (0.87 lower to 2.53 higher)	-	(2 RCTs)	⨁⨁⨁⨁ HIGH [j]	Resistance training does not seem to have a beneficial effect on word fluency

*__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). **Higher SMD = better cognition**.
CI: Confidence interval; **SMD:** Standardised mean difference

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

Explanations

a. Although heterogeneity was not formally assessed, of the three studies included (Alves et al., Ansai et al., Komulainen et al.), only one (Alves et al.) showed a significant negative correlation between resistance training and global cognition. The remaining studies reported no correlation. The effect was therefore only driven by one single study, which also had the smallest number of participants in both the control and the intervention arms: 14 participants/arm versus 23/arm (Ansai et al.) and ~230 (Komulainen et al.).

b. One study (Alves et al.) was conducted only on women and another study (Ansai et al.) was conducted on oldest old (80+) participants.

c. In all the three studies included (Alves et al., Ansai et al., Komulainen et al.), the intervention on resistance training was only one component of different types of multimodal interventions, therefore only small subgroups of participants were included in the meta-analysis of the systematic review. The authors of the systematic review reported only the total number of participants included in the meta-analysis but did not clarify the specific number per study and per arm (intervention and control).

d.Total 757 participants for global functioning, but no numbers reported per arm (intervention or control).

e. Downgraded due to three studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence.

f. Total 626 participants for executive functioning, but no numbers reported per arm (intervention or control).

g. Downgraded due to two studies included in the pooled analysis deemed at risk of bias for random allocation, allocation sequence.

h. Total 904 participants for episodic memory, but no numbers reported per arm (intervention or control).

i. Total 728 participants for visuospatial function, but no numbers reported per arm (intervention or control).

j. Total 735 participants for word fluency, but no numbers reported per arm (intervention or control).

References:

Alves et al. PLoS One. 2013 Oct 3;8(10):e76301

Ansai et al. Geriatr Gerontol Int. 2015 Sep;15(9):1127-34.

Komulainen et al. European Geriatric Medicine. 2010;1:266–272

Table 3

Multimodal exercise compared to usual care or active control for reducing risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing risk of dementia and/or cognitive decline in adults with normal cognition
Setting:
Intervention: Multimodal exercise
Comparison: usual care or active control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or active control	Risk with Multimodal exercise				
Incidence of Dementia (Dementia) assessed with: new diagnosis of dementia follow up: mean 12 months	61 per 1,000	**34 per 1,000** (14 to 83)	**RR 0.56** (0.23 to 1.36)	1966 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	Multimodal exercise does not seem to reduce the risk of dementia onset
MCI (MCI) assessed with: new diagnosis follow up: mean 24 months	91 per 1,000	**102 per 1,000** (74 to 141)	**RR 1.12** (0.81 to 1.55)	1368 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	Multimodal exercise does not seem to reduce the risk of MCI onset
Global cognition (Cognition) assessed with: MMSE Scale from: 0 to 30	-	SMD **0.16 SD higher** (0.14 lower to 0.47 higher)	-	(N/A)	⨁⨁◯◯ LOW [c,d,e]	Multimodal exercise does not seem have beneficial effect on global cognition
Attention (Cognition) assessed with: a range of different tests Scale from: N/A to N/A	-	SMD **0.27 SD higher** (0.41 higher to 0.41 higher)	-	(N/A)	⨁⨁◯◯ LOW [c,d,e]	Multimodal exercise seems to have beneficial effect on attention

Multimodal exercise compared to usual care or active control for reducing risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing risk of dementia and/or cognitive decline in adults with normal cognition
Setting:
Intervention: Multimodal exercise
Comparison: usual care or active control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or active control	Risk with Multimodal exercise				
Executive functioning (Cognition) assessed with: a range of different tests Scale from: N/A to N/A	-	SMD **0.34 SD higher** (0.2 higher to 0.47 higher)	-	(N/A)	⨁⨁◯◯ LOW [c,d,e]	Multimodal exercise seems to have beneficial effect on executive functioning
Memory (Cognition) assessed with: a range of different tests Scale from: N/A to N/A	-	SMD **0.36 SD higher** (0.22 higher to 0.5 higher)	-	(N/A)	⨁⨁◯◯ LOW [c,d,e]	Multimodal exercise seems to have beneficial effect on memory
Working memory (Cognition) assessed with: a range of different test Scale from: N/A to N/A	-	SMD **0.29 SD higher** (0.12 higher to 0.45 higher)	-	(N/A)	⨁⨁◯◯ LOW [c,d,e]	Multimodal exercise seems to have beneficial effect on attention
Drop-out assessed with: Percentages follow up: mean 12 months	Drop-out rates of the 5 studies included were reported individually and not included into any meta-analysis: CONTROL GROUP mean =14.2 range = 6.7% to 28%; INTERVENTION GROUP mean= 21.4%, range= 9.2% to 46.2%			(5 RCTs)	⨁◯◯◯ VERY LOW [b,d,f]	Drop-outs in the intervention group seem to be moderate to high

Multimodal exercise compared to usual care or active control for reducing risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing risk of dementia and/or cognitive decline in adults with normal cognition
Setting:
Intervention: Multimodal exercise
Comparison: usual care or active control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or active control	Risk with Multimodal exercise				

*__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).
Higher SMD = better cognition.
CI: Confidence interval; **RR:** Risk ratio

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

Explanations
a. Downgraded due significant heterogeneity (I2=63).
b. Downgraded due to no adequate investigation of the publication bias, partially incomplete search strategies and no detailed description of reason for exclusion in the systematic review.
c. Downgraded due to studies judged at high risk of bias allocation concealment, sequence generation, and incomplete outcome data.
d. Downgraded due to significant heterogeneity across studies. Q-statistic was applied to assess heterogeneity, p-value obtained was <0.01, showing significant heterogeneity across studies.
e. A total of 36 studies were included overall in the quantitative synthesis. However, not all the studies were included into the analysis of each cognitive domain and, for each cognitive outcome, the review provided only a number of size effect and no other information necessary to identify the exact studies considered included into the analysis of each cognitive domain.
f. Downgraded due to studies judged at high risk of bias for blinding of the participants, allocation concealment.

Table 4

Aerobic exercise intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Multimodal exercise intervention				
Global Cognition (Cognition) assessed with: a range of measurements	Out of the two studies included, only one reported a significant improvement of global cognition following aerobic exercise intervention (SMD 0.58 95% CI:0.18–0.98)[1]		-	132 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Aerobic exercise seems to have beneficial effect on global cognition
Executive functioning (Cognition) assessed with: Verbal fluency, Stroop test Scale from: N/A to N/A follow up: mean 6.5 months	-	SMD **0.03 SD higher** (0.26 lower to 0.32 higher)	-	215 (3 RCTs)	⨁⨁◯◯ LOW [c,d]	Aerobic exercise does not seem to have beneficial effect on executive functioning
Memory (Cognition) assessed with: Immediate recall follow up: mean 6 months	-	SMD **0.01 SD higher** (0.22 lower to 0.24 higher)	-	340 (4 RCTs)	⨁⨁◯◯ LOW [a,c]	Aerobic exercise does not seem to have beneficial effect on memory

Aerobic exercise intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Multimodal exercise intervention				
Memory (Cognition) assessed with: Delayed recall follow up: mean 6 months	-	SMD **0.04 SD higher** (0.06 lower to 0.15 higher)	-	340 (4 RCTs)	⨁⨁◯◯ LOW [a,c]	Aerobic exercise does not seem to have beneficial effect on memory

***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). Higher SMD = better cognition.
CI: Confidence interval; **SMD:** Standardised mean difference

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

Explanations
a. Downgraded due to allocation, and selection bias in the studies included.
b. Downgraded due to low sample size.
c. No formal analysis for publication bias was conducted, the search was carried out on a limited number of databases and no other source was included.
d. Downgraded due to presence of allocation, and selection bias in two studies included in the analysis.
Reference:

2. Lautenschlager, N., Cox, K., Flicker, L., Foster, J., Bockxmeer, F., Xiao, J., Almeida, O., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer's disease: a randomized trial. J. Am. Med. Assoc. 300 (9), 1027–1037.

Table 5

Resistance training intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Multimodal exercise intervention				
Global Cognition (Cognition) assessed with: a range of measurements	-	SMD **0.41 SD higher** (0.01 higher to 0.80 higher)	-	102 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Resistance training seem to have beneficial effect on global cognition
Executive functioning (Cognition) assessed with: Verbal fluency, Stroop test Scale from: N/A to N/A follow up: mean 6.5 months	Out of the three studies considered, significant improvement in executive functioning was identified only in the one with the longest follow up.[1]		-	127 (3 RCTs)	⨁◯◯◯ VERY LOW [b,c,d]	Resistance training seems to have beneficial effect on executive functioning, but only in the study with the longest follow up.
Memory (Cognition) assessed with: Immediate recall follow up: mean 6 months	-	SMD **0.12 SD higher** (0.24 lower to 0.48 higher)	-	158 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Resistance training exercise does not seem to have beneficial effect on memory

Resistance training intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Intervention: Aerobic exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Multimodal exercise intervention				
Memory (Cognition) assessed with: Delayed recall follow up: mean 6 months	-	SMD **0.19 SD higher** (0.17 lower to 0.55 higher)	-	158 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Resistance training exercise does not seem to have beneficial effect on memory

***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). Higher SMD = better cognition.
CI: Confidence interval; **SMD:** Standardised mean difference

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

Explanations
a. Downgraded due to allocation, and selection bias in the studies included.
b. Downgraded due to low sample size.
c. No formal analysis for publication bias was conducted, the search was carried out on a limited number of databases and no other source was included.
d. Downgraded due to presence of allocation, and selection bias in two studies included in the analysis.
Reference:

1. Nagamatsu, L.S., Chan, A., Davis, J.C., Beattie, B.L., Graf, P., Voss, M.W., Liu-Ambrose, T., 2013. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. J. Aging Res.

Table 6

Multimodal exercise intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Intervention: Multimodal exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Multimodal exercise intervention				
Global Cognition (Cognition) assessed with: a range of measurements	-	SMD **0.30 SD higher** (0.10 lower to 0.49 higher)	-	628 (7 RCTs)	⨁⨁◯◯ LOW [a,b]	Multimodal exercise seems to have beneficial effect on global cognition
Executive functioning (Cognition) assessed with: Verbal fluency, Stroop test Scale from: N/A to N/A follow up: mean 6.5 months	-	SMD **0.12 SD higher** (0.04 lower to 0.29 higher)	-	850 (9 RCTs)	⨁⨁◯◯ LOW [a,b]	Multimodal exercise does not seem to have beneficial effect on executive functioning
Memory (Cognition) assessed with: Immediate recall/Delayed recall follow up: mean 6 months	-	SMD **0.04 SD higher** (0.06 lower to 0.15 higher)	-	567 (8 RCTs)	⨁⨁◯◯ LOW [a,b]	Multimodal exercise does not seem to have beneficial effect on executive functioning

Multimodal exercise intervention compared to no intervention for reducing risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing risk of dementia and/or cognitive decline in adults with MCI
Setting: Adults with MCI
Intervention: Multimodal exercise intervention
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with Multimodal exercise intervention				
Health related quality of life (HRQoL) assessed with: Questionnaires follow up: mean 15 months	No significant difference was observed in health-related quality of life			(2 RCTs)	⨁⨁⨁◯ MODERATE [b]	Multimodal exercise does not seem have beneficial effect on quality of life
Drop-out assessed with: number reported	Drop-out rates of two included studies: 25% and 20.8%			(2 RCTs)	⨁⨁◯◯ LOW [b,c]	The drop-out rates were moderate for multimodal exercise intervention

***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). Higher SMD = better cognition.
CI: Confidence interval; **SMD:** Standardised mean difference

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

Explanations
a. Downgraded due to allocation, and selection bias in some of the studies included.
b. No formal analysis for publication bias was conducted, the search was carried out on a limited number of databases and no other source was included.
c. Downgraded due to presence of allocation and selection blinding bias in one study included in the analysis.

Evidence-to-Decision Table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide ageing of populations is strongly associated with dementia, causing major health, economic and social burdens. In 2015, it has been estimated that there were 50 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 82 million in 2030 and 152 million in 2050.[1] Since no cure is available for Alzheimer's disease, the main cause of dementia, prevention could be crucial in halting the rapid increase in the prevalence of this condition and international experts have called upon world-wide governments to make prevention of dementia one of their key health priorities..	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Physical activity has rather consistently reported small but beneficial effects on cognition. There is enough low to moderate quality evidence supporting these effects. It is important to consider that in order to achieve maximum benefit, it is crucial to start such interventions in at-risk people[21]. Earlier, the better. Even in MCI populations, low evidence suggests cognitive benefits of physical exercise. The effect of these interventions seems to be mostly due to aerobic exercise.	- effect size larger for aerobic training versus resistance training -less interventions for resistance/multicomponent training -stronger evidence for persons with normal cognition (especially aerobic training) -no clinical trials for MCI or incidence of dementia, but this evidence is available from observational studies - A Cochrane review was published in 2015[35] (not included because the systematic search started form 2016) on effect of aerobic exercise on cognitive function in older people with normal cognition. Although the trend of the results was always towards a minimal beneficial effect of the intervention, for none of the outcomes the results were significant. The review overall included a smaller sample size than the one presented in GRADE table 1, therefore it is plausible to conclude that no

		important evidence was missed by not including this review.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Most of the clinical trials do not report any adverse events after exercise.[36] It is difficult to know whether adverse events did not occur or whether they were not reported. Higher risk of any adverse event may occur in some older people after intense exercise who already have pre-existing health problems, limited functional capacity or those who are sedentary.	The Cochrane review by Young et al.[35] on the effect of aerobic exercise on cognitive function in older people with normal cognition assessed dropout rates as indicator of adverse events. When aerobic exercise interventions were compared with no intervention a higher odd ratio (OR) for drop-out was reported (1.84, CL 0.79-4.29).
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
In adults with normal cognition ○ Very low ○ Low ● Moderate ○ High ○ No included studies ***In adults with MCI*** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	Moderate quality evidence indicates beneficial effects of physical activity interventions on cognition in healthy individuals. Moderate quality evidence suggests that physical activity does not seem to affect risk of MCI and dementia. Low quality evidence indicates beneficial effects of physical activity interventions on cognition in adults with MCI. However, these benefits are not consistent across all cognitive domains.	-moderate for aerobic training, less evidence for resistance training - no sufficient evidence for mci/dementia (or low quality)

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cognitive impairment and dementia can have a major impact in the life not only of the person affected but also of the close network of family and friends, as well as caregivers and health professional in general.[37,38] Decreasing functional ability and dependency are the major components of this effect. Furthermore, dementia is the main cause of disability and institutionalization among older adults[1]. Hence, reducing or delaying the risk/onset of dementia could results in lower costs for public healthcare services. Patients, caregivers, and policy makers are likely to be the people who will value these recommendations.	
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	Evidence suggests that the desirable effects of the physical activity interventions are more that the undesirable effects. Common barriers to exercise are costs, lack of motivation, lack of time, and physical limitations. Low to moderate quality evidence suggests benefits to physical activity compared to the controls.	-systematic reviews did not report undesirable effects. -physical activity has benefits for other outcomes
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	The physical activity interventions evaluated in the included trials were resource-intensive since such interventions are usually supervised and are conducted in a facility. However, some aspects of these interventions, could be adapted to particular settings, and could be conducted by suitably trained and supported non-specialists. Resources strictly depends on the intervention design. Potentially lower costs for aerobic training compared to resistance.	For more information: 'Best buys' and other recommended interventions to address non-communicable diseases (NCDs) http://apps.who.int/iris/bitstream/handle/10665/259232/WHO-NMH-NVI-17.9-eng.pdf?sequence=1

		-trials setting versus possibilities to implement in wider community -aerobic exercise easily available in all settings
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	No evidence for the present review is available.	See citation above
Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Worldwide costs for health care systems attributable to physical inactivity were estimated to be 54 billion (INT$) in 2013 and it has been stated that a 20% reduction of inactivity rates on the population level would already yield important cost savings.[39]	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced	Lower socioeconomic groups are more likely to have earlier onset of dementia than higher socioeconomic groups. Older people from lower socioeconomic backgrounds are also more likely to	- can be advertised via mass media

○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	experience cognitive dysfunction at earlier stages of cognitive decline and cognitive impairment, and will have fewer resources to cope with the symptoms than their counterparts from higher socioeconomic groups People from lower socioeconomic groups are more likely to live, work and age in physical and economic environments that do not support social connectedness, physical activity or mental stimulation. this can increase the risk of cognitive impairment and dementia in later life.[40] Based on this it is believed that interventions to reduce risk of cognitive decline and dementia will increase equity in health. Furthermore, women are disproportionally affected with AD. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men.[41]	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Physical activity interventions have consistent benefits on cognition and other health parameters.[36]	Acceptability may vary depending upon lifestyle patterns -adaptations to different cultures/settings -cultural acceptability
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Varies. The most common barriers to exercise are costs, lack of motivation, lack of time, and physical limitations.[36]	

Reference

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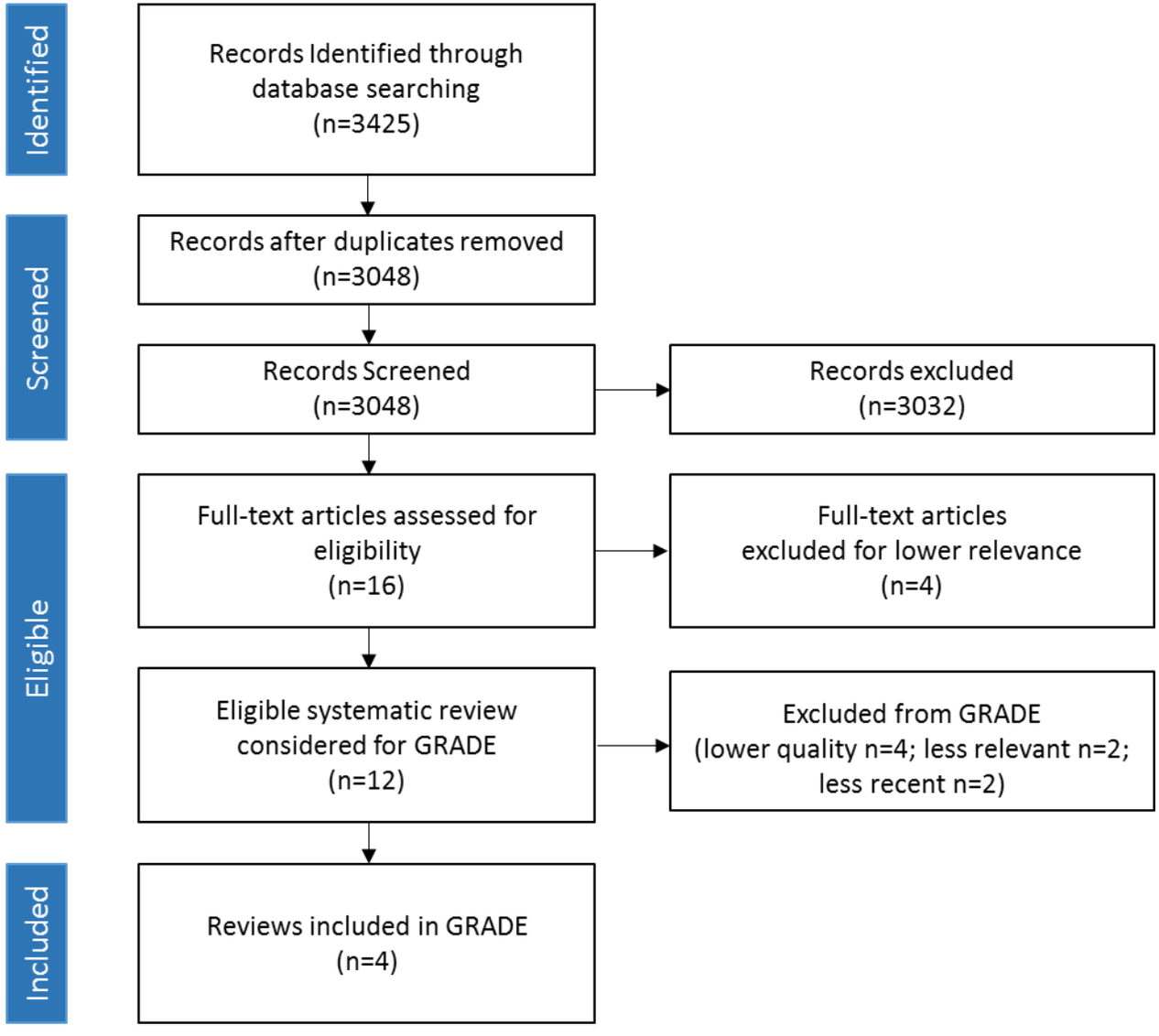
Annex: PRISMA[2] flow diagram for systematic review of the reviews – cognitive decline interventions[2]



[2] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For more information: http://www.prisma-statement.org

Risk reduction guidelines for cognitive decline and dementia

Evidence profile: Tobacco cessation and cognitive decline or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment who use tobacco, are interventions for tobacco cessation more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

As the number of older adults increases worldwide, a rise in dementia and Alzheimer's disease (AD) has also been reported,[1] causing health, economic and social burdens.[2,3] In 2015, it has been estimated that there were 46.8 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050.[1] Since no cure is available, prevention could be crucial in halting the rapid increase in the prevalence of dementia, as some projection models suggested.[4,5] AD/dementia has been linked to modifiable, lifestyle-related, vascular risk factors,[1-3,6] but the extent to which cognitive impairment can be prevented is under debate.

Tobacco dependence is the leading cause of preventable death globally, causing an estimated five million deaths/year[7] and word-wide medical costs ranging in billions of US dollars.[8] Tobacco is the major risk factor for a number of conditions namely many types of cancers, cardiovascular diseases and risk factors, and respiratory disorders[9] and tobacco cessation has been demonstrated to significantly reduce these health risks.[10] Tobacco cessation has also been associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke.[11]

Tobacco dependence has been also associated to other disorders and age related conditions such as frailty and work ability in the elderly,[12,13] as well as AD, dementia and cognitive decline.[14] One of the proposed mechanisms, whereby tobacco would increase the risk of AD, is by smoking-related cerebral oxidative stress,[14] but there is also evidence of a relationship between smoking and shorter telomere length, which may imply other possible mechanisms linking tobacco smoke exposure to ageing-related disease.[15]

Interventions to treat tobacco dependence can be very diverse, based on either or both behavioural/psychological strategies and various pharmacological treatments. Tobacco cessation is a complex process, like in any other addictions and although most smokers report wanting to quit, many continue as they report that smoking provides them with mental health benefits.[16] Non-pharmacological interventions can have mixed results.[17] Counselling is the most frequently used approach, but others have also been explored, such as mindfulness-based approaches, cognitive behavioural therapy, behavioural activation therapy, motivational interviewing, contingency management, and exposure and/or aversion to smoking. Among the pharmacological therapies for tobacco cessation, nicotine replacement therapy, bupropion and varenicline are the most common, but low overall treatment efficacy and adverse effects are key limitations.[18] Combinations of non-pharmacological and pharmacological approaches seem to be the most effective in supporting tobacco cessation.[18]

This review of systematic reviews was carried out to search, identify, and synthesise the evidence currently available on the efficacy of behavioural/psychological or pharmacological intervention aimed at tobacco cessation in reducing the risk of dementia and/or cognitive impairment.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment who use tobacco, are interventions for tobacco cessation more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

- ✓ P: Adults with normal cognition or mild cognitive impairment who use tobacco
- ✓ I: Interventions for tobacco cessation (behavioural interventions and pharmacological interventions including nicotine replacement therapy, bupropion, varenicline)
- ✓ C: Care as usual or no intervention
- ✓ O: *Critical*
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Dementia

  Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Date of search: 02nd of May 2018

Search starting time: 31st December 2012

Full search terms

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Tobacco OR smoking OR Tobacco use cessation OR giving up smoking OR quitting smoking OR stopping smoking OR smoking cessation OR smoking reduction OR tobacco use cessation products OR varenicline OR nicotinic agonists OR Nicotine Inhalant OR Nicotine Lozenge OR Nicotine Lozenges OR Nicotine Nasal Spray OR Nicotine Patch OR Nicotine Polacrilex OR Nicotine Replacement Products OR Nicotine Transdermal Patch OR Smoking Cessation Products) AND (Behavior OR behaviour OR drug therapy OR pharmacologic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment)

Simplified search terms

(dementia OR MCI OR cognition OR Quality of Life OR ADL OR Adverse Effects OR Drop-out) AND smoking AND smoking cessation

*Searches were conducted in the following databases**:

- Cochrane
- Pubmed
- NICE Guidelines
- Embase
- PsycInfo
- Global Health Library (Including WHOLIS, PAHO, AIM, LILACS)
- Database of impact evaluations
- AFROLIB
- ArabPsycNet
- HERDIN NeON
- HrCak

- IndMED
- KoreaMed
- AJOL

* Please note that the EurasiaHealth database did not return any meaningful answer to the search.

List of systemic reviews identified by the search process

No systematic review of intervention studies that matched the PICO question was identified through the present search. A further search with similar strategy was carried out (in PubMed only) for the previous 5 years (from 31.12.2007 to 31.12.2012), and, in addition, reference lists from observational evidence obtained during the main search were checked. This search not only did not yield any systematic review, but neither any evidence of the existence of intervention studies for tobacco cessation that have evaluated the impact of the intervention on dementia and/or cognitive impairment. A search in five of the largest clinical trials registers (ClinicalTrials.gov; EudraCT; ISRCTN; JPRN; and ANZCTR) for completed or ongoing trials relevant to the PICO question was conducted but results were negative (Searches conducted by Mariagnese Barbera and Krister Håkansson).

Narrative description of the observational evidence on the correlation between tobacco consumption and increased risk of dementia

Although the present search did not gather any evidence from intervention studies aimed at investigating the effect of tobacco cessation on the risk of dementia and/or cognitive decline, observational evidence of a correlation between tobacco consumption and increased risk of dementia are widely available. In particular, three systematic reviews (one including meta-analysis), two meta-analysis, and one multi-cohort study reporting observational evidence of the correlation between tobacco and risk of dementia and/or cognitive decline were identified and selected for this narrative description.

Beydoun et al., published in 2014 a systematic review and meta-analysis on modifiable risk factors for dementia and cognitive decline.[19] Epidemiological studies (including cross-sectional) on the relation between dementia and/or cognition with education, smoking, alcohol, physical activity, caffeine, antioxidants, homocysteine (Hcy), or n-3 fatty acids were systematically searched in MEDLINE from January 1990 through October 2012. Only cohort studies of at least 300 participants were included in the search. A total of 247 studies were identified across all the risk factors and seven cross-sectional studies investigation the possible correlation between smoking and cognition and/or dementia were identified. Of these seven studies only 2 (representing the 28.6% of the pooled cohort) found a significant association between smoking and cognitive decline, and two more detected it in sub-group analysis. A meta-analysis on nine studies that reported relative risk (RR) for dementia in relation to the smoking status showed that smoking seems to increase risk of dementia (RR 1.37; 95% CI 1.23 to 1.52) but significant heterogeneity was detected using Q^2 statistics $p<0.001$).

In the same year another systematic review (without meta-analysis) was published on modifiable risk factors for dementia.[20] The search was carried out on a wider range of databases (PubMed, Ovid MEDLINE, In-Process & Other Non-Indexed Citations and Ovid MEDLINE, and PsycINFO) compared to the previous review and included also more recent publications (up to December 2013). 75 papers from 33 epidemiologic studies met the inclusion criteria and 15 of these investigated the correlation between smoking and dementia. In nine out of these 15 examined publications a significant correlation between smoking status (especially current smoking) and dementia was identified. Two studies reported about the role of ApoE Ɛ4 in increasing the risk of dementia in current smokers. Evidence was limited by the fact that only studies investigating on the incidence of dementia, and not on cognitive performance outcomes, were included.

North and colleagues published in 2015 a multi-cohort study (9 British cohorts; n=26692) investigating the association between smoking status and cognitive performance/decline.[21] The study included older adults (mean age range 50-79) of European ancestry. Participants were classified at baseline as current, ex or never smokers; cognitive performance was measured with range of assessments: crystallised intelligence (indicator of knowledge accumulated across the life course), fluid intelligence (measuring problem-solving skills), semantic fluency, phonemic fluency, search speed, word recall, four choice reaction time, logical memory, and Raven's Progressive Matrices (for abstract reasoning and fluid intelligence). The results were statistically combined in a general fluid (Gf) cognitive ability score that allowed to compare and pool the data from different cohorts. Compared to both ex-smokers and never smokers, current smokers consistently showed a worse cognitive performance in all the cognitive areas (significant results in the majority of the cases). This evidence was gathered from a single multi cohort study, and not from a systematic review and/or meta-analysis, however the sample and the effect size support the quality of the evidence, which clearly points toward a link between smoking and cognitive decline.

Also, a meta-analysis of observational evidence of the role of modifiable risk factors for Alzheimer's disease was published in 2015.[22] Xu and colleagues systematically searched PubMed and the Cochrane database of systematic reviews from inception to July 2014 for cohort studies and retrospective case–control studies reporting on risk factors for Alzheimer's disease (AD) and dementia. Studies were included if: they reported original data concerning odds ratio (OR) or risk ratio (RR) of AD using a longitudinal cohort study or retrospective case–control study design; the study population was representative of the general population and; modifiable risk factors were included. A

total of 323 papers were included in the meta-analysis. Concerning smoking Grade I evidence was identified from nine studies of a significant correlation between current smoker status and increased risk of AD (RR/OR 1.87; 95% Cl 0.99-2.75). The pooled analysis however was limited by significant heterogeneity (I^2=67), but sensitivity analyses conducted to reduce heterogeneity still showed a significant association between smoking and increased risk of AD. Publication bias was investigated but undetected using Egger's test (p=0.657).

A second meta-analysis[23] of observational studies was published in the same year, focusing specifically on the association between smoking and increased risk of dementia. The authors search PubMed, Embase, Cochrane Library and Psychinfo for studies that provided risk estimates on smoking and incidence of dementia. The search yielded 37 studies and the meta-analysis showed that compared with never smokers, current smokers had an increased risk of all-cause dementia (RR 1.30; 95% CI 1.18–1.45). Statistically significant moderate heterogeneity (I2=50.6) was identified but no evidence of publication bias was found for any association by Begg's test and Egger's test (p>0.05). A dose-response analysis reported that for all-cause dementia, the risk increased by 34% for every 20 cigarettes per day (RR 1.34, 95%CI 1.25–1.43), and a subgroup analysis indicated that the significantly increased risk of AD from current smoking was mostly driven by ApoE ε4 noncarriers.

More recently, Lafortune and colleagues conducted a rapid systematic review on the lifestyle risk factors correlated to different ageing conditions including dementia.[24] The search was made on longitudinal cohort studies in several relevant databases starting from 2000 and identified 164 studies that were included in a qualitative synthesis. Nine studies reported about the correlation between smoking and dementia and/or cognitive decline. In most studies smoking was strongly associated with dementia, and subsequent risk of hospitalisation. Two studies showed also an association between smoking and cognition.

In conclusion, despite the overall lack of intervention trials aimed at investigating the effect of tobacco cessation on the risk of dementia and/or cognitive decline, there is strong and consistent observational evidence demonstrating the association between tobacco consumption (including in mid-life) and dementia, or cognitive decline, in later life. In addition to this, the WHO guidelines for the treatment of tobacco dependence[25] represent the most relevant evidence and recommendations to which refer for the management of tobacco dependence in the normal population.

Other relevant guidelines

WHO's training package on Strengthening health systems for treating tobacco dependence in primary care (2013)[25] represent the most relevant evidence and recommendations to which refer for the management of tobacco dependence in the general population.

http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/

Part 2: From evidence to decisions

Evidence-to-Decision Table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide ageing of populations is strongly associated with dementia, causing major health, economic and social burdens. In 2015, it has been estimated that there were 50 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 82 million in 2030 and 152 million in 2050.[1] Since no cure is available for Alzheimer's disease, the main cause of dementia, prevention could be crucial in halting the rapid increase in the prevalence of this condition and international experts have called upon world-wide governments to make prevention of dementia one of their key health priorities.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The present systematic search did not identify any systematic review nor single study aimed at investigating the effect of tobacco cessation intervention on the risk of dementia and/or cognitive decline. However, there is a large and consistent body of observational evidence demonstrating the association between tobacco smoking (including in mid-life) and dementia, or cognitive decline, in later life.	-no trials carried out, but there is substantial evidence from observational studies that smoking increases the risk of dementia/cognitive decline -high attributable risk globally[2]
Undesirable Effects How substantial are the undesirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Dizziness, dyspnoea, nausea, heart rate increased, and tremor are the most common adverse events reported for pharmacological treatment for tobacco cessation.[26] Lifestyle interventions are mostly based on cognitive/behavioural interventions and no evidence of adverse events (apart from those related to withdrawal syndrome) have been identified.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Evidence related to the desirable effect are based on a large body of observational evidence, mostly systematic reviews of longitudinal cohort studies.	- strong evidence from observational studies, including evidence from current/previous/non-smokers.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cognitive impairment and dementia can have a major impact in the life not only of the person affected but also of the close network of family and friends, as well as caregivers and health professional in general.[27,28] Functional ability and dependency are playing are the major component of this effect. Furthermore, dementia, the main cause of disability and institutionalization among older adults[1], therefore reducing or delaying the onset of dementia could results in lower costs for public healthcare services. Patients, caregivers, and policy makers are likely to be the people who will value these recommendations the most.	
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	Only limited adverse events have been reported and only for pharmacological interventions. A substantial body of observational evidence associates tobacco smoking with an increased risk of dementia and cognitive decline. Therefore, any type of intervention aimed at tobacco cessation is likely to be more beneficial than detrimental.	- No evidence for cognition, but large body of evidence of tobacco use on other health-related adverse outcomes -substantial established harm
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Cost can vary significantly based on the strategy applied. For lifestyle intervention the main costs are represented by the qualified healthcare professional that delivers the intervention. Data from Australia[29] have estimate the overall costs of different interventions on tobacco cessation: physician advice ($3,800AUD); telephone counselling ($3,029); NRT with counselling ($41,163); bupropion with counselling ($35,258); and NRT + bupropion with counselling ($69,842). More recently, Cost-effectiveness analysis of smoking cessation interventions using cell phones in a low-income population,[30] showed that Cell phone interventions for low socioeconomic groups are a cost-effective use of healthcare resources. Cost-effectiveness can vary a lot between interventions at individual level and community-based ones, generally in favour of interventions on a larger scale.[31,32]	The World Health Assembly has endorsed a set of WHO "best buys" and other recommended interventions for governments to implement for the prevention and control of noncommunicable diseases. Tobacco and CVD control feature prominently among these "best buys", as proven, cost-effective measures that can be scaled up in countries. The MPOWER measures feature prominently in the "best buys" [MPOWER package: M-onitor tobacco use and prevention policies, P-rotect people from tobacco smoke, O-ffer help to quit tobacco use, W-arn about the dangers of tobacco, E-nforce bans on advertising, R-aise taxes on tobacco. This technical package is intended to assist in reducing the demand for tobacco products at country level]
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Resources requirements for different types of tobacco cessation interventions (at individual level or population based) are clearly reported.[30-32]	See above. Evidence of cost of intervention is well documented in the report.

Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	In general interventions to reduce smoking are resource-intensive as they may require professional guidance and supervision. The systematic review and meta-analyses by Ali et al. (2018)[33] comparing cost effectiveness of all types of treatments for smokers who are not ready to quit (over 30% of current smokers) showed that behavioural interventions were the most cost effective and pharmacological interventions the least. However, pharmacological interventions were the most effective, whereas behavioural interventions were the least effective. The average cost of pharmacological interventions was driven up by high costs of nicotine replacement therapy and bupropion interventions. Among pharmacological interventions, varenicline was the most cost effective and was slightly more cost effective than the pooled behavioural intervention estimate. The prevention of fatal diseases by reducing smoking rates is of great value for improving population health and the prevention of fatal diseases can reduce health-care spending over the medium term of around 15 years. However, the decrease in costs may be illusionary, because over the longer term, there may be increase in both health-care spending and a worsening of government finances.[34] Group-based guidance and e-interventions are probably a way to reduce costs	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Lower socioeconomic groups are more likely to have earlier onset of dementia than higher socioeconomic groups. Older people from lower socioeconomic backgrounds are also more likely to experience cognitive dysfunction at earlier stages of cognitive decline and cognitive impairment, and will have fewer resources to cope with the symptoms than their counterparts from higher socioeconomic groups People from lower socioeconomic groups are more likely to live, work and age in physical and economic environments that do not support social connectedness, physical activity or mental stimulation. this can increase the risk of cognitive impairment and dementia in later life.[35] Based on this it is believed that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	

	Furthermore, women are disproportionally affected with AD. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men.[36]	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Very scarce evidence is available on acceptability of tobacco cessation interventions in older adults or in relevant population. A study on Acceptability of an Internet-based contingency management intervention for tobacco cessation, showed that this is an acceptable method to support people in tobacco cessation.[37] Acceptability probably varies between pharmacological and non-pharmacological interventions.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Interventions aimed at smoking cessation can be based on behavioural/psychological and/or pharmacological strategies. Key barriers are costs and lack of motivation.	-population/political level versus individual level

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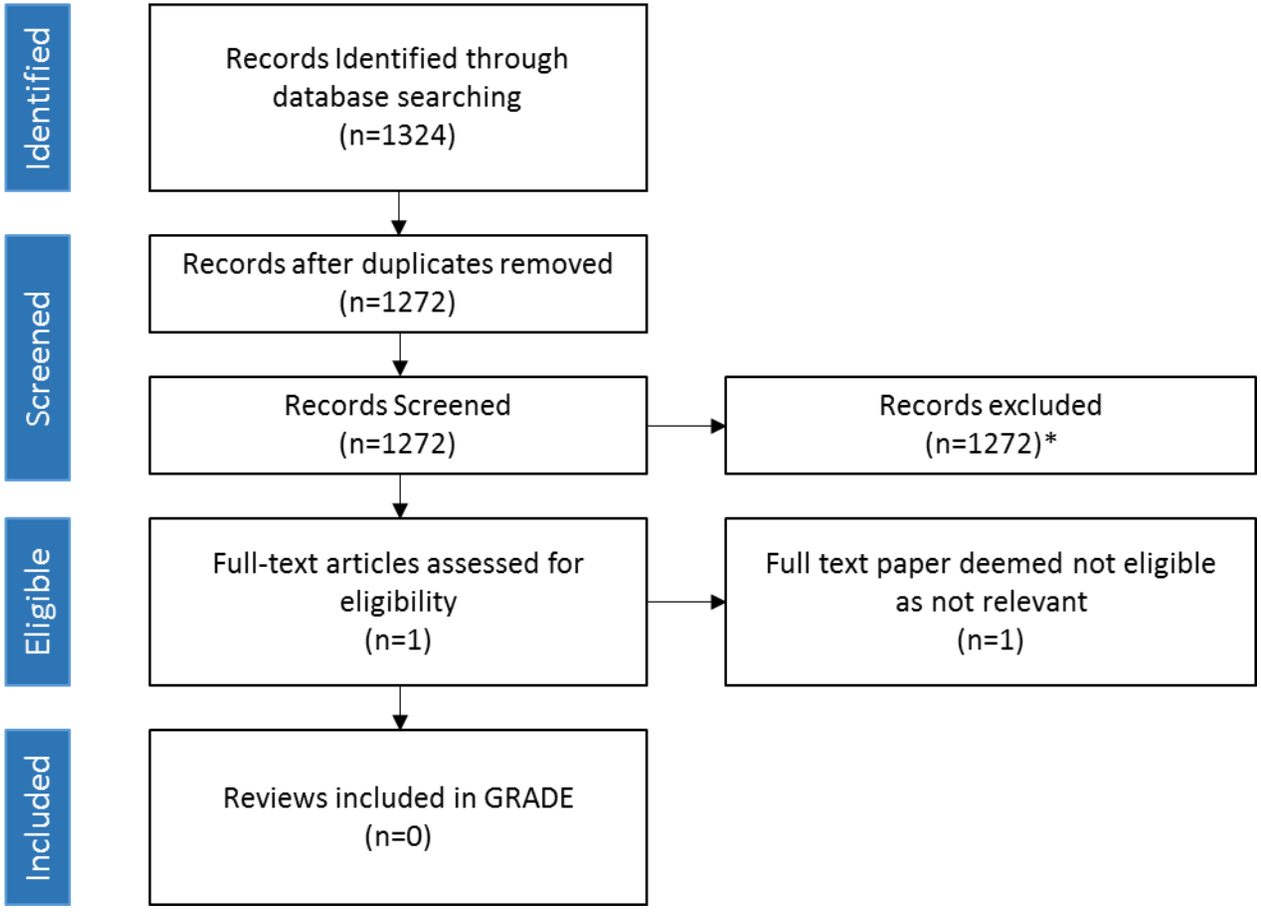
Annex: PRISMA flow diagram for systematic review of the reviews – cognitive decline interventions[1]



* 3 systematic reviews (one including meta-analysis), 2 meta-analysis and 1 multi-cohort study (n>26000) included in the narrative description of observational evidence

[1] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For more information: http://www.prisma-statement.org

Risk reduction guidelines for cognitive decline and dementia

Evidence profile:
Diet and cognitive decline or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment, are nutritional interventions such as dietary supplements or healthy dietary patterns (eg. Mediterranean diet) more effective than usual care or no intervention in reducing the risk/progression of cognitive decline and/or dementia?

Background

As the number of older adults increases worldwide, a rise in dementia and Alzheimer's disease (AD) has also been reported,[1] causing health, economic and social burdens.[2,3] In 2015, it has been estimated that there were 46.8 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050.[1] AD/dementia has been linked to modifiable, lifestyle-related and cardiovascular risk factors[1-4] and since the management of cardiovascular diseases is still suboptimal in many countries, especially among older adults and no cure is available for AD, management of cardiovascular risks could be crucial in halting the rapid increase in the prevalence of dementia, as some projection models suggested.[5,6]

Healthy diet throughout the life-course plays a crucial role in maintaining health and preventing non-communicable diseases. Adherence to healthy dietary patterns has been associated with lower risk of diabetes,[7,8] cardiovascular disease,[9,10] and cancer.[11,12] Previous dietary intervention studies have shown that dietary changes are involved in prevention of many conditions that increase the risk of dementia, such as diabetes[13,14] and cardiovascular disease.[15] Mechanistic and animal models have suggested a variety of pathways that link dietary factors to neuropathological changes in the development of dementia, for example oxidative stress, mitochondrial dysfunction, deficits in cellular energy production, as well as inflammatory mechanisms.[16] Therefore, dietary factors may be involved in the development of dementia, both directly and through their role on other risk factors, and healthy diet may have a great preventive potential for cognitive impairment.

The Mediterranean Diet (MeDi) is most extensively studied dietary approach, in general as well as in relation to cognitive performance. Several systematic reviews of observational studies already concluded that high adherence to MeDi is associated with decreased risk of mild cognitive impairment (MCI) and AD, but not modest adherence was not.[17,18] Among participants with normal cognition, higher adherence is associated with better episodic memory and global cognition.[19] Other promising dietary approaches, which correlated with better cognitive function include: dietary approaches to stop hypertension (DASH);[20-22] the dietary inflammatory index;[23,25] and the brain health-specific Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND).[21,26,27]

Concerning individual foods and nutrients, consumption of fruit and vegetables[28,29] and fish[30,31] are most consistently associated with decreased risk of dementia. Higher fish consumption has been linked to lower memory decline among healthy participants in many studies,[32] as well as intake of fish-derived fatty acids.[31] Other foods and nutrients that have been associated with risk of dementia or cognitive impairment are nuts, olive oil, and coffee.[33] evidence have been reported also concerning folate, vitamin E, carotenes, vitamin C, and vitamin D,[34-37] but findings are inconsistent.

This review of systematic reviews was carried out to search, identify, and synthesise the evidence currently available on the efficacy of dietary interventions (dietary supplements or healthy dietary patterns) aimed at reducing the risk of dementia and/or cognitive impairment.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment, are nutritional interventions such as dietary supplements or healthy dietary patterns (eg. Mediterranean diet) more effective than usual care or no intervention in reducing the risk/progression of cognitive decline and/or dementia?

- ✓ P: Adults with normal cognition or mild cognitive impairment
- ✓ I: a. dietary supplements; b. healthy dietary patterns (e.g. Mediterranean diet)
- ✓ C: Care as usual or no intervention
- ✓ O: *Critical*
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Dementia

  Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Date of search: 01st June 2018

Search starting time: 31st December 2012

Full search terms

(dementia OR cognit* OR "mild cognitive impairment" OR "Alzheimer disease" OR Alzheimer* OR "dementia vascular" OR "dementia multi-infarct" OR MCI OR "cognitive dysfunction" OR neuropsychologi* OR "Health-Related Quality Of Life" OR "life quality" OR "quality of life" OR "Activities of Daily Living" OR "Chronic Limitation of Activity" OR "Limitation of Activity, Chronic" OR ADL OR "activities of daily living" OR "Drug-Related Side Effects and Adverse Reactions" OR "Adverse Drug Event" OR "Adverse Drug Reaction" OR "Long Term Adverse Effects" OR "Adverse Effects, Long Term" OR "Disease-Free Survival" OR "Event-Free Survival" OR "Adverse effects") AND ("Dietary supplements" OR "Dietary Supplementations" OR "Food Supplementations" OR "Food Supplements" OR "Herbal Supplements" OR Neutraceuticals OR Nutraceuticals OR Nutriceuticals OR diet or vitamin or food)

Simplified search terms

(dementia OR cognit* OR "mild cognitive impairment" OR Alzheimer* OR neuropsychologi* OR "Health-Related Quality Of Life") AND (Dietary OR Herbal OR Neutraceuticals OR Nutraceuticals OR Nutriceuticals OR diet or vitamin or food)

*Searches were conducted in the following databases**:

- Cochrane
- Pubmed
- NICE Guidelines
- Embase
- PsycInfo
- Global Health Library (Including WHOLIS, PAHO, AIM, LILACS)
- Database of impact evaluations
- AFROLIB
- ArabPsycNet
- HERDIN NeON
- HrCak
- IndMED
- KoreaMed

- AJOL

* Please note that the EurasiaHealth database did not return any meaningful answer to the search.

List of systemic reviews identified by the search process

Included in GRADE[1] tables:

Comparison 1: Supplement multi-complexes vs placebo in adults with normal cognition

D'Cunha NM, Eorgousopoulou EN, Dadigamuwage L, Kellett J, Panagiotakos DB, Thomas J, McKune AJ, Mellor DD, Naumovski N. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. Br J Nutr. 2018 Feb;119(3):280-298.

Comparison 2: Supplement multi-complexes vs placebo in adults with MCI

Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. CMAJ Open. 2015 Dec 1;3(4):E419-27.

Comparison 3: Poly Unsaturated Fatty Acids (PUFAs) vs placebo

Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.

Comparison 4: Vitamin B vs placebo

Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.

Comparison 5: Vitamin E vs placebo

Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.

Comparison 6: Polyphenols vs placebo

Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V,Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R, Bellomo A, Greco A,Daniele A, Seripa D, Sabbà C, Logroscino G, Panza F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy OlderAdults: A Systematic Review. J Alzheimers Dis. 2018 May 26.

[1] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

Comparison 7: Protein supplementation vs placebo

Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V,Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R, Bellomo A, Greco A,Daniele A, Seripa D, Sabbà C, Logroscino G, Panza F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy OlderAdults: A Systematic Review. J Alzheimers Dis. 2018 May 26.

Comparison 8: Chicken essence vs placebo

Teoh SL, Sudfangsai S, Lumbiganon P, Laopaiboon M, Lai NM, Chaiyakunapruk N. Chicken Essence for Cognitive Function Improvement: A Systematic Review and Meta-Analysis. Nutrients. 2016 Jan 20;8(1).

Comparison 9: Mediterranean diet vs alternate or usual diet

Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA.Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. Am J Clin Nutr. 2018 Mar 1;107(3):389-404.

PICO Table

Serial Number	Intervention vs Comaprison & Population	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1.	Multi-complex supplements vs placebo in adults with normal cognition	Incidence of dementia	D'Cunha NM, eorgousopoulou EN, Dadigamuwage L, Kellett J, Panagiotakos DB,Thomas J, McKune AJ, Mellor DD, Naumovski N. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. Br J Nutr. 2018 Feb;119(3):280-298.	Most recent (moderate quality) systematic review including evidence on the effect of multi-complex supplements on the incidence of dementia in adults with normal cognition
		MCI	D'Cunha NM, eorgousopoulou EN, Dadigamuwage L, Kellett J, Panagiotakos DB,Thomas J, McKune AJ, Mellor DD, Naumovski N. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. Br J Nutr. 2018 Feb;119(3):280-298.	Most recent (moderate quality) systematic review including evidence on the effect of multi-complex supplements on the incidence of dementia in adults with normal cognition
		Cognitive function	D'Cunha NM, eorgousopoulou EN, Dadigamuwage L, Kellett J, Panagiotakos DB,Thomas J, McKune AJ, Mellor DD, Naumovski N. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. Br J Nutr. 2018 Feb;119(3):280-298.	Most recent (moderate quality) systematic review investigating the effect of multi-complex supplements on cognition in adults with normal cognition.
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
2.		Incidence of dementia	No relevant systematic review available	N/A

	Multi-complex supplements vitamiPoluvs placebo in adults with MCI	MCI	No relevant systematic review available	N/A
		Cognitive function	Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. CMAJ Open. 2015 Dec 1;3(4):E419-27.	Most recent (moderate quality) systematic review investigating the effect of multi-complex supplements on cognition in adults with MCI.
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. CMAJ Open. 2015 Dec 1;3(4):E419-27.	Most recent (moderate quality) systematic review investigating the effect of multi-complex supplements on serious adverse events in adults with normal cognition.
		Dropout Rates	No relevant systematic review available	N/A
3.	Poly Unsaturated Fatty Acids (PUFAs) vs placebo	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.	Most recent (moderate quality) systematic review and meta-analysis investigating the effect of PUFA on cognition
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
4.	Vitamin B vs placebo	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A

		Cognitive function	Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.	Most recent (moderate quality) systematic review and meta-analysis investigating the effect of B vitamins on cognition
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
5.	Vitamin E vs placebo	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.	Most recent (moderate quality) systematic review and meta-analysis investigating the effect of E vitamins on cognition
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
6.	Polyphenols vs placebo	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V,Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R, Bellomo A, Greco A,Daniele A, Seripa D, Sabbà C, Logroscino G, Panza F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy OlderAdults: A Systematic Review. J Alzheimers Dis. 2018 May 26.	Only available (low quality) systematic review investigating the effect of polyphenols on cognition

		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
7.	Protein supplementation vs placebo	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V,Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R, Bellomo A, Greco A,Daniele A, Seripa D, Sabbà C, Logroscino G, Panza F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy OlderAdults: A Systematic Review. J AlzheimersL-carnitine Dis. 2018 May 26.	Only available (low quality) systematic review investigating the effect of protein supplementation on cognition
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A
8.	chicken essence vs placebo	Incidence of dementia	No relevant systematic review available	N/A
		MCI	No relevant systematic review available	N/A
		Cognitive function	Teoh SL, Sudfangsai S, Lumbiganon P, Laopaiboon M, Lai NM, Chaiyakunapruk N. Chicken Essence for Cognitive Function Improvement: A Systematic Review and Meta-Analysis. Nutrients. 2016 Jan 20;8(1).	Only available (moderate quality) systematic review investigating the effect of chicken essence on cognition
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	Teoh SL, Sudfangsai S, Lumbiganon P, Laopaiboon M, Lai NM, Chaiyakunapruk N. Chicken Essence for Cognitive Function Improvement: A Systematic Review and Meta-Analysis. Nutrients. 2016 Jan 20;8(1).	Only available (moderate quality) systematic review investigating the effect of chicken essence on cognition

				including assessment of adverse events.
		Dropout Rates	No relevant systematic review available	N/A
9.	Mediterranean diet vs alternate or usual diet	Incidence of dementia	Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA.Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. Am J Clin Nutr. 2018 Mar 1;107(3):389-404.	Most recent, best quality (moderate) systematic review investigating the effect of Mediterranean diet on incidence of dementia.
		MCI	Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA.Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. Am J Clin Nutr. 2018 Mar 1;107(3):389-404.	Most recent, best quality (moderate) systematic review investigating the effect of Mediterranean diet on incidence of MCI.
		Cognitive function	Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA.Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. Am J Clin Nutr. 2018 Mar 1;107(3):389-404.	Most recent, best quality (moderate) systematic review (and only available with meta-analysis) investigating the effect of Mediterranean diet on cognition.
		Quality of Life	No relevant systematic review available	N/A
		Functional levels (ADL)	No relevant systematic review available	N/A
		Adverse events	No relevant systematic review available	N/A
		Dropout Rates	No relevant systematic review available	N/A

Narrative descriptions of the studies that went into the analysis

GRADE tables 1-2: Multi-supplement complexes in adults with normal cognition or MCI

Grade tables 1-2 present the evidence from two systematic reviews that assessed the effects of multi-supplement complexes on cognitive decline and dementia incidence in adults with normal cognition[38] and in adults with MCI.[39]

D'Cunha et al. (2018) systematically reviewed the evidence for the long-term use of common nutraceuticals and dietary supplements to improve cognition in elderly participants (65+ years).[38] Trials with intervention duration of at least 1 year were considered and full-text articles were reviewed and independently assessed for risk of bias by two researchers using the Cochrane guidelines criteria. 25 studies were included; of these, five reported evidence on multi-supplement complexes.[40-44] The main outcomes included MMSE, Telephone Interview of Cognitive Status (TICS), ADAS-cog, mRAVLT, The Clinical Dementia Rating Scale (CDR), CVLT, Alzheimer's Disease Cooperative Study-activities of daily living inventory and East Boston Memory Test (EBMT).

One study[44] reported on incident dementia (N=2034) but found no significant (p=0.64) association with between the treatment and the outcome. A very small number of newly diagnosed cases of dementia were included in trials, which limited the statistical power. In addition, publication bias was suspected due to the search conducted in a very limited number of databases, and no other source of evidence. The same study reported about incidence of MCI, but again, with no significant (p=0.72) results. For cognitive function a total of 12888 participants were included in the five trials considered which included different types of multi-complex supplements in their intervention (n-3 Fatty Acids; multivitamin; multivitamin and multimineral; vitamins C and E; and calcium and vitamin D3). None of the study showed a statistically significant correlation between treatment and cognitive outcomes. Also, selection and attrition bias was identified in some of these studies and publication bias was suspected due to the search conducted in a very limited number of databases and no other source of evidence (GRADE table 1).

Fitzpatrick-Lewis et al (2015) conducted a systematic review to evaluate the effectiveness and harm of various treatments for MCI in 65 years old or older.[39] The articles identified were reviewed by two independent researchers and assessed using the Cochrane risk-of-bias tool. The authors identified four studies that reported on the effect of dietary supplements or vitamin complexes.[45-48] The interventions included: folic acid + cyanocobalamin + pyridoxine HCl; docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA); vitamins C + E; vitamin E + multivitamin. Cognition was assessed with MMSE. The meta-analysis carried out showed no difference between the intervention and control groups (MD 0.2; 95% CI -0.04-0.43). Three studies[48-50] were identified reporting about the effect of multi-supplement complexes on serious adverse events. Two of the interventions were different from those of the studies included in the cognitive assessment (DHA + EPA + vitamin E +soy phospholipids + tryptophan + melatonin; vitamin E + multivitamin; lyophilised royal jelly + gingko biloba + panax ginseng). For adverse events, none of the studies (total N=860) reported any serious adverse event during the follow up period. Overall, Publication bias was suspected due to search limited to the previous 2.5 years (GRADE table 2).

GRADE tables 3-8: individual supplements or single nutraceuticals categories

GRADE tables 3-8 present the evidence on individual categories of supplements and nutraceuticals on dementia and/or cognitive decline.

A systematic review and meta-analyses[51] investigated the effect of various nutrients and dietary supplements on cognition in non-demented people aged 40 and older. The authors followed the Cochrane guidelines for systematic reviews and the reporting was done in accordance to the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA).[52] Risk of bias was assessed using the Cochrane criteria. Meta-analyses were conducted if three or more studies with the same outcome measure were identified.

For PUFA, Forbes et al. (2015)[51] identified six studies examining the effects of omega-3 fatty acid supplementation on cognitive functioning and five[53-57] were included in the meta-analyses which investigated the effect of the treatment on global cognition and memory. Among these studies, large variability was reported concerning to the dosage used (400 mg to 2200 mg) and duration of the intervention (6 months to 3.3 years). Evidence were downgraded for risk of bias, because one of the studies included (accounting from more than 50% of the overall population) was deemed at high risk for randomisation and blinding bias. In the meta-analyses (GRADE table 3), the interventions showed no significant effect neither on global cognition (mean 0.06; 95%CI -0.08-0.19) nor memory (mean 0.02; 95%CI -0.3-0.25).

Forbes et al. (2015) also reviewed RCTs investigating the effects of vitamin B on dementia and cognitive decline.[51] They identified seven studies reporting about interventions that included various combinations of folate, B6 and/or B12 vitamins on cognition and three[47,58,59] were included in the meta-analysis. Interventions varied in regard to dose, intervention duration (12 weeks to 6.6 years), participant health status (suffering from or at risk for cardiovascular disease to healthy community-dwelling individuals), and cognitive outcomes assessed. Inconsistent results were seen with some studies reporting modest benefits in at least one cognitive domain, while others found no effect. The effect of the intervention on the MMSE scores in the three pooled studies (GRADE table 4) was non-significant (SMD 0.02; 95% CI -0.22 - 0.25).

Forbes et al. (2015)[51] also reviewed the evidence of the effect of vitamin E on cognitive function. The authors identified three trials[48,60,61] (total N=9970) investigating the effect of vitamin E supplementation (duration of the trials 3-9.6 years). One trial was limited to participants with amnestic mild cognitive impairment. No statistically significant effect on any of the cognitive outcomes examined was found (GRADE table 5). Evidence was downgraded due to high risk of randomisation and blinding bias in two of three studies (which accounted for 92% of the overall population).

Evidence related to the effect of polyphenols on risk of cognitive decline was reviewed recently by Solfrizzi et al. (2018)[62]. The review was conducted according to the PRISMA guidelines. The authors identified eight RCTs[63-70] that evaluated the effect of non-flavonoid flavonoids polyphenols and on late life cognitive disorders and dementia in cognitively healthy subjects aged 60 years or more. All three[63-65] studies included in the systematic reviews that investigated the effect of non-flavonoids polyphenols reported an improvement in the cognitive status upon treatment, in at least one of the cognitive outcomes. Four[66,68-70] of the fives studies included in the systematic review that investigated the effect of flavonoids polyphenols reported an improvement of the cognitive status upon treatment. Evidence were downgraded due to indirectness, since 53% of the participants were represented by an over-selected population (post-menopausal women). Publication bias was also suspected, because of limited search terms and data sources were used (GRADE table 6).

In the same systematic review,[64] Solfrizzi et al (2018) also investigated the effect of protein supplementation in reducing risk of dementia and cognitive decline in cognitively healthy persons aged 60 or older. The authors identified a total of five studies[71-75] that investigated the effect of different protein-related supplementation interventions (protein mix; chicken meat extract containing 40% of carnosine related compounds (CRC); imidazole dipeptide formula containing CRCs (n= 2 studies); and L-carnitine) on several cognitive domains (episodic memory; attention and working memory; information processing speed; and executive functioning). The four interventions which included[71-74] a treatment with protein complexes, showed significant improvements in at least one of the cognitive outcomes (reaction time, construction/copying, recall, episodic memory). RCTs reported also promising results not only in terms of cognitive outcomes, but also magnetic resonance imaging (MRI) findings. In addition, protein supplementation improved functional status in pre-frail older adults without effect on cognitive function. Evidence was downgraded due to low due to small sample size (N=186) of overall population and publication bias was suspected due to limited search terms, data sources and time-span of the search (GRADE table 7).

Finally, Teoh et al. (2016)[76] conducted a systematic review and meta-analyses assessing the effect of chicken essence (CE) on executive functioning and short-term memory. Systematic review was performed according to PRISMA guidelines. Studies were screened by two independent reviewers and the Cochrane's Risk of Bias tool was used to assess their quality. Seven[77-83] trials (six on healthy subjects and one on individuals with poorer cognition), were identified and included in meta-analysis. Meta-analysis was conducted on three cognitive outcomes; CE showed a significant beneficial effect on executive function measured with Nagai's mental arithmetic test or serial seven (SMD -0.55; 95%Cl -1.04 - -0.06), but not when this cognitive domain was assessed with Digit tests (SMD 0.70; 95% Cl -0.001- 1.40); CE showed also a non-significant effect on short-term memory (SMD 0.63; 95% Cl -0.16 - 1.42). Evidence was downgraded due to: high risk of bias for sequence generation, blinding, incomplete outcome data, and selective reporting identified in some of the studies considered; low sample size; and heterogeneity. (GRADE table 8).

GRADE table 9: Mediterranean diet

A very recent systematic review by Radd-Vagenas et al. (2018)[84] reviewed the evidence on the effect of MeDi on the risk of dementia and/or cognitive decline, according to the PRISMA guidelines. Studies that described their intervention as a Mediterranean diet or Mediterranean-style dietary pattern were both included. The comparator included an alternate (low fat) or usual diet. Outcomes included incident dementia and MCI as well as cognitive assessments. A meta-analyses were conducted on the cognitive outcomes. Nine articles[85-93] from five different RCTs (N=1888) were identified. The intervention varied considerably between studies. Concerning the incident dementia and MCI outcomes, no significant differences were identified between the control and the intervention group. The meta-analyses on cognitive outcomes showed a significant beneficial effect of MeDi only on verbal and visual memory (SMD 0.19; 95% Cl 0.03-0.36); however a positive trend was identified for all the other outcomes and global cognition was extremely close to statistical significance (SMD 0.24; 95% Cl-0.00 – 0.47). Quality of the evidence was in moderate in six out of the seven cognitive outcomes and very low in one (GRADE table 9). Evidence were mostly downgraded due to: risk of blinding or reporting bias; heterogeneity; and indirectness, when a large proportion of the control population received a low-fat diet.

Additional evidence

Also five additional systematic reviews assessing the effects of single nutrients/supplements on cognition were identified. These systematic reviews were not included in GRADE due to their critically low quality or if a more recent reviews of the same quality were available covering the same intervention/comparison but for completeness, main findings from these systematic reviews are presented here.

Jiao et al.[94] conducted a systematic review (moderate quality) assessing the effects of n-3 PUFA supplementation on cognitive function throughout the life span from infancy to old age. The review included RCTs that provided treatment with n-3 PUFA for 3 months or more. A total of 12 out of 34 RCTs investigated cognitive function, cognitive decline and related diseases in older people (n=6794). Different interventions with vegetable oils vs placebo were used. N-3 PUFA supplementation significantly improved the attention domain among elderly (0.29; 95% CI 0.10, 0.47) but cognitive decline measured using MMSE, in the elderly, was not affected. Further, n-3 PUFAs did not have any positive effects on any cognitive domains. The authors concluded that n-3 PUFA supplementation does not appear to improve cognitive function in elderly nor does it prevent cognitive decline.

Ford at al. (2012)[95] conducted a systematic review and meta-analysis (moderate quality) of 19 (N=5 398) English language randomised, placebo-controlled trials of homocysteine lowering B-vitamin supplementation of individuals with and without cognitive impairment. Trials with two arms (i.e. placebo versus a vitamin comparator)

were included in the meta-analysis. 62 different cognitive tests were included in the meta-analysis. The primary outcome of interest was change in cognitive function associated with treatment with B-vitamins or placebo in older adults with and without cognitive impairment. B-vitamin supplementation did not show an improvement in cognitive function for individuals with (SMD = 0.10; 95%CI −0.08 to 0.28) or without (SMD =−0.03; 95%CI −0.1 to 0.04) significant cognitive impairment. Additionally, no benefit for B-vitamins was found when the authors restricted the analyses to trials from areas of low/medium folate availability. The authors concluded that supplementation of vitamins B12, B6, and folic acid alone or in combination does not appear to improve cognitive function in individuals with or without existing cognitive impairment.

Thaung Zaw et al. (2017)[96] conducted a systematic review (critically low quality) examining the effects of phytoestrogen supplementation on cognition. Cognitive outcomes evaluated objectively by neuropsychological test batteries were included in the review. The authors identified 23 RCTs, 15 with isoflavone and eight with resveratrol or grape formulations. The duration of supplementation in the included studies varied from 4 weeks to 2.5 years. Six soy isoflavone studies showed positive cognitive effects of medium size. Greater benefits were seen in women who were <10 years postmenopausal and supplemented for <6months. Small-to-medium effect–size cognitive benefits of resveratrol were reported in four studies of older adults of mixed gender and in postmenopausal women who took 150–200 mg resveratrol daily for at least 14 weeks. No benefits were seen in three studies using red clover or grape formulations. Supplementation with either soy isoflavone or resveratrol improved executive function and memory domains of cognitively normal older adults in half of the included studies, mostly with medium effect sizes. The cognitive benefit of resveratrol was related to improved cerebral perfusion. The authors conclude that effects of isoflavone supplementation on human cognition remains conflicting, with less than half of the included studies showing beneficial effects.

Lamport et al. (2014)[97] conducted a review (critically low quality) including epidemiological and intervention studies examining the cognitive effects of fruit, vegetable, and juice consumption. The authors identified altogether 25 suitable studies that met the criteria for inclusion: 19 epidemiological studies and 6 dietary intervention studies. A total of 3 of 6 intervention studies reported significant benefits of fruit, vegetable, or juice consumption for cognitive performance. Positive findings were reported by the studies in which grape or blueberry juice was consumed daily by participants for a period of 12–16 weeks. However, the sample sizes were small (ranging from 9 to 21). The authors concluded that very limited data from acute interventions indicated that consumption of fruit juices can have immediate benefits for memory function in adults with mild cognitive impairment but acute benefits were not observed in healthy adults.

Finally, loughrey et al. (2017)[19] conducted a systematic review and meta-analyses examining the impact of the Mediterranean diet on the cognitive functioning of healthy older adults. Review included 2 RCTs (n=471). Meta-analysis of RCTs showed that compared with controls, the Mediterranean diet improved delayed recall, working memory and global cognition, but not other cognitive domains (episodic memory, immediate recall, paired associates, attention, processing speed or verbal fluency). Because of a lack of RCTs, the results were observed in single trials rather than in pooled analyses, making any conclusions tentative.

WHO's Healthy Diet fact sheet provides the key elements of a healthy diet (summarized below) to protect against noncommunicable diseases (NCDs), including diabetes, heart disease, stroke and cancer[105].

- Energy intake (calories) should be in balance with energy expenditure. Evidence indicates that total fat should not exceed 30% of total energy intake to avoid unhealthy weight gain. Intake of saturated fats should be less than 10 % of total energy intake and trans-fats to less than 1% of total energy intake, with a shift in fat consumption away from saturated fats and trans-fats to unsaturated fats, and towards the elimination of industrial trans fats.
- Limiting intake of free sugars to less than 10% of total energy intake is part of a healthy diet. A further reduction to less than 5% of total energy intake is suggested for additional health benefits.

- Keeping salt intake to less than 5 g per day helps prevent hypertension and reduces the risk of heart disease and stroke in the adult population

GRADE Tables

GRADE table 1

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Multi-supplement complexes compared to placebo for reducing the risk of dementia and/or cognitive decline in adults with normal cognition
Setting:
Bibliography: D'Cunha NM, Eorgousopoulou EN, Dadigamuwage L, Kellett J, Panagiotakos DB, Thomas J, McKune AJ, Mellor DD, Naumovski N. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. Br J Nutr. 2018 Feb;119(3):280-298.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Incidence of dementia (follow up: mean 7 years; assessed with: newly diagnosed dementia cases)									
1	randomised trials	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	A total of 2034 participants were included in the trial[1] and no significant (p=0.64) association between treatment and incident dementia was identified.	⨁⨁◯◯ LOW	CRITICAL
Incidence of MCI (follow up: mean 7 years; assessed with: newly diagnosed cases of MCI)									
1	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	A total of 2034 participants were included in the trial[1] and no significant (p=0.72) association between treatment and incident MCI was identified.	⨁⨁⨁◯ MODERATE	CRITICAL
Cognitive function (follow up: mean 8.2 years; assessed with: a range of neuropsychological tests)									
5	randomised trials	serious [c]	not serious	not serious	not serious	publication bias strongly suspected [b]	A total of 12888 participants were included in the five trials[2] considered which included different types of multi-complex supplements in their intervention. None of the study showed a statistically significant correlation between treatment and cognitive outcomes.	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval
Explanations
a. Downgraded due to a very small number of newly diagnosed cases of dementia (39 and 37 in the intervention and control arms respectively) which limited the statistical power.
b. Publication bias suspected due to the search been conducted on a limited number of database and no other source of evidence.
c. Downgraded due to selection and attrition bias identified in some of the studies, which accounts for a large part (84%) of the overall population included.

Intervention description

1. Calcium and vitamin D_3
2. n-3 Fatty Acids; multivitamin; multivitamin and multimineral; vitamins C and E; calcium and vitamin D3

GRADE table 2

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Multi-supplement complexes compared to placebo for reducing the risk of dementia and/or cognitive decline in adults with MCI
Setting:
Bibliography: Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. CMAJ Open. 2015 Dec 1;3(4):E419-27.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**multi-complex supplements**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognitive function (follow up: immediate post-intervention; assessed with: MMSE; Scale from: 0 to 30; higher score = better cognition)												
4	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	511 [1]	519 [1]	-	MD **0.2 higher** (0.04 lower to 0.43 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: mean 32.4 months; assessed with: reported adverse events)												
3	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [a]	None of the studies[2] (total N=860) reported any serious adverse event during the follow up period.				⊕⊕⊕◯ MODERATE	IMPORTANT

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

Explanations

a. Publication bias suspected due to search limited to the previous 2.5 years.

Intervention description

1. folic acid + cyanocobalamin + pyridoxine HCl; docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA); vitamins C + E; vitamin E + multivitamin.
2. DHA + EPA + vitamin E +soy phospholipids + tryptophan + melatonin; vitamin E + multivitamin; lyophilised royal jelly + gingko biloba + panax ginseng.

GRADE table 3

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: PUFA compared to placebo for reducing risk of dementia and/or cognitive decline
Setting:
Bibliography: Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PUFA**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognition MMSE (follow up: mean 36.1 months; assessed with: MMSE; Scale from: 0 to 30; higher score = better cognition)												
4	randomised trials	serious [a]	not serious	not serious	not serious	none	1350	1363	-	mean **0.06 points higher** (0.08 lower to 0.19 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognition Memory (follow up: mean 19.3 months; assessed with: Digit Span forward; Scale from: 1 to 19; higher score = better cognition)												
3	randomised trials	not serious	not serious	not serious	not serious	none	577	476	-	mean **0.02 points lower** (0.3 lower to 0.25 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval
Explanations
a. One of the studies included (accounting from more than 50% of the overall population) was deemed at high risk for randomisation and blinding bias.

GRADE table 4

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Vitamin B compared to placebo for reducing risk of dementia and/or cognitive decline
Setting:
Bibliography: Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**vitamin B**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognition MMSE (follow up: mean 2 years; assessed with: MMSE; higher score = better cognition)												
3	randomised trials	not serious	not serious	not serious	not serious	none	335	362	-	mean **0.02 points higher** (0.22 lower to 0.25 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval

GRADE table 5

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Vitamin E compared to placebo for reducing the risk of dementia and/or cognitive decline
Setting:
Bibliography: Forbes SC, Holroyd-Leduc JM, Poulin MJ, Hogan DB. Effect of Nutrients, Dietary Supplements and Vitamins on Cognition: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Can Geriatr J. 2015 Dec 23;18(4):231-45.

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Cognitive function (follow up: mean 7.9 years; assessed with: a range of neuropsychological tests)									
3	randomised trials	serious [a]	not serious	not serious	not serious	none	In none of the three studies (total N=9970) a statistically significant effect on any of the cognitive outcomes examined was found.	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval
Explanations
a. Downgraded due to moderate risk of bias for randomisation and blinding identified in two of the three studies included which account for 92% of the overall population.

GRADE table 6

Author(s): Mariagnese Barbera; Jenni Kulamala; Jenni Lethisalo
Date:
Question: Polyphenols compared to placebo for reducing the risk of dementia and/or cognitive decline
Setting:
Bibliography: Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V,Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R, Bellomo A, Greco A,Daniele A, Seripa D, Sabbà C, Logroscino G, Panza F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy Older Adults: A Systematic Review. J Alzheimers Dis. 2018 May 26.

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Cognitive function (follow up: mean 16.3 months; assessed with: a range of neuropsychological tests and assessments)									
8	randomised trials	not serious	not serious	serious [a]	not serious	publication bias strongly suspected [b]	All three studies included in the systematic reviews that investigated the effect of non-flavonoids polyphenols[1] reported an improvement in the cognitive status upon treatment, in at least one of the cognitive outcomes. Four of the fives studies included in the systematic review that investigated the effect of flavonoids polyphenols[2] reported an improvement of the cognitive status upon treatment.	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval
Explanations
a. Downgraded due to the presence of a significant proportion (53%) of over-selected participants (post-menopausal women) in the overall population.
b. Publication bias suspected due to a limited search both in terms of sources (6 databases and no other source) and period of search (4 previous years).
Intervention Description
1. Resveratrol + quercetin; resveratrol; Biocurcumax™ (curcumin extract).
2. Flavanol (2 studies); isoflavone-rich soy protein; high flavanone drink; mixed berry beverage.

GRADE table 7

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Protein supplementation compared to placebo for reducing the risk of dementia and/or cognitive decline
Setting:
Bibliography: Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Valiani V,Sardone R, Dibello V, Di Lena L, Lamanna A, Stallone R, Bellomo A, Greco A,Daniele A, Seripa D, Sabbà C, Logroscino G, Panza F. Nutritional Intervention as a Preventive Approach for Cognitive-Related Outcomes in Cognitively Healthy Older Adults: A Systematic Review. J Alzheimers Dis. 2018 May 26.

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Cognitive function (follow up: mean 3.8 months; assessed with: a range of neuropsychological tests)									
5	randomised trials	not serious	not serious	not serious	serious [a]	publication bias strongly suspected [b]	Interventions in the four studies that included a treatment with protein complex supplementation[1], conducted in older adults, showed significant improvements in at least one of the cognitive outcomes. The only study that included an intervention with L-creatinine supplementation reported that the intervention had no significant effect on cognitive function.	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval
Explanations
a. Downgraded due to sample size of the overall population (N=186).
b. Publication bias suspected due to limited search both in terms of sources (6 databases and no other source) and time-span of the search (previous 4 years).
Intervention description
1. protein mix; chicken meat extract containing 40% of carnosine related compounds (CRC); imidazole dipeptide formula containing CRCs (n= 2 studies); L-carnitine.

GRADE table 8

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Chicken essence compared to placebo for reducing the risk of dementia and/or cognitive decline
Setting:
Bibliography: Teoh SL, Sudfangsai S, Lumbiganon P, Laopaiboon M, Lai NM, Chaiyakunapruk N. Chicken Essence for Cognitive Function Improvement: A Systematic Review and Meta-Analysis. Nutrients. 2016 Jan 20;8(1).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**chicken essence**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognition Executive function (1) (follow up: mean 9.1 days; assessed with: Nagai's Mental Arithmetic Test; Serial seven; Scale from: N/A to N/A; lower SMD = better cognition)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	68	60	-	SMD **0.55 SD lower** (1.04 lower to 0.06 lower)	⨁⨁◯◯ LOW	CRITICAL
Cognition Executive Function (2) (follow up: mean 11.2 days; assessed with: Digist Span Test; Digit Span Backwards; Scale from: N/A to N/A; higher SMD = better cognition)												
3	randomised trials	serious [c]	serious [d]	not serious	not serious	none	264	198	-	SMD **0.70 SD higher** (0.001 lower to 1.4 higher)	⨁⨁◯◯ LOW	CRITICAL
Cognition Short-term Memory (follow up: mean 11.2 days; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A)												
3	randomised trials	serious [c]	serious [e]	not serious	not serious	none	264	198	-	SMD **0.63 SD higher** (0.16 lower to 1.42 higher)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Downgraded due to high risk of bias for sequence generation and blinding identified in the two either of the included studies.
b. Downgraded due to low sample size.
c. Downgraded due to high risk of bias identified in the included studies for blinding, incomplete outcome data, and selective reporting.
d. Downgraded die to significant heterogeneity (I2=77.7, p=0.01).
e. Downgraded due to significant heterogeneity (I2=82.9, p=0.00).

GRADE table 9

Author(s): Mariagnese Barbera; Jenni Kulmala; Jenni Lehtisalo
Date: 22 June 2018
Question: Mediterranean diet compared to alternate or usual diet for reducing the risk of dementia and/or cognitive decline
Setting:
Bibliography: Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA.Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. Am J Clin Nutr. 2018 Mar 1;107(3):389-404.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mediterranean diet**	**alternate or usual diet**	**Relative (95% CI)**	**Absolute (95% CI)**		
Incidence of Dementia (follow up: mean 6.5 years; assessed with: newly diagnosed cases of dementia)												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	No significant difference in the incident dementia was identified between the control and intervention groups (total N=522)				⨁⨁◯◯ LOW	CRITICAL
Incidence of MCI (follow up: mean 5.6 years; assessed with: newly reported cases of MCI)												
3	randomised trials	not serious	not serious	serious [a]	serious [c]	none	A slightly but not statistically significant incidence of MCI was reported in the intervention group of all the three studies included (N=1254).				⨁⨁◯◯ LOW	CRITICAL
Cognition Global (follow up: mean 4.1 years; assessed with: MMSE; Scale from: 0 to 30; higher SMD = better cognition)												
2	randomised trials	not serious	not serious	serious [a]	not serious	none	239	96	-	SMD **0.24 SD higher** (0 to 0.47 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Cognition Attention (follow up: mean 2.2 months; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A; higher SMD = better cognition)												
3	randomised trials	serious [d]	serious [e]	not serious	serious [f]	none	125	125	-	SMD **1.89 SD lower** (3.82 lower to 0.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognition Working Memory (follow up: mean 37.5 months; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A; higher SMD = better cognition)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mediterranean diet**	**alternate or usual diet**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomised trials	not serious	not serious	serious [g]	not serious	none	413	335	-	SMD **0.2 SD higher** (0.02 lower to 0.42 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognition Processing Speed (follow up: mean 37.5 months; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A; higher SMD = better cognition)												
4	randomised trials	not serious	not serious	serious [g]	not serious	none	254	214	-	SMD **0.07 SD higher** (0.11 lower to 0.25 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognition Verbal and Visual Memory (follow up: mean 37.5 months; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A; higher SMD = better cognition)												
4	randomised trials	not serious	not serious	serious [g]	not serious	none	951	520	-	SMD **0.19 SD higher** (0.03 higher to 0.36 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognition Language (follow up: mean 40.5 months; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A; higher SMD = better cognition)												
2	randomised trials	not serious	not serious	serious [h]	not serious	none	206	164	-	SMD **0.19 SD lower** (0.4 lower to 0.02 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognition Executive Function (follow up: mean 40.5 months; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A; higher SMD = better cognition)												
2	randomised trials	not serious	not serious	serious [h]	not serious	none	206	164	-	SMD **0.22 SD higher** (0.04 lower to 0.48 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

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

Explanations

a. Downgraded due to the control conditions being a low-fat diet.

b. The outcome was ascertained from medical records rather than actual assessment, which could have led to have underestimated the number of cases.

c. Downgraded due to the outcome been ascertained from medical records rather than actual assessment in a large (42%) proportion of the overall population.

d. Downgraded due to all studies deemed at high risk of blinding and reporting bias.

e. Downgraded due to significant heterogeneity (I2=97, p<0.00001).

f. Downgraded due to wide 95% Cls and sample size.

g. Downgraded due to the control being a low fat diet in a large proportion (67%) of the overall population.

h. Downgraded due to the control condition being a low fat diet in a large proportion (73%) of the overall population.

Part 2: From evidence to recommendations

Summary of Findings

Summary of Findings Table 1

Multi-supplement complexes compared to placebo for reducing the risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing the risk of dementia and/or cognitive decline in adults with normal cognition
Setting:
Intervention: multi-supplement complexes
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Incidence of dementia (dementia) assessed with: newly diagnosed dementia cases follow up: mean 7 years	A total of 2034 participants were included in the trial and no significant (p=0.64) association between treatment and incident dementia was identified.	(1 RCT) [1]	⨁⨁◯◯ LOW [a,b]	Multi-supplement complexes do not seem to affect the risk of dementia in adults with normal cognition
Incidence of MCI (MCI) assessed with: newly diagnosed cases of MCI follow up: mean 7 years	A total of 2034 participants were included in the trial and no significant (p=0.72) association between treatment and incident MCI was identified.	(1 RCT) [1]	⨁⨁⨁◯ MODERATE [b]	Multi-supplement complexes do not seem to affect the risk of MCI in adults with normal cognition
Cognitive function (Cognition) assessed with: a range of neuropsychological tests follow up: mean 8.2 years	A total of 12888 participants were included in the five trials considered which included different types of multi-complex supplements in their intervention. None of the study showed a statistically significant correlation between treatment and cognitive outcomes.	(5 RCTs) [2]	⨁⨁◯◯ LOW [b,c]	Multi-supplement complexes do not seem to have an effect on cognition in adults with normal cognition

***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

Multi-supplement complexes compared to placebo for reducing the risk of dementia and/or cognitive decline in adults with normal cognition

Patient or population: reducing the risk of dementia and/or cognitive decline in adults with normal cognition
Setting:
Intervention: multi-supplement complexes
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

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

Explanations

a. Downgraded due to a very small number of newly diagnosed cases of dementia (39 and 37 in the intervention and control arms respectively) which limited the statistical power.
b. Publication bias suspected due to the search been conducted on a limited number of database and no other source of evidence.
c. Downgraded due to selection and attrition bias identified in some of the studies, which accounts for a large part (84%) of the overall population included.

Intervention description

1. Calcium and vitamin D_3

2. n-3 Fatty Acids; multivitamin; multivitamin and multimineral; vitamins C and E; calcium and vitamin D3.

Summary of Findings Table 2

Multi-supplement complexes compared to placebo for reducing the risk of dementia and/or cognitive decline in adults with MCI

Patient or population: reducing the risk of dementia and/or cognitive decline in adults with MCI
Setting:
Intervention: multi-complex supplements
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with multi-complex supplements				
Cognitive function (Cognition) assessed with: MMSE Scale from: 0 to 30 follow up: immediate post-intervention	-	The mean cognitive function in the intervention group was **0.2 higher** (0.04 lower to 0.43 higher)	-	1030 (4 RCTs) [1]	⊕⊕⊕◯ MODERATE [a]	Multi-supplement complexes do not seem to have an effect cognition in adults with MCI
Serious adverse events (Adverse events) assessed with: reported adverse events follow up: mean 32.4 months	None of the studies (total N=860) reported any serious adverse event during the follow up period.			(3 RCTs) [2]	⊕⊕⊕◯ MODERATE [a]	Multi-supplement complexes do not seem to affect the risk of serious adverse events in adults with MCI

***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).
Higher outcome = better cognition
CI: Confidence interval; **MD:** Mean difference

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

Explanations
a. Publication bias suspected due to search limited to the previous 2.5 years.
Intervention description

1. folic acid + cyanocobalamin + pyridoxine HCl; docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA); vitamins C + E; vitamin E + multivitamin.
2. DHA + EPA + vitamin E +soy phospholipids + tryptophan + melatonin; vitamin E + multivitamin; lyophilised royal jelly + gingko biloba + panax ginseng.

Summary of Findings Table 3

PUFA compared to placebo for reducing risk of dementia and/or cognitive decline

Patient or population: reducing risk of dementia and/or cognitive decline
Setting:
Intervention: PUFA
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PUFA				
Cognition MMSE (MMSE) assessed with: MMSE Scale from: 0 to 30 follow up: mean 36.1 months	-	The mean cognition MMSE in the intervention group was **0.06 points higher** (0.08 lower to 0.19 higher)	-	2713 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	PUFA supplementation does not seem to have an effect on cognition assessed through MMSE
Cognition Memory (Memory) assessed with: Digit Span forward Scale from: 1 to 19 follow up: mean 19.3 months	-	The mean cognition Memory in the intervention group was **0.02 points lower** (0.3 lower to 0.25 higher)	-	1053 (3 RCTs)	⨁⨁⨁⨁ HIGH	PUFA supplementation is likely to not have an effect on memory

***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).
Higher score = better cognition.
CI: Confidence interval

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

Explanations
a. One of the studies included (accounting from more than 50% of the overall population) was deemed at high risk for randomisation and blinding bias.

Summary of Findings Table 4

Vitamin B compared to placebo for reducing risk of dementia and/or cognitive decline

Patient or population: reducing risk of dementia and/or cognitive decline
Setting:
Intervention: vitamin B
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin B				
Cognition MMSE (MMSE) assessed with: MMSE follow up: mean 2 years	-	The mean cognition MMSE in the intervention group **was 0.02 points higher** (0.22 lower to 0.25 higher)	-	697 (3 RCTs)	⨁⨁⨁⨁ HIGH	Vitamin B supplementation likely does not have an effect on cognition

***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).
Higher score = better cognition.
CI: Confidence interval

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

Summary of Findings Table 5

Vitamin E compared to placebo for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: vitamin E
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Cognitive function (Cognition) assessed with: a range of neuropsychological tests follow up: mean 7.9 years	In none of the three studies (total N=9970) a statistically significant effect on any of the cognitive outcomes examined was found.	(3 RCTs)	⨁⨁⨁◯ MODERATE [a]	Vitamin E supplementation does not seem to have an effect of cognition

*__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

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

Explanations
a. Downgraded due to moderate risk of bias for randomisation and blinding identified in two of the three studies included, which account for 92% of the overall population.

Summary of Findings Table 6

Polyphenols compared to placebo for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: polyphenols
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Cognitive function (Cognition) assessed with: a range of neuropsychological tests and assessments follow up: mean 16.3 months	All three studies included in the systematic reviews that investigated the effect of non-flavonoids polyphenols[1] (N=222) reported an improvement in the cognitive status upon treatment, in at least one of the cognitive outcomes. Four of the fives studies included in the systematic review that investigated the effect of flavonoids polyphenols[2] (N=504) reported an improvement of the cognitive status upon treatment.	726 (8 RCTs)	⨁⨁◯◯ LOW [a,b]	Polyphenols seem to have a beneficial effect on cognition

*__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

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

Explanations
a. Downgraded due to the presence of a significant proportion (53%) of over-selected participants (post-menopausal women) in the overall population.
b. Publication bias suspected due to a limited search both in terms of sources (6 databases and no other source) and period of search (4 previous years).
Intervention Description
1. Resveratrol + quercetin; resveratrol; Biocurcumax™ (curcumin extract).
2. Flavanol (2 studies); isoflavone-rich soy protein; high flavanone drink; mixed berry beverage.

Summary of Findings Table 7

Protein supplementation compared to placebo for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: protein supplementation
Comparison: placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Cognitive function (Cognition) assessed with: a range of neuropsychological tests follow up: mean 3.8 months	Interventions in the four studies that included a treatment with protein complex supplementation, conducted in older adults, showed significant improvements in at least one of the cognitive outcomes. The only study that included an intervention with L-creatinine supplementation reported that the intervention had no significant effect on cognitive function.	236 (5 RCTs) [1]	⨁⨁◯◯ LOW [a,b]	Protein supplementation in older adults seems to have a beneficial effect cognition

*__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

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

Explanations
a. Downgraded due to sample size of the overall population (N=236).
b. Publication bias suspected due to limited search both in terms of sources (6 databases and no other source) and time-span of the search (previous 4 years).
Intervention description
1. protein mix; chicken meat extract containing 40% of carnosine related compounds (CRC); imidazole dipeptide formula containing CRCs (n= 2 studies); L-carnitine.

Summary of Findings Table 8

Chicken essence compared to placebo for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: chicken essence
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with chicken essence				
Cognition Executive function (1) (Executive function) assessed with: Nagai's Mental Arithmetic Test; Serial seven follow up: mean 9.1 days	-	SMD **0.55 SD lower** (1.04 lower to 0.06 lower)	-	128 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	Chicken essence seem to have a beneficial effect on cognition measured with Nagai's Mental Arithmetic Test or Serial seven.
Cognition Executive Function (2) (Executive Function) assessed with: Digist Span Test; Digit Span Backwards (lower SMD = better cognition) follow up: mean 11.2 days	-	SMD **0.70 SD higher** (0.001 lower to 1.4 higher)	-	462 (3 RCTs)	⨁⨁◯◯ LOW [c,d]	Chicken essence does not seem to have an effect on cognition measured with Digit Span tests.
Cognition Short-term Memory (Short-term Memory) assessed with: a range of neuropsychological tests (lower SMD = better cognition) follow up: mean 11.2 days	-	SMD **0.63 SD higher** (0.16 lower to 1.42 higher)	-	462 (3 RCTs)	⨁⨁◯◯ LOW [c,e]	Chicken essence seem to have a beneficial effect on short-term memory.

***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

Chicken essence compared to placebo for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: chicken essence
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with chicken essence				

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

Explanations

a. Downgraded due to high risk of bias for sequence generation and blinding identified in the two either of the included studies.
b. Downgraded due to low sample size.
c. Downgraded due to high risk of bias identified in the included studies for blinding, incomplete outcome data, and selective reporting.
d. Downgraded die to significant heterogeneity (I2=77.7, p=0.01).
e. Downgraded due to significant heterogeneity (I2=82.9, p=0.00).

Summary of Findings Table 9

Mediterranean diet compared to alternate or usual diet for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: Mediterranean diet
Comparison: alternate or usual diet

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with alternate or usual diet	Risk with Mediterranean diet			
Incidence of Dementia (Dementia) assessed with: newly diagnosed cases of dementia follow up: mean 6.5 years	No significant difference in the incident dementia was identified between the control and intervention groups (total N=522)		522 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Mediterranean diet does not seem to have an effect on the risk of dementia
Incidence of MCI (MCI) assessed with: newly reported cases of MCI follow up: mean 5.6 years	A slightly lower but not statistically significant incidence of MCI was reported in the intervention group of all the three studies included (N=1254).		1254 (3 RCTs)	⨁⨁◯◯ LOW [a,c]	Mediterranean diet does not seem to have an effect on the risk of MCI
Cognition Global (Global) assessed with: MMSE Scale from: 0 to 30 follow up: mean 4.1 years	-	SMD **0.24 SD higher** (0 to 0.47 higher)	335 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Mediterranean diet does not seem to have an effect on global cognition
Cognition Attention (Attention) assessed with: a range of neuropsychological tests follow up: mean 2.2 months	-	SMD **1.89 SD lower** (3.82 lower to 0.03 higher)	250 (3 RCTs)	⨁◯◯◯ VERY LOW [d,e,f]	Mediterranean diet does not seem to have an effect on attention
Cognition Working Memory (Working Memory) assessed with: a range of neuropsychological tests follow up: mean 37.5 months	-	SMD **0.2 SD higher** (0.02 lower to 0.42 higher)	748 (4 RCTs)	⨁⨁⨁◯ MODERATE [g]	Mediterranean diet does not seem to have an effect on working memory

Mediterranean diet compared to alternate or usual diet for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: Mediterranean diet
Comparison: alternate or usual diet

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with alternate or usual diet	Risk with Mediterranean diet			
Cognition Processing Speed (Processing Speed) assessed with: a range of neuropsychological tests follow up: mean 37.5 months	-	SMD **0.07 SD higher** (0.11 lower to 0.25 higher)	468 (4 RCTs)	⨁⨁⨁◯ MODERATE [g]	Mediterranean diet does not seem to have an effect on processing speed
Cognition Verbal and Visual Memory (V&V Memory) assessed with: a range of neuropsychological tests follow up: mean 37.5 months	-	SMD **0.19 SD higher** (0.03 higher to 0.36 higher)	1471 (4 RCTs)	⨁⨁⨁◯ MODERATE [g]	Mediterranean diet seems to have a beneficial effect on verbal and visual memory
Cognition Language (Language) assessed with: a range of neuropsychological tests follow up: mean 40.5 months	-	SMD **0.19 SD lower** (0.4 lower to 0.02 higher)	370 (2 RCTs)	⨁⨁⨁◯ MODERATE [h]	Mediterranean diet does not seem to have an effect on language
Cognition Executive Function (Executive Function) assessed with: a range of neuropsychological tests follow up: mean 40.5 months	-	SMD **0.22 SD higher** (0.04 lower to 0.48 higher)	370 (2 RCTs)	⨁⨁⨁◯ MODERATE [h]	Mediterranean diet does not seem to have an effect on executive function

***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).
Higher SMD = better cognition.
CI: Confidence interval; **SMD:** Standardised mean difference

Mediterranean diet compared to alternate or usual diet for reducing the risk of dementia and/or cognitive decline

Patient or population: reducing the risk of dementia and/or cognitive decline
Setting:
Intervention: Mediterranean diet
Comparison: alternate or usual diet

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with alternate or usual diet	Risk with Mediterranean diet			

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

Explanations
a. Downgraded due to the control conditions being a low-fat diet.
b. The outcome was ascertained from medical records rather than actual assessment, which could have led to have underestimated the number of cases.
c. Downgraded due to the outcome been ascertained from medical records rather than actual assessment in a large (42%) proportion of the overall population.
d. Downgraded due to all studies deemed at high risk of blinding and reporting bias.
e. Downgraded due to significant heterogeneity (I2=97, p<0.00001).
f. Downgraded due to wide 95% Cls and sample size.
g. Downgraded due to the control being a low fat diet in a large proportion (67%) of the overall population.
h. Downgraded due to the control condition being a low fat diet in a large proportion (73%) of the overall population.

Evidence to Decision Table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide ageing of populations is strongly associated with dementia, causing major health, economic and social burdens. In 2015, it has been estimated that there were 50 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 82 million in 2030 and 152 million in 2050.[1] Since no cure is available for Alzheimer's disease, the main cause of dementia, prevention could be crucial in halting the rapid increase in the prevalence of this condition and international experts have called upon world-wide governments to make prevention of dementia one of their key health priorities.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Different aspects of healthy nutrition are consistently reported to have beneficial association with cognitive performance in observational studies, but the evidence from trials is more inconsistent. It is important to consider that interventions with dietary modification that are able to improve several aspects of dietary intake are more likely to establish cognitive benefits as compared to supplementation with only some nutrients, although they are more demanding to execute. Dietary factors may have synergistic effects that are only evident in combinations of foods.[98] The review of evidence presented here have identified 9 different interventions/comparisons: 1. Supplement multi-complexes vs placebo in adults with normal cognition 2. Supplement multi-complexes vs placebo in adults with MCI 3. Poly Unsaturated Fatty Acids (PUFAs) vs placebo 4. Vitamin B vs placebo 5. Vitamin E vs placebo 6 Polyphenols vs placebo 7. Protein supplementation vs placebo 8. Chicken essence vs placebo 9. Mediterranean diet vs alternate or usual diet For the outcomes of ***incident dementia and MCI***, evidence was reported only for comparison 1 and 9 and neither supplementation with multi-complexes of vitamins and nutraceuticals, neither MeDi showed a direct effect in reducing the incidence of dementia and/or MCI. All the intervention/comparison included reported about ***cognitive outcomes***. Polyphenols was the only category of supplement and nutraceuticals that was shown consistently to affect cognition beneficially, but evidence were deemed of low quality. Protein supplementations seems also to have	

	beneficial effect on cognition, in older adults, but the results are more inconsistent, and evidence were also deemed of low quality. There is evidence of moderate quality that MeDi can improve verbal and visual memory, almost significant results were obtained for global cognition (SMD 0.24; 95% Cl-0.00 – 0.47) and a consistently positive, but not significant trend was reported for all the other cognitive outcomes (attention; working memory; processing speed; language; and executive function). In conclusion evidence of no effects was reported for multi complex, vitamin B and E, and PUFA supplementation, low quality evidence were reported of a beneficial effect of protein and polyphenols supplementation, and moderate evidence of a beneficial effect of MeDi was reported.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Only one review considered here reported about adverse events.[39] Three multi-supplement complex interventions (DHA + EPA + vitamin E +soy phospholipids + tryptophan + melatonin; vitamin E + multivitamin; lyophilised royal jelly + gingko biloba + panax ginseng) were considered and none (N=860) showed an increased risk of any serious adverse event during the follow up period (moderate quality evidence). Overall dietary modification is safe and adverse events are rare, although they are more common in case of dietary supplementation interventions, especially of single nutrient, rather than intervention to promote healthy dietary patterns. Vitamin E and protein supplementation at high doses have been correlated to undesirable non-anticipated effects.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Evidence related to the efficacy of polyphenols and protein supplementation on cognition are of low quality. More certain (moderate quality) seems to be the beneficial effect of MeDi on some cognitive domains. It is important to notice that most of the trials are conducted in unselected populations in terms of nutrient status and focusing the supplement interventions on those with deficiencies in that specific nutrient may be a better strategy. No evidence is available of adverse effects of these interventions. In particular, the recommendation of not using supplements, if not needed for other reasons, should be emphasised.	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cognitive impairment and dementia can have a major impact in the life not only of the person affected but also of the close network of family and friends, as well as caregivers and health professional in general.[99,100] Decreasing functional ability and dependency are the major components of this effect. Furthermore, dementia is the main cause of disability and institutionalization among older adults[1]. Hence, reducing or delaying the risk/onset of dementia could results in lower costs for public healthcare services. Patients, caregivers, and policy makers are likely to be the people who will value these recommendations.	
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ● Varies ○ Don't know	Evidence suggests that the desirable effects of the dietary interventions are larger than the undesirable effects. Low to moderate quality evidence suggests benefits of polyphenols, protein supplementation, and MeDi. Evidence on adverse events are not generally well reported but rare. MeDi probably favours the intervention Supplementation does not favour either intervention nor comparison.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	In general interventions to establish healthy dietary patterns (like MeDi) are resource-intensive as they do require professional guidance and supervision. Group-based guidance and e-interventions are probably a way to reduce the costs. Intervention at a population level can also reduce costs. Supplemental interventions are cheaper and easier to execute. Healthy diets and supplements can be expensive in some countries. Dietary patterns may be hard to maintain, with increased costs in long term.	For more information: 'Best buys' and other recommended interventions to address non-communicable diseases (NCDs) http://apps.who.int/iris/bitstream/handle/10665/259232/WHO-NMH-NVI-17.9-eng.pdf?sequence=1
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No direct evidence available from the studies considered.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Although direct evidence was not identified in the present search, in general, dietary modification interventions (like MEDI) are resource-intensive and do require guidance and supervision but they are also the one more likely to have a beneficial effect[98]. Group-based guidance and e-interventions are probably a way to reduce the costs. MeDi was shown to be cost-effective against degenerative pathologies.[101] On the other hand, supplemental interventions are cheaper and easier to execute but they are also less likely to have a wide variety of benefits in many outcomes (which is the case in dietary modification) so they are also less promising in terms of benefits.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know	Lower socioeconomic groups are more likely to have earlier onset of dementia than higher socioeconomic groups. Older people from lower socioeconomic backgrounds are also more likely to experience cognitive dysfunction at earlier stages of cognitive decline and cognitive impairment, and will have fewer resources to cope with the symptoms than their counterparts from higher socioeconomic groups People from lower socioeconomic groups are more likely to live, work and age in physical and economic environments that do not support social connectedness, physical activity or mental stimulation. this can increase the risk of cognitive impairment and dementia in later life.[102] Based on this it is believed that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	

	Furthermore, women are disproportionally affected with AD. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men.[103]	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Dietary interventions (especially the ones aimed at modified overall dietary patterns) have consistent benefits on cognition and other health parameters[98]. Unhealthy diets and low physical activity contribute to many chronic diseases and disability; they are responsible for some 2 in 5 deaths worldwide and for about 30% of the global disease burden.[104]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Costs and need of qualified staff have been identified as the key barriers; motivation will depend on the good planning of the intervention.	

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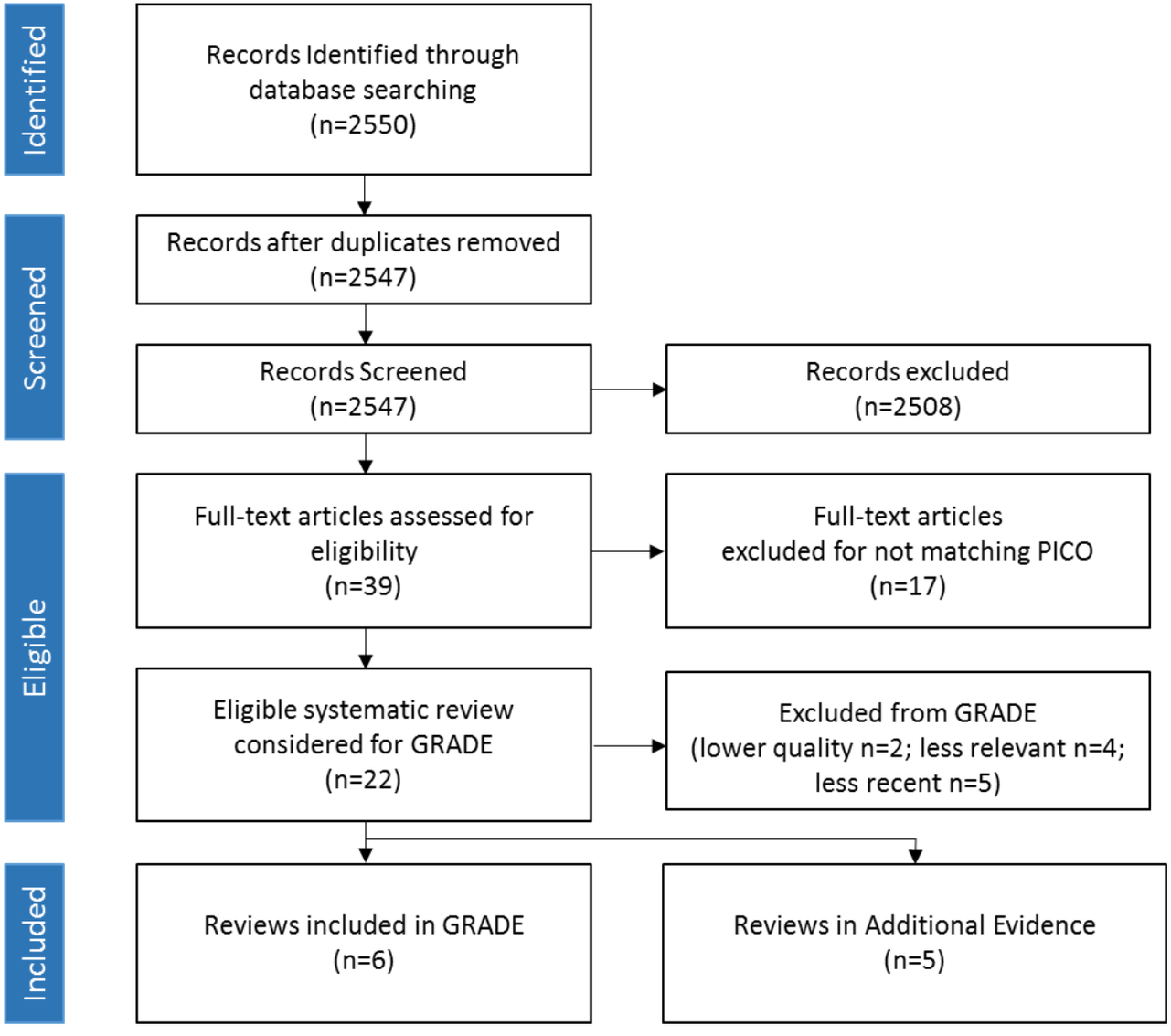
Annex: PRISMA[2] flow diagram for systematic review of the reviews – cognitive decline interventions[2]



[2] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For more information: http://www.prisma-statement.org

Risk reduction guidelines for cognitive decline and dementia

Evidence profile:
Treatment of alcohol use disorder and cognitive decline or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment and alcohol use disorder, are behavioural and psychological interventions to treat alcohol use disorder more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

As the number of older adults increases worldwide, a rise in dementia and Alzheimer's disease (AD) has also been reported,[1] causing health, economic and social burdens.[2,3] In 2015, it has been estimated that there were 46.8 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050.[1] Since no cure is available, prevention could be crucial in halting the rapid increase in the prevalence of dementia, as some projection models suggested.[4,5] AD/dementia has been linked to modifiable, lifestyle-related, vascular risk factors,[1-3,6] but the extent to which cognitive impairment can be prevented is under debate, and the role of prevention, aimed to reduce or delay disease development, is currently under investigation.[7-9]

Hazardous alcohol use of alcohol and alcohol use disorders constitutes a public health as well as social problem. Excessive alcohol consumption is common in many countries:[10] in 2012 5.9% of all deaths world-wide (about 3.3 million) were directly attributable to harmful use of alcohol use.[11] Furthermore, excessive consumption of alcohol is one of the leading causes of general disability globally,[12] being a direct cause in more than 200 diseases and injury conditions.[13]

Although some studies demonstrated that a light to moderate intake of alcohol was associated with lower risk of dementia,[14] there is much more extensive evidence on excessive alcohol consumption as a risk factors for dementia and cognitive decline.[15-17] A recent systematic review and meta-analysis[18] on prospective studies, investigating the potential dose-response of alcohol towards cognitive decline, identified ≤12.5 g/day as the dose associated with a reduced risk of dementia (especially in the population younger than 60 years old) and ≥38 g/day as the dose that may elevate the risk of dementia. Recent nationwide cohort study has shown that alcohol use disorders were a major risk factor for onset of dementia (https://www.ncbi.nlm.nih.gov/pubmed/29475810?dopt=Abstract).

Several approaches have been applied in interventions aimed at hazardous and harmful use of alcohol. Pharmacological therapies with different types of drugs (e.g. opioid antagonists, ALDH2 inhibitors) have shown various degrees of efficacy for adults with alcohol use disorders, although none of them showed to be superior in comparison trials.[19] Behaviour and psychological interventions have shown to be effective in alcohol use disorders, and especially among those with hazardous and harmful drinking (https://www.cochrane.org/CD004148/ADDICTN_effectiveness-brief-alcohol-interventions-primary-care-populations). Screening and brief intervention in primary care is one of the most cost-effective means of reducing alcohol-attributable morbidity and deaths (with ICER less than $2000 per QALY gain(Angus et al., 2016, 2014; Solberg et al., 2008). However, more evidence are needed to identify most effective components of interventions and their implementation in different groups and settings.[20]Tax increases, making alcohol more expensive and less available, banning alcohol advertising, enforcement of drink-driving laws are among highly cost-effective strategies to reduce harm associated with alcohol (Anderson et al., 2009), especially in countries with a high prevalence of heavy drinking (Levin and Chisholm, 2016).

This review of systematic reviews was carried out to search, identify, and synthesise the evidence currently available on the efficacy of behavioural/psychological or pharmacological intervention aimed at reducing or ceasing hazardous or harmful drinking in reducing the risk of dementia and/or cognitive impairment.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment and alcohol use disorder, are behavioural and psychological interventions to treat alcohol use disorder more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

- ✓ P: Adults with normal cognition or mild cognitive impairment with and excessive use of alcohol
- ✓ I: Behavioural and psychological interventions to treat alcohol use disorder (e.g. motivational interviewing)
  Pharmacological interventions to treat alcohol use disorders
- ✓ C: Placebo or no intervention
- ✓ O: *Critical*
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Dementia

  Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Date of search: 18th of April 2018

Search starting time: 31st December 2012

Full search terms
(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Alcohol drinking OR Binge drinking OR Drunkenness OR alcohol intoxication OR alcoholism OR alcohol withdrawal) AND (Add in Behaviour OR behaviour OR drug therapy OR pharmacological therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioral therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment)

Simplified search terms
(dementia OR MCI OR cognition OR Quality of Life OR ADL OR Adverse Effects OR Drop-out) AND alcohol use disorder AND alcohol reduction therapy

*Searches were conducted in the following databases**:

- Cochrane
- Pubmed
- NICE Guidelines
- Embase
- PsycInfo
- Global Health Library (Including WHOLIS, PAHO, AIM, LILACS)
- Database of impact evaluations
- AFROLIB
- ArabPsycNet
- HERDIN NeON
- HrCak
- IndMED
- KoreaMed

- AJOL

* Please note that the EurasiaHealth database did not return any meaningful answer to the search.

List of systemic reviews identified by the search process

No systematic review of intervention studies that matched the PICO question was identified through the present search

Comparison: Behavioural or psychological intervention vs No intervention

Kelly S, Olanrewaju O, Cowan A, Brayne C, Lafortune L. Interventions to prevent and reduce excessive alcohol consumption in older people: a systematic review and meta-analysis. Age Ageing. 2018 Mar 1;47(2):175-184.

The only evidence identified, which matches with the PICO question, is represented by this very recent, high quality systematic review, set up with the aim of assessing the efficacy of behavioural, psychological, and lifestyle intervention in reducing excessive alcohol consumption and the risk of dementia and/or cognitive decline.

The authors carried out a very comprehensive search including any type of behavioural and psychological strategy to reduce alcohol consumption, and focused specifically on both dementia and cognitive outcomes. The database search included publications from 2000 onwards, but reference lists were also searched for pre-2000 studies. The review focused mainly on older adults (55+ years), but evidence for younger adults were included and discussed in a narrative fashion. Search was carried out also for systematic reviews.

As stated in the review, the authors were not able to identify any intervention study nor systematic review that assessed the efficacy of interventions aimed at preventing or reducing excessive alcohol consumption and had dementia or any cognitive function measurement as outcomes.

(Search and screening: Mariagnese Barbera; Jenni Kulmala)

Comparison: Pharmacological intervention vs Placebo or No intervention

No Reviews were identified. The search focused also on single-trial publications on pharmacological intervention aimed at reducing excessive alcohol consumption, which also included outcomes related to dementia and/or cognitive impairment but it returned no results.

Narrative description of the observational evidence on the correlation between alcohol misuse and increased risk of dementia

Although with the present search evidence was gathered that there are no intervention studies aimed at investigating the effect of the reduction of harmful alcohol consumption on the risk of dementia and/or cognitive decline,[20] observational evidence of a correlation between excessive alcohol consumption and increased risk of dementia are widely available. In particular, five systematic reviews (one including a meta-analysis) and one overview of systematic reviews investigating observational evidence of the correlation between alcohol consumption and risk of dementia and/or cognitive decline were identified.

In 2013, Piazza-Gardner et al.[21] published a qualitative systematic review conducted to assess observational evidence on whether alcohol serves as a protective agent against the development of AD, as well as the role played by quantity and/or frequency of drinking. The search led to the identification of 19 studies with mixed evidence regarding alcohol's impact on AD. Seven studies suggested that moderate alcohol intake decreases the risk of AD, three studies found a correlation between drinking and increased risk of AD, whereas the remaining nine reported no association between alcohol consumption and AD. Overall, the authors identified validity and consistency of both alcohol and AD measures across studies as a severe limitation and concluded that alcohol should not be considered a mean to decrease the risk of AD.

Conflicting evidence were also identified in a second systematic review published a year later, that investigated several modifiable risk factors potentially associated with cognition and dementia.[22] The search was carried out in Medline publications from 1990 to 2012 were considered. 30 studies relevant to the potential link between alcohol and cognition decline were included in the review. Alcohol was found in general to have a U-shaped association with the risk of cognitive decline, suggesting a possible protective role of light to moderate consumption and confirming an increased risk for higher consumption levels. However, results were generally inconsistent throughout the studies and methodological differences limited the comparison of the results.

A synthesis of systematic reviews, in 2015, critically evaluated published systematic reviews on the epidemiologic association between alcohol consumption and the risk of dementia and/or cognitive decline.[23] The search, carried out in MEDLINE, EMBASE and PsycINFO from inception to 2014, yielded three moderate quality systematic reviews (two including meta-analysis), which included a total of 45 unique studies. The overall evidence pointed towards a protective effect of light to moderate drinking (AD, pooled risk ratio [RR] 0.72; 95% confidence interval [CI] 0.61-0.86; dementia, RR 0.74; 95%CI 0.61-0.91) and no effect of heavy to excessive drinking (RR 0.92; 95%CI 0.59-1.45 and RR 1.04; 95%CI 0.69-1.56, for AD and dementia, respectively). In one systematic review, two studies reported a link between alcohol consumption and the development of AD.

Lafortune and colleagues conducted, in 2016, a rapid systematic review on the lifestyle risk factors correlated to different ageing conditions including dementia.[24] The search was done on longitudinal cohort studies in several relevant databases starting from 2000 and identified 164 studies that were included in a qualitative synthesis. The results concerning alcohol consumption as exposure factor showed consistent evidence demonstrating an association between heavy drinking and cognitive impairment and only one study reported no association between alcohol consumption and cognitive impairment or dementia.

More recently a systematic review and meta-analysis was conducted investigating the dose-response effect of alcohol consumption on risk of dementia.[18] Electronic databases were searched from inception to end of 2016 for prospective studies investigating the association between dementia and alcohol intake and a total of 16 and 15 studies were included in qualitative and quantitative synthesis, respectively. A U-shaped correlation between alcohol consumption and risk of dementia was identified in the qualitative analysis; substantial low publication bias was quantitatively assessed by the authors. From the dose-response meta-analysis the authors found that the dose

of alcohol associated with lower risk was about 12 g/day (about 7.5 drinks/week) being 6 g/day (4 drinks/week) the dose corresponding to the lowest risk. The risk of dementia was instead significantly elevated for alcohol consumption of 38 g/day (23 drinks/week) or more.

Finally, Hersi et al.[25] published a systematic review and qualitative synthesis of risk factors associated with progression to AD. The authors searched for both primary observational studies and systematic reviews and a total of 10 systematic reviews were identified and used for the qualitative synthesis of the evidence on the correlation between alcohol consumption and the risk of AD. A U-shaped correlation was again identified with increased risk of AD for excessive alcohol drinking levels.

In conclusion, despite the lack of evidence from intervention trials aimed at reducing alcohol consumption on the effect of such interventions on the risk of dementia and cognitive decline, wide observational evidence is available on the correlation of heavy alcohol drinking and increased risk of cognitive impairment.

Additional evidence

Interventions to reduce excessive alcohol consumption can often include a pharmacological component or even be completely based on a pharmacological treatment. However, no evidence of the existence of systematic reviews or even single RCTs aimed at reducing excessive alcohol consumption with pharmacological intervention and that also included dementia, MCI or cognition among their outcomes was identified through the present search.

The Mental Health Gap Action Programme (mhGAP) guidelines[26] on interventions for mental, neurological and substance use disorders, is, in this case, the most relevant source of evidence and recommendations to which refer for interventions in the normal population.

WHO guidelines for general population

The mhGAP Intervention guide recommends the following:

- Harmful use of alcohol
  - Provide psychoeducation and emphasize that the level/pattern of alcohol use is causing harm to health.
  - Explore the person's motivations for alcohol use. Conduct Motivational Interviewing.
  - Advise stopping alcohol completely or consuming at a non-harmful level (if a non-harmful level exists) and indicate
  - your intention in supporting the person in doing so. Ask the person if they are ready to try to make this change.
  - Explore strategies for reducing or stopping use and strategies for reducing harm.
  - Address food, housing, and employment needs.
  - Offer regular follow up
- Alcohol dependence:
  - Thiamine during alcohol use
  - Diazepam during alcohol detoxification to treat withdrawal symptoms
  - Naltrexone, acamprosate or disulfiram to prevent relapse after detoxification

- Psychosocial interventions if available, e.g. CBT, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups

Part 2: From evidence to decisions

Summary of Findings

Interventions aimed at reducing alcohol consumption compared to no intervention for reducing risk of cognitive decline and/or dementia

Patient or population: normal or with mild cognitive impairment
Setting: Any
Intervention: Alcohol reductions
Comparison: No intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Control of hypercholesterolemia through treatment with statins**				
Dementia	N/A	N/A	N/A	N/A	N/A	One review[20] was identified which specifically searched, but could not identify, intervention studies aimed at reduction of excessive alcohol consumption that also have incidence of dementia and/or cognitive performance as outcomes.
MCI	N/A	N/A	N/A	N/A	N/A	N/A
Cognitive function	N/A	N/A	N/A	N/A	N/A	One review[20] was identified which specifically searched, but could not identify, intervention studies aimed at reduction of excessive alcohol consumption that also have incidence of dementia and/or cognitive performance as outcomes.
Quality of life	N/A	N/A	N/A	N/A	N/A	N/A.

Interventions aimed at reducing alcohol consumption compared to no intervention for reducing risk of cognitive decline and/or dementia

Patient or population: normal or with mild cognitive impairment
Setting: Any
Intervention: Alcohol reductions
Comparison: No intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Control of hypercholesterolemia through treatment with statins**				
Functioning	N/A	N/A	N/A	N/A	N/A	N/A
Adverse events	N/A	N/A	N/A	N/A	N/A	N/A
Dropout rated	N/A	N/A	N/A	N/A	N/A	N/A

***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; **OR:** Odds ratio; **MD:** Mean difference

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

Evidence-to-Decision Table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide ageing of populations is strongly associated with dementia, causing major health, economic and social burdens. In 2015, it has been estimated that there were 50 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 82 million in 2030 and 152 million in 2050.[1] Since no cure is available for Alzheimer's disease, the main cause of dementia, prevention could be crucial in halting the rapid increase in the prevalence of this condition and international experts have called upon world-wide governments to make prevention of dementia one of their key health priorities.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The present systematic search did not identify any systematic review nor single study aimed at investigating the effect of alcohol reduction intervention on the risk of dementia and/or cognitive decline. However, a large body of observational evidence is available on the correlation of heavy alcohol drinking and increased risk of cognitive impairment and dementia. Generally single studies did not always show similar results (mostly due to differences in study design) but the most consistent pattern is that of a U-shape d relationship between alcohol consumption and dementia and/or cognitive impairment, which clearly links excessive alcohol consumption to a significantly increased risk. In this U-shaped relationship, abstinence seems to be correlated with slightly higher risk of cognitive decline and dementia, in keeping with other alcohol-related harmful effects.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	A range of adverse events have been reported for pharmacological interventions aimed at reducing excessive alcohol consumption[27] including abdominal pain, nausea, anorexia and dizziness, and hepatotoxicity in some cases. Lifestyle interventions are mostly based on behavioural interventions and no evidence of adverse events (apart from those related to withdrawal syndrome) have been identified.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Evidence related to the desirable effect are based on a large body of observational evidence, mostly systematic reviews of longitudinal cohort studies.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cognitive impairment and dementia can have a major impact in the life not only of the person affected but also of the close network of family and friends, as well as caregivers and health professional in general.[28,29] Functional ability and dependency are the major component of this effect. Furthermore, dementia, the main cause of disability and institutionalization among older adults[1], therefore reducing or delaying the onset of dementia could results in lower costs for public healthcare services. Patients, caregivers, and policy makers are likely to be the people who will value these recommendations the most.	
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	Significant adverse events have been reported only for pharmacological interventions. Although the evidence related to the desirable effects are only observational and epidemiological, at least for lifestyle interventions aimed at reduction of excessive alcohol consumption the balance is likely to favour the intervention.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The work of qualified healthcare professionals is the main cost of lifestyle interventions. Data from US trial have estimated the overall monthly costs of a lifestyle intervention is about 200USD.[27] Concerning pharmacological treatments, the cost of a full treatment for the alcohol abuse through acamprosate strategy has been estimated at around €5000.[27] Individual level interventions are more resource intensive compared to population/political level interventions.	The economic and human resource capacity to implement psychosocial interventions varies among countries, settings and among the specific type and length of intervention.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	For lifestyle interventions costs can vary significantly from country to country and depending on the specific design of the intervention. Costs for pharmacological interventions are better established.	

Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	A growing number of economic evaluations speak in favour of investing in interventions to prevent and treat substance use disorders. Tax increases, making alcohol more expensive and less available, banning alcohol advertising, enforcement of drink-driving laws are among highly cost-effective strategies to reduce harm(Anderson et al., 2009),[30] especially in countries with a high prevalence of heavy drinking (Levin and Chisholm, 2016).[31] Screening and brief intervention in primary care is one of the most cost-effective means of reducing alcohol-attributable morbidity and deaths (with ICER less than $2000 per QALY(Angus et al., 2016, 2014; Solberg et al., 2008)).[32,33] Group-based guidance and e-interventions are probably a way to reduce costs	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Lower socioeconomic groups are more likely to have earlier onset of dementia than higher socioeconomic groups. Older people from lower socioeconomic backgrounds are also more likely to experience cognitive dysfunction at earlier stages of cognitive decline and cognitive impairment, and will have fewer resources to cope with the symptoms than their counterparts from higher socioeconomic groups People from lower socioeconomic groups are more likely to live, work and age in physical and economic environments that do not support social connectedness, physical activity or mental stimulation. this can increase the risk of cognitive impairment and dementia in later life.34 Based on this it is believed that interventions to reduce risk of cognitive decline and dementia will increase equity in health. Furthermore, women are disproportionally affected with AD. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men.[35]	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Lifestyle behavioural interventions to reduce alcohol consumption in adult with hypertension showed a retention rate of 80.7% showing that these types of intervention are generally accepted.[36] Intervention design plays a key role in this. However significant differences may be reported among different types of intervention.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Interventions aimed at reducing excessive alcohol consumption can be based on behavioural/psychological and/or pharmacological strategies. Key barriers are costs and lack of motivation.	

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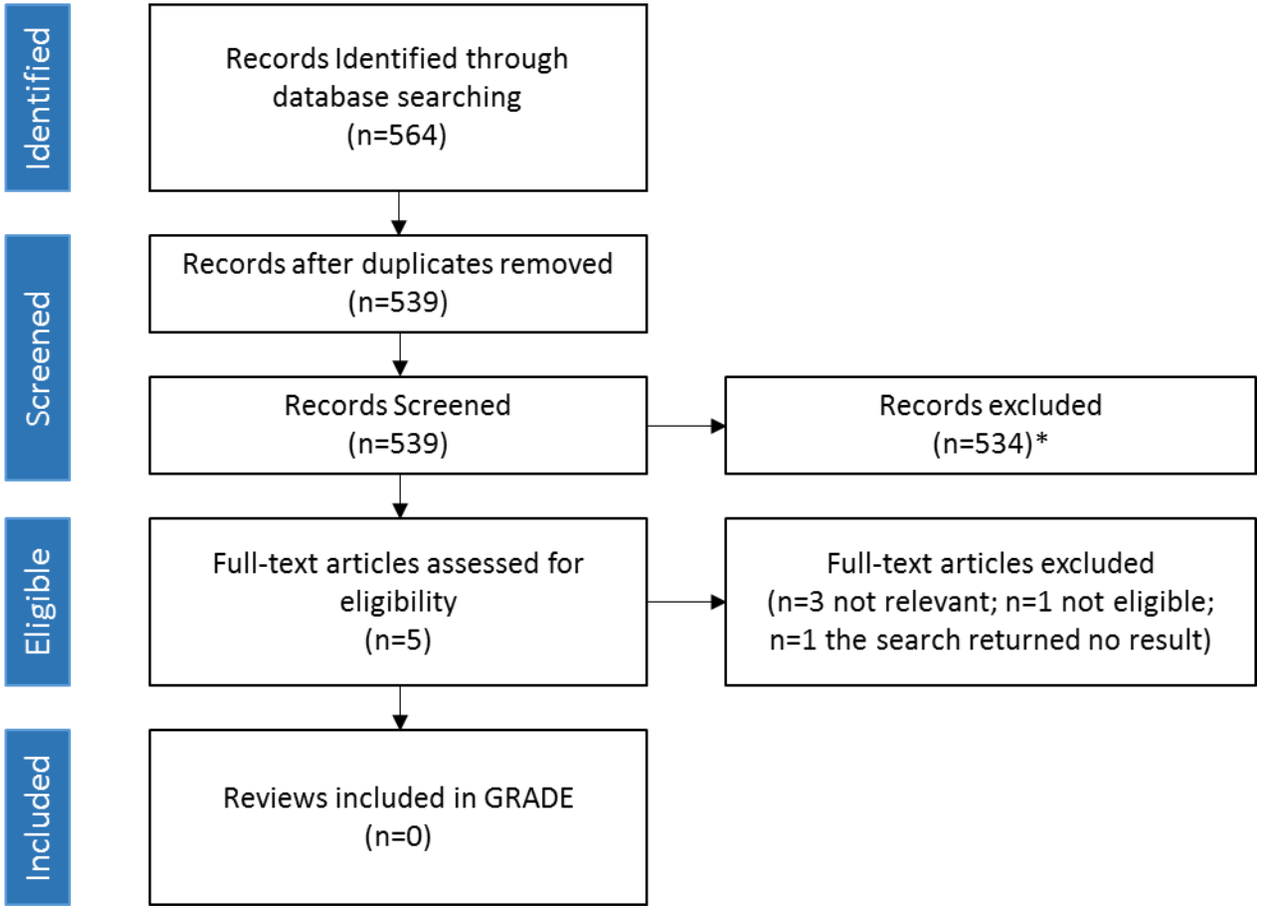
Annex: PRISMA[1] flow diagram for systematic review of the reviews – cognitive decline interventions[1]



* 5 systematic reviews of observational evidence and 1 overview of systematic reviews included in the narrative description of observational evidence

[1] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For more information: http://www.prisma-statement.org

Guidelines for risk reduction of cognitive decline and dementia

Evidence profile:
cognitive stimulation and training for reducing the risk of cognitive decline and/or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment, is cognitive stimulation or cognitive training more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

Dementia is preceded by cognitive decline, however not everyone who is exposed to dementia risk factors will go on to develop cognitive impairment. The concept of cognitive reserve has been proposed as a protective factor to reduce risk of clinical onset of dementia and cognitive decline[1]. Cognitive reserve refers to the brains ability to cope with or compensate for neuropathology or damage[1]. Studies have shown that increased cognitive activity can have a buffering effect against rapid cognitive decline[2].

Increased cognitive activity can be achieved through cognitive stimulation therapy and/or cognitive training. Cognitive stimulation therapy refers to "the participation in a range of activities aimed at improving cognitive and social functioning"[3] while cognitive training refers to "the guided practice of specific standardized tasks designed to enhance particular cognitive functions"[3].

In general, observational studies find that increased cognitive stimulation is related to slower cognitive decline over time[4]. However, the type of stimulation (e.g. passive vs active participation) can modify this effect[5]. Currently, it is not clear whether cognitive training helps in reducing cognitive decline or the onset of dementia as cognitive training studies are subject to a range of limitations. For instance, there is a shortage of long-term follow-up studies, a lack of consistent outcome measures across the literature and varied definitions of what classifies as a training activity[6, 7].

The review included here outlines the most recent systematic reviews that have been published which examine the effectiveness of cognitive stimulation and training on improving cognitive functioning and/or reducing cognitive decline.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment is cognitive stimulation or cognitive training more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Populations

- Adults with normal cognition or mild cognitive impairment

Interventions

- Cognitive stimulation[1]
- Cognitive training[2]

Comparison

- Care as usual or no intervention

Outcomes

- Critical:
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Incident Dementia
- Important:
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

[1] The participation in a range of activities aimed at improving cognitive and social functioning(3)

[2] The guided practice of specific standardized tasks designed to enhance particular cognitive functions(3)

Search Strategy

Searches using the following strategies (or similar) were conducted as follows

- (systemati* or meta analys*) and (dementia or cognit* or MCI or neuropsycholog* or Alzheimer*) and ("Brain training" OR "cognitive training" OR "Brain fitness" OR Games OR "Memory training" OR (Stimulation AND cognit*))[3]

Searches were conducted in:

- Medline
- Cochrane
- PsycInfo
- Embase
- NICE
- Global index medicus/Global Health Library
    - WHO regional data base
    - WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth

[3] Dates searched were 1 May 2016 - 1 May 2018. Additionally, the 2016 AHRQ review[(11)] was consulted for relevant records which systematically searched the literature between Jan 2009 – Sept 2016. In combination, the search period spanned >9 years. All abstracts were screened by two independent reviewers and with any discrepancies resolved by discussion. Full text articles were read by the same two independent reviewers and any discrepancy resolved by discussion.

List of systematic reviews identified by the search process

Included in GRADE[4] tables

- Strout, K. A., David, D. J., Dyer, E. J., Gray, R. C., Robnett, R. H., & Howard, E. P. (2016). Behavioral interventions in six dimensions of wellness that protect the cognitive health of community-dwelling older adults: A systematic review. *J Am Geriatr Soc, 64*(5), 944-958
- Chiu, H.-L., Chu, H., Tsai, J.-C., Liu, D., Chen, Y.-R., Yang, H.-L., & Chou, K.-R. (2017). The effect of cognitive-based training for the healthy older people: A meta-analysis of randomized controlled trials. *PLoS ONE Vol 12(5), 2017, ArtID e0176742, 12*(5).
- Sherman, D. S., Mauser, J., Nuno, M., & Sherzai, D. (2017). The Efficacy of Cognitive Intervention in Mild Cognitive Impairment (MCI): a Meta-Analysis of Outcomes on Neuropsychological Measures. *Neuropsychol Rev, 27*(4), 440-484. doi:10.1007/s11065-017-9363-3
- Chandler, M., Parks, A., Marsiske, M., Rotblatt, L., & Smith, G. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: A systematic review and meta-analysis. *Neuropsychology Review, 26*(3), 225-251.

[4] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO table

GRADE table number	Population	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Adults with normal cognition	Cognitive stimulation versus usual care or no intervention	Cognitive function (or cognitive test results using validated instruments) • Various subdomain measures of executive function, attention, memory, language and processing speed	Strout, K. A., David, D. J., Dyer, E. J., Gray, R. C., Robnett, R. H., & Howard, E. P. (2016). Behavioral interventions in six dimensions of wellness that protect the cognitive health of community-dwelling older adults: A systematic review. *J Am Geriatr Soc, 64*(5), 944-958	Systematic review on cognitive stimulation interventions and cognitive function in a healthy older population of adults. RCTs were included. AMSTAR 2[5] rating is Low.
			Incident MCI	No reviews identified.	No reviews identified.
			Incident Dementia	No reviews identified.	No reviews identified.
			Quality of life	No reviews identified.	No reviews identified.
			Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
			Adverse events	No reviews identified.	No reviews identified.
			Drop-out rates	No reviews identified.	No reviews identified.

[5] AMSTAR: A Measurement Tool to Assess Systematic Reviews. More information: https://amstar.ca/index.php

2	Adults with normal cognition	Cognitive training versus usual care or no intervention	Cognitive function (or cognitive test results using validated instruments) • MoCA, RBANS, MMSE, ADAS-Cog, CDRS	Chiu, H.-L., Chu, H., Tsai, J.-C., Liu, D., Chen, Y.-R., Yang, H.-L., & Chou, K.-R. (2017). The effect of cognitive-based training for the healthy older people: A meta-analysis of randomized controlled trials. *PLoS ONE Vol 12(5), 2017, ArtID e0176742, 12*(5).	Systematic review on cognitive training interventions and cognitive function in a healthy older population of adults. Includes meta-analysis of RCTs. AMSTAR 2[5] rating is Moderate.
			Incident MCI	No reviews identified.	No reviews identified.
			Incident Dementia	No reviews identified.	No reviews identified.
			Quality of life	No reviews identified.	No reviews identified.
			Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
			Adverse events	No reviews identified.	No reviews identified.
			Drop-out rates	No reviews identified.	No reviews identified.
3	Adults with Mild Cognitive Impairment	Cognitive stimulation versus usual care or no intervention	Cognitive function (or cognitive test results using validated instruments)	No reviews identified.	No reviews identified.
			Incident MCI	No reviews identified.	No reviews identified.
			Incident Dementia	No reviews identified.	No reviews identified.

			Quality of life	No reviews identified.	No reviews identified.
			Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
			Adverse events	No reviews identified.	No reviews identified.
			Drop-out rates	No reviews identified.	No reviews identified.
4	Adults with Mild Cognitive Impairment	Cognitive training versus usual care or no intervention	Cognitive function (or cognitive test results using validated instruments) • MMSE, RBANS, ADAS-Cog, DRS-2, RBMT, RBMT –II CMMSE, MOCA, Cattell CFT, CAMCOG-R	Sherman, D. S., Mauser, J., Nuno, M., & Sherzai, D. (2017). The Efficacy of Cognitive Intervention in Mild Cognitive Impairment (MCI): a Meta-Analysis of Outcomes on Neuropsychological Measures. *Neuropsychol Rev, 27*(4), 440-484. doi:10.1007/s11065-017-9363-3	Systematic review on cognitive training interventions and cognitive functioning in a population with Mild Cognitive Impairment. Includes meta-analysis of RCTs. AMSTAR 2[5] rating is Moderate.
			Incident MCI	No reviews identified.	No reviews identified.
			Incident Dementia	Chandler, M., Parks, A., Marsiske, M., Rotblatt, L., & Smith, G. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: A systematic review and meta-analysis. *Neuropsychology Review, 26*(3), 225-251.	Systematic review on cognitive training interventions and onset of dementia in a population with Mild Cognitive Impairment. RCTs were included. AMSTAR 2[5] rating is Critically Low*.

					*Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria.
			Quality of life WBS, Quality of Life Face scale, QOLQ, QOL-AD, KQOL-AD, RAND, ICQ	Chandler, M., Parks, A., Marsiske, M., Rotblatt, L., & Smith, G. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: A systematic review and meta-analysis. *Neuropsychology Review, 26*(3), 225-251.	Systematic review on cognitive training interventions and quality of life measures in a population with Mild Cognitive Impairment. Includes meta-analysis of RCTs and CTs. AMSTAR 2[5] rating is Critically Low* *Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria.
			Functional level (ADL, IADL) BADL, IADL, DAFS-R, E-Cog, RBMT, MMQ, CDAD, CDR, MFQ, CDR, ADLS, SAILS. LIADL, ADL-PI, MMA, FRSSD, EFPT	Chandler, M., Parks, A., Marsiske, M., Rotblatt, L., & Smith, G. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: A systematic review and meta-analysis. *Neuropsychology Review, 26*(3), 225-251.	Systematic review on cognitive training interventions and functional level in a population with Mild Cognitive Impairment. Includes meta-analysis of RCTs and CTs. AMSTAR 2[5] rating is Critically Low*

					*Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria
			Adverse events	No reviews identified.	No reviews identified.
			Drop-out rates	No reviews identified.	No reviews identified.

Narrative descriptions of the studies that went into the analysis

GRADE table 1: cognitive stimulation versus usual care or no intervention in healthy older adults

Strout et al.[8] conducted a systematic review investigating the effects of cognitively stimulating behavioural interventions in preventing cognitive decline in healthy older adults in the community. Behavioural interventions targeting occupational, social, intellectual, physical, emotional and/or spiritual wellbeing, were examined. 18 RCTs were included in the review and specifically 10 of these, (N = 4755) targeted intellectual wellbeing (included brain exercises, learning a musical instrument, memorising lines and helping children in school). Results were reported in narrative form and no meta-analysis was conducted. The authors reported that half of the intellectual interventions evaluated in the review proved to be effective in improving cognitive outcomes in at least one cognitive domain (executive function, attention, memory, language and/or processing speed). The AMSTAR 2 rating of this review was Low. It was missing details relating to studies that were excluded from the review and an assessment of biases.

GRADE table 2: cognitive training versus usual care or no intervention in healthy older adults

Chiu et al.[9] conducted a meta-analysis which examined the effect of cognitive based training for improving cognition in older adults with normal cognition. A total of 31 RCTs were included in the study but only 14 of these included overall cognitive functioning as an outcome measure. The review reported that cognitive-based training has a significant and moderate positive effect on overall cognitive functioning (Hedges' g = 0.419; 95% CI = 0.205 to 0.634). They also reported that attending an intervention for 3 or more times a week, 24 or more training sessions and/or 8 or more weeks in total, yields a greater effect size. The AMSTAR 2 rating of this review was moderate.

GRADE table 3: cognitive stimulation versus usual care or no intervention in older adults with Mild Cognitive Impairment

No systematic review was found.

GRADE table 4: cognitive training versus usual care or no intervention in older adults with Mild Cognitive Impairment

Sherman et al.[6] conducted a meta-analysis to examine the effectiveness of cognitive interventions for adults with MCI. 26 RCTs were included in the review. The summary effect of all interventions included in the review showed high heterogeneity between studies but an overall significant, moderate positive effect of cognitive training on cognition (Hedges' g = 0.454; 95% CI 0.156 to 0.753). The review of studies that specifically examined mental status/general cognition found a significant, small positive effect of cognitive training on cognition (Hedges' g = 0.216; 95% CI 0.076 to 0.356), however showed signs of publication bias. The review concluded that individuals with MCI who attend multicomponent/multidomain training were likely to show improvements in cognitive outcomes post-intervention. The AMSTAR 2 rating of this review was moderate.

Chandler et al.[10] conducted a systematic review and meta-analysis to assess the effectiveness of cognitive interventions on improving

the outcomes of individuals with MCI. Computerised, therapy-based and multimodal interventions were included in the study. A total of 30 controlled trials (RCT & CT) were reviewed. Of these, 20 trials measured activities of daily living (ADL) and 11 assessed quality of life (QoL). The review examined the mean (ADL d = 0.32, 95% CI 0.16 to 0.47; QoL d = 0.06, 95% CI -0.11 to 0.22) and median (ADL d= 0.23; QoL d = 0.10) effect sizes and concluded that significant, small positive effects of intervention were found for ADLs but not for QoL. Two studies also reported on the incidence of dementia in their trials and the review reported these results narratively. The AMSTAR 2 rating of this review was critically low. No risk of bias assessment was conducted.

GRADE table 1: Cognitive stimulation versus usual care or no intervention in reducing the risk of cognitive decline and/or dementia in healthy older adults

Author(s): Nicole Ee, Lidan Zheng, Ruth Peters

Date: June 2018

Question: Cognitive stimulation compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Setting: Community

Bibliography: Strout, K. A., David, D. J., Dyer, E. J., Gray, R. C., Robnett, R. H., & Howard, E. P. (2016). Behavioral interventions in six dimensions of wellness that protect the cognitive health of community-dwelling older adults: A systematic review. J Am Geriatr Soc, 64(5), 944-958

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cognitive Function (follow up: range 4 weeks to 1 years; assessed with: subdomain measures of executive function, attention, memory, language and processing speed)									
10	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	none [e]	Cognitive outcomes were assessed in the subdomains of executive function, attention, memory, language and processing speed. No numerical results are provided. The review reported that half of the interventions showed positive outcomes.	⨁◯◯◯ VERY LOW	CRITICAL
Incident MCI - not measured									
-	-	-	-	-	-	-	No data available	-	CRITICAL
Incident Dementia - not measured									
-	-	-	-	-	-	-	No data available	-	CRITICAL
Quality of life - not measured									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Functional level (ADL, IADL) - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Adverse events - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Drop-out rates - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT

CI: Confidence interval

Explanations

a. Risk of bias: Downgraded once as of the 10 studies 5 studies were rated as high quality; 1 rated as moderate quality, 4 rated as low quality. (Review authors assessed quality of primary studies with CONSORT guidelines and ranked high quality as scores ranging from 30-35, moderate quality as 24-29, 18-23 as low quality and <18 as poor)

b. Inconsistency: Downgraded once as 6 of the studies found significant results in at least one cognitive measure, while the remaining four found no effect. No meta-analysis conducted. No numerical data on CIs or I^2 or effect sizes across primary studies.

c. Indirectness: Downgraded once as cognitive stimulation was poorly defined and a large number of measures (59 different assessments) were used to assess the cognitive domains in the review.

d. Imprecision: Downgraded once as sample sizes generally were small (majority n>200); no numerical results on CIs available.

e. Publication bias: Grey literature and selection of retrieved articles were search. Search strategy comprehensive and no apparent reason that bias would be present; no formal assessment of publication bias was carried out.

GRADE table 2: Cognitive training versus usual care or no intervention in reducing the risk of cognitive decline and/or dementia in healthy older adults

Author(s): Nicole Ee, Lidan Zheng, Ruth Peters
Date: June 2018
Question: Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in healthy older adults
Setting: Community
Bibliography: Chiu, H. L., Chu, H., Tsai, J. C., Liu, D., Chen, Y. R., Yang, H. L., & Chou, K. R. (2017). The effect of cognitive-based training for the healthy older people: A meta-analysis of randomized controlled trials. PloS one, 12(5), e0176742.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**cognitive training**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognitive function (follow up: range 4 weeks to 24 weeks; assessed with: MoCA, RBANS, MMSE, ADAS-Cog, CDRS (higher scores indicate better cognition))												
14	randomised trials	serious [a]	serious [b]	not serious [c]	not serious [d]	none [e]	803	787	-	SMD **0.419 SD higher** (0.205 higher to 0.634 higher)	⊕⊕◯◯ LOW	CRITICAL
Incident MCI - not measured												
-	-	-	-	-	-	-	No data available				-	CRITICAL
Incident Dementia - not measured												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**cognitive training**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
-	-	-	-	-	-	-	No data available				-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT
Functional level (ADL, IADL) - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT
Adverse events - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT
Drop-out rates - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT

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

Explanations

a. Risk of Bias: Downgraded once as allocation concealment unclear in 7 out of the 14 studies.

b. Inconsistency: Downgraded once as I^2 = 72.963 which indicates moderate to high degree of heterogeneity

c. Indirectness: population, intervention, outcomes and comparisons are relevant. All research design was compliance with randomisation, control and experimental implementation. Intervention could include single or mixed cognitive based training and this was compared to control. Population was older persons with normal cognition without MCI or dementia.

d. Imprecision: Downgraded once as the overall effect was Hedge's g =0.419, CI: 0.025-0.634 and sample sizes of the individuals studies were small (n<200).

e. Publication bias: Funnel plot was generally symmetrical and value of p for Egger's regression intercept was 0.425 indicated it was not significant.

GRADE table 3: Cognitive stimulation versus usual care or no intervention in reducing the risk of cognitive decline and/or dementia in older adults with mild cognitive impairment

Author(s): Nicole Ee, Lidan Zheng, Ruth Peters

Date: June 2018

Question: Cognitive stimulation compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in older adults with mild cognitive impairment

Setting:

Bibliography: -

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cognitive Function - not measured									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident MCI - not measured									
-	-	-	-	-	-	-	No data available	-	CRITICAL
Incident Dementia - not measured									
-	-	-	-	-	-	-	No data available	-	CRITICAL
Quality of life - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Functional level (ADL, IADL) - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Adverse events - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Drop-out rates - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT

CI: Confidence interval

GRADE table 4: Cognitive training versus usual care or no intervention in reducing the risk of cognitive decline and/or dementia in older adults with mild cognitive impairment

Author(s): Nicole Ee, Lidan Zheng, Ruth Peters
Date: June 2018
Question: Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in older adults with Mild Cognitive Impairment
Setting:
Bibliography: Sherman, D. S., Mauser, J., Nuno, M., & Sherzai, D. (2017). The Efficacy of Cognitive Intervention in Mild Cognitive Impairment (MCI): a Meta-Analysis of Outcomes on Neuropsychological Measures. Neuropsychology review, 1-45 Chandler, M. J., Parks, A. C., Marsiske, M., Rotblatt, L. J., & Smith, G. E. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: a systematic review and meta-analysis. Neuropsychology review, 26(3), 225-251.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**cognitive training**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognitive Function (assessed with: MMSE, RBANS, ADAS-Cog, DRS-2, RBMT, RBMT–II CMMSE, MOCA, Cattell CFT, CAMCOG-R (higher scores indicate better cognition))												
16	randomised trials	serious [a]	not serious [b]	not serious [c]	not serious [d]	publication bias strongly suspected [e]	641	605	-	SMD **0.216 SD higher** (0.076 higher to 0.356 higher)	⊕⊕◯◯ LOW	CRITICAL
Incident MCI - not measured												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**cognitive training**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
-	-	-	-	-	-	-	No data available.				-	CRITICAL
Incident Dementia												
2	randomised trials	serious [f]	serious [g]	not serious [h]	serious [i]	publication bias strongly suspected [j]	Two RCTs reported incidence of dementia in their results. One study found that half of the control group, but none of the intervention group, developed dementia at the 8 month follow up. Another study found that 6.7% of the control group and 11.9% of the intervention group developed dementia at the 2 year follow up.				⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (follow up: range 2 weeks to 28 months; assessed with: WBS, Quality of Life Face scale, QOLQ, QOL-AD, KQOL-AD, RAND, ICQ (higher scores indicate better quality of life))												
11	randomised trials [k]	serious [l]	not serious [m]	serious [n]	not serious [h]	none [o]	329	323	-	SMD **0.06 SD higher** (0.11 lower to 0.22 higher)	⨁⨁◯◯ LOW	IMPORTANT
Functional level (ADL, IADL) (follow up: range 2 weeks to 2 years; assessed with: BADL, IADL, DAFS-R, E-Cog, RBMT, MMQ, CDAD, CDR, MFQ, CDR, ADLS, SAILS. LIADL, ADL-PI, MMA, FRSSD, EFPT (higher scores indicate better functional level))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**cognitive training**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
20	randomised trials [p]	serious [l]	not serious [q]	serious [n]	not serious [r]	none [s]	774	716	-	SMD **0.32 SD higher** (0.16 higher to 0.47 higher)	⨁⨁◯◯ LOW	IMPORTANT
Adverse events - not measured												
-	-	-	-	-	-	-	No data available.				-	IMPORTANT
Drop-out rates - not measured												
-	-	-	-	-	-	-	No data available.				-	IMPORTANT

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

Explanations

a. Risk of bias: Downgraded once as half of the primary studies had a standardised NIH quality score below the mean, and not majority of the studies were single blinded or blinding unclear. Review authors rated quality of papers with 14-item NIH instrument which covers randomisation, blinding, drop out rates etc. Only the standardised z-score was reported no details provided about exact scores or domains of biases.

b. Inconsistency: I^2 = 22.928%, considered low heterogeneity (I^2<25%)

c. Indirectness: population, intervention, outcomes and comparisons are relevant. Only RCTs included, only populations meeting MCI criteria were used, mixed populations excluded. Comparisons were to active or inactive controls and outcomes were primarily accepted measures of cognition.

d. Imprecision: Results were reasonably precise with reported variance small (0.005) and CIs narrow Hedge's g= 0.216 (0.076, 0.0356). While sample size were small across all studies (n < 201) results were reasonably precise and effect size small.

e. Review states "[there was] a very small adjusted point estimate reflective of probable publication bias (Adjusted point estimate = 0.073; 95% CI [−0.087, 0.233]; Q = 44.231)"

f. Risk of bias: Downgraded once as primary study limitations were unclear and review lacks formal assessment of risk of bias.

g. Inconsistency: Downgraded once the two studies showed conflicting results, one study found that intervention group had a lower rate of incident dementia while the other study found that the intervention group had a higher rate of incident dementia. No meta-analysis was conducted and no data on CIs, I^2 or effect sizes were available.

h. Indirectness: population, intervention, outcomes and comparisons are relevant. Only CTs and RCTs included in populations with MCI, comparisons were sham, waitlist or inactive control, Quality of life measured.

i. Imprecision: Downgraded once as one study had a small sample size (N = 20) and a large event rate (50% and 0%), while the other study had a larger sample size (N = 127) but a small event rate (6.7% and 11.9%).

j. Publication bias: Downgraded once as only published records in English were included, grey literature was not searched and no formal assessment of publication bias was carried out.

k. Includes 9 RCT, 2 CT

l. Risk of bias: Downgraded once review lacks assessment of bias. Additionally, 2 trials lacked random allocation.

m. Inconsistency: tau squared was small <0.00, representing negligible heterogeneity.

n. Indirectness: Downgraded once as some of the control groups were active controls (i.e. engaged in alternative treatment)

o. Publication bias: Begg and Mazumdar's rank correlation non-significant (0.10, p=0.43) indicating no bias

p. Includes 18 RCT, 2 CT

q. Inconsistency: tau squared was small (0.09), representing little heterogeneity.

r. Indirectness: population, intervention, outcomes and comparisons are relevant. Only CTs and RCTs included in populations with MCI, comparisons were sham, waitlist or inactive control, ADLs

s. Publication bias: Begg and Mazumdar's rank correlation non-significant (-0.11, p=0.66) indicating no bias

References

1. Sherman, D. S., Mauser, J., Nuno, M., & Sherzai, D. (2017). The Efficacy of Cognitive Intervention in Mild Cognitive Impairment (MCI): a Meta-Analysis of Outcomes on Neuropsychological Measures. Neuropsychology review, 1-45.

2. Chandler, M. J., Parks, A. C., Marsiske, M., Rotblatt, L. J., & Smith, G. E. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: a systematic review and meta-analysis. Neuropsychology review, 26(3), 225-251

Additional evidence not mentioned in GRADE tables

Cognitive training in healthy older adults and older adults with MCI

Kane et al.[11] carried out a peer reviewed systematic review of interventions to prevent age-related cognitive decline, mild cognitive impairment and clinical Alzheimer's type dementia. The review was prepared for the United States Agency for Healthcare Research and Quality (AHRQ). The authors reviewed the literature from Jan 09 to Sept 2016 and for evidence published prior to Jan 2009, they drew on a prior version of the review also prepared for the AHRQ. The review was rigorous. It rates as a moderate quality review when rated using the AMSTAR 2 quality rating only losing points for a lack of information related to excluded articles and a lack of detail as to the funding sources for each included study. The review focused on populations who were cognitively normal or may have age-related changes or MCI but do not yet have dementia. The review did not include dementia due to specific, identifiable conditions such as Lewy body, infectious diseases, frontotemporal, and traumatic brain injury.

In the section regarding cognitive training, 11 studies were included that examined the effect of cognitive training on people with normal cognition or MCI. The review reported that the majority of these studies showed mixed results. 4 studies were reviewed separately because they analysed data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. The ACTIVE trial (N = 2,832) looked at different types of cognitive training and their impact on daily life outcomes (e.g. IADLs). Outcomes were assessed at 2 years, 5 years and 10 years. The review reported that these studies showed (with moderate-strength evidence at 2 years, low-strength evidence at 5 and 10 years) that cognitive training can improve cognitive function in the domain trained, but not in other domains.

Butler et al.[12] conducted a review to summarize the evidence on the impact of cognitive training on cognitive performance and the incidence of dementia in healthy older adults and older adults with MCI. They found 11 trials in total (6 healthy, 5 MCI). In healthy adults, they reported that cognitive training improved outcomes in the targeted domain (but did not transfer to other domains). In adults with MCI, they reported no effect of training on performance. Overall, they reported that the evidence for cognitive training in preventing cognitive decline and/or dementia was insufficient.

Santos et al.[13] reviewed 23 Brazilian studies that examined cognitive training in healthy elderly adults. 8 of these studies examined training programs that targeted multiple cognitive domains while the other 15 examined training programs that only targeted one domain. They reported that 47.6% of the studies showed positive results in favour of cognitive training in at least one cognitive domain.

Strategy-based cognitive training in healthy older adults

Mowszowski et al.[14] evaluated the literature on strategy-based cognitive training (i.e. explicit instruction and/or guided practice provided in group format or at home) for improving executive functioning in healthy older adults. The authors conducted a systematic review and found 13 controlled trials that provided

strategy-based cognitive training specifically targeting executive function. The review reported that 11 of the 13 trials found significant improvements in executive functioning at follow-up and sustained benefits for up to 10 years (ACTIVE trial). Some improvements were also found in measures of daily functioning (although few studies investigated this measure).

Computerized and video game training in healthy older adults

Shah et al.[15] reviewed the effectiveness of computerized cognitive training in preventing cognitive decline in healthy older adults. 7 computerized cognitive training programs were analysed across 26 studies. The review reported that 3 programs showed Level I evidence (multiple well designed RCTs), 3 programs showed Level II evidence (at least one high quality, well-designed RCT) and 2 programs had Level III evidence (some supportive research, but moderately designed RCT). The review concluded that at some commercially available computerized brain training products can assist in promoting healthy brain aging.

Sala et al.[16] reviewed the impact of video game training on cognitive ability in healthy adults. They conducted three meta-analyses that looked at: a) the correlation between video game skills and cognitive ability, b) the differences in cognitive ability between people who played video games and people who did not, c) the effects of video game training on cognitive ability. The first meta-analysis showed that there was a weak correlation (r = 0.07, 95% CI 0.05 to 0.09) between video game skills and cognitive ability. The second meta-analysis showed that there was a significant positive effect size (g = 0.33, 95% CI 0.28 to 0.39) of playing video games versus not playing video games on cognitive ability. The third meta-analysis showed that there was no effect (g = 0.07, 95% CI 0.02 to 0.12) of video game training on overall cognitive ability. The authors concluded that overall video game skill and cognitive ability were only weakly related.

Computerized cognitive training in older adults with MCI

Hill et al.[7] conducted a systematic review and meta-analysis to examine the impact of computerized cognitive training on the cognitive abilities of older adults with MCI or dementia. 17 trials were identified that examined the impact of computerized cognitive training on adults with MCI specifically. The review reported that there was a significant, moderate effect of cognitive training on overall cognitive outcomes combined across the 17 studies (aka overall effect size, g = 0.35, 95% CI 0.20 to 0.51) and a significant, moderate effect of cognitive training on global cognitive measures (which were only included in 12 studies, g = 0.38, 95% CI 0.14 to 0.62). Additionally, they reported there was a significant, moderate effect of training on psychosocial functioning (g = 0.52, 95% CI 0.01 to 1.03) in adults with MCI. Overall, the review reported that computerized cognitive training has a positive effect on global cognition and psychosocial functioning in adults with MCI.

Memory focused interventions in adults with cognitive disorders

Yang et al.[17] conducted a systematic review and meta-analysis evaluating the efficacy of memory focused interventions for people with cognitive disorders (consisting of people with MCI, age-related cognitive decline and dementia). 27 RCTs were identified and included in the analysis. The review reported a significant, medium-to-large effect of memory-focused interventions on improving objective learning and memory function (Hedges' g = 0.62, 95% CI

0.39 to 0.84) and subjective (self-report) memory performance (Hedges' g = 0.67, 95% CI 0.41 to 0.94), but no effect on global cognitive functioning (Hedges' g = 0.27, 95% CI -0.05 to 0.48). The review concluded that memory focused interventions improved memory-related performance in people with cognitive disorders.

Other relevant guidelines

WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings: http://www.who.int/mental_health/mhgap/evidence/en/

WHO Guidelines on Integrated Care for Older People (ICOPE): http://www.who.int/ageing/publications/guidelines-icope/en/

Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset: https://www.nice.org.uk/guidance/ng16

Part 2: From evidence to decisions

Summary of evidence table 1

Cognitive stimulation compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in healthy older adults

Patient or population: Healthy older adults

Setting: Community

Intervention: Cognitive stimulation

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive stimulation**				
Cognitive Function assessed with: subdomain measures of executive function, attention, memory, language and processing speed follow up: range 4 weeks to 1 years	Cognitive outcomes were assessed in the subdomains of executive function, attention, memory, language and processing speed. No numerical results are provided. The review reported that half of the interventions showed positive outcomes.			(10 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d,e]	
Incident MCI	No data available			(0 studies)	-	
Incident Dementia	No data available			(0 studies)	-	
Quality of life	No data available			(0 studies)	-	

Cognitive stimulation compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in healthy older adults

Patient or population: Healthy older adults

Setting: Community

Intervention: Cognitive stimulation

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive stimulation**				
Functional level (ADL, IADL)	No data available			(0 studies)	-	
Adverse events	No data available			(0 studies)	-	
Drop-out rates	No data available			(0 studies)	-	

***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

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

Explanations

a. Risk of bias: Downgraded once as of the 10 studies 5 studies were rated as high quality; 1 rated as moderate quality, 4 rated as low quality. (Review authors assessed quality of primary studies with CONSORT guidelines and ranked high quality as scores ranging from 30-35, moderate quality as 24-29, 18-23 as low quality and <18 as poor)

b. Inconsistency: Downgraded once as 6 of the studies found significant results in at least one cognitive measure, while the remaining four found no effect. No meta-analysis conducted. No numerical data on CIs or I^2 or effect sizes across primary studies.

c. Indirectness: Downgraded once as cognitive stimulation was poorly defined and a large number of measures (59 different assessments) were used to assess the cognitive domains in the review.

d. Imprecision: Downgraded once as sample sizes generally were small (majority n>200); no numerical results on CIs available.

e. Publication bias: Grey literature and selection of retrieved articles were searched. Search strategy comprehensive and no apparent reason that bias would be present; no formal assessment of publication bias was carried out.

Summary of evidence table 2

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in healthy older adults

Patient or population: Healthy older adults

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				
Cognitive function assessed with: MoCA, RBANS, MMSE, ADAS-Cog, CDRS (higher scores indicate better cognition) follow up: range 4 weeks to 24 weeks	-	SMD **0.419 SD higher** (0.205 higher to 0.634 higher)	-	1590 (14 RCTs)	⨁⨁◯◯ LOW [a,b,c,d,e]	
Incident MCI - not measured				(0 studies)	-	
Incident Dementia - not measured				(0 studies)	-	
Quality of life - not measured				(0 studies)	-	

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in healthy older adults

Patient or population: Healthy older adults

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				
Functional level (ADL, IADL) - not measured				(0 studies)	-	
Adverse events - not measured				(0 studies)	-	
Drop-out rates - not measured				(0 studies)	-	

***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

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in healthy older adults

Patient or population: Healthy older adults

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				

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

Explanations

a. Risk of Bias: Downgraded once as allocation concealment unclear in 7 out of the 14 studies.

b. Inconsistency: Downgraded once as I^2 = 72.963 which indicates moderate to high degree of heterogeneity

c. Indirectness: population, intervention, outcomes and comparisons are relevant. All research design was compliance with randomisation, control and experimental implementation. Intervention could include single or mixed cognitive based training and this was compared to control. Population was older persons with normal cognition without MCI or dementia.

d. Imprecision: Downgraded once as the overall effect was Hedge's g =0.419, CI: 0.025-0.634 and sample sizes of the individuals studies were small (n<200).

e. Publication bias: Funnel plot was generally symmetrical and value of p for Egger's regression intercept was 0.425 indicated it was not significant.

Summary of evidence table 3

Cognitive stimulation versus usual care or no intervention in reducing the risk of cognitive decline and/or dementia in older adults with mild cognitive impairment

Patient or population: Adults with mild cognitive impairment

Setting: Community

Intervention: Cognitive stimulation

Comparison: Care as usual or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Cognitive Function - not measured	No data available.	-	-
Incident MCI - not measured	No data available	-	-
Incident Dementia - not measured	No data available	-	-
Quality of life - not measured	No data available	-	-
Functional level (ADL, IADL) - not measured	No data available	-	-
Adverse events - not measured	No data available	-	-
Drop-out rates - not measured	No data available	-	-

Cognitive stimulation versus usual care or no intervention in reducing the risk of cognitive decline and/or dementia in older adults with mild cognitive impairment

Patient or population: Adults with mild cognitive impairment

Setting: Community

Intervention: Cognitive stimulation

Comparison: Care as usual or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

*__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

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

Summary of evidence table 4

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in older adults with Mild Cognitive Impairment

Patient or population: Older adults with Mild Cognitive Impairment

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				
Cognitive Function assessed with: MMSE, RBANS, ADAS-Cog, DRS-2, RBMT, RBMT–II CMMSE, MOCA, Cattell CFT, CAMCOG-R (higher scores indicate better cognition)	-	SMD **0.216 SD higher** (0.076 higher to 0.356 higher)	-	1246 (16 RCTs)[1]	⨁⨁◯◯ LOW [a,b,c,d,e]	
Incident MCI - not measured				(0 studies)	-	

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in older adults with Mild Cognitive Impairment

Patient or population: Older adults with Mild Cognitive Impairment

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				
Incident Dementia	Two RCTs reported incidence of dementia in their results. One study found that half of the control group, but none of the intervention group, developed dementia at the 8 month follow up. Another study found that 6.7% of the control group and 11.9% of the intervention group developed dementia at the 2 year follow up.			(2 RCTs)[2]	⨁◯◯◯ VERY LOW [f,g,h,i,j]	
Quality of life assessed with: WBS, Quality of Life Face scale, QOLQ, QOL-AD, KQOL-AD, RAND, ICQ (higher scores indicate better quality of life) follow up: range 2 weeks to 28 months	-	SMD **0.06 SD higher** (0.11 lower to 0.22 higher)	-	652 (11 RCTs) [2] [g]	⨁⨁◯◯ LOW [h,l,m,n,o]	

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in older adults with Mild Cognitive Impairment

Patient or population: Older adults with Mild Cognitive Impairment

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				
Functional level (ADL, IADL) assessed with: BADL, IADL, DAFS-R, E-Cog, RBMT, MMQ, CDAD, CDR, MFQ, CDR, ADLS, SAILS. LIADL, ADL-PI, MMA, FRSSD, EFPT (higher scores indicate better functional level) follow up: range 2 weeks to 2 years	-	SMD **0.32 SD higher** (0.16 higher to 0.47 higher)	-	1490 (20 RCTs) [2] [i]	⨁⨁◯◯ LOW [l,n,q,r,s]	
Adverse events - not measured				(0 studies)	-	
Drop-out rates - not measured				(0 studies)	-	

Cognitive training compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in older adults with Mild Cognitive Impairment

Patient or population: Older adults with Mild Cognitive Impairment

Setting:

Intervention: Cognitive training

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with cognitive training**				

***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

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

Explanations

a. Risk of bias: Downgraded once as half of the primary studies had a standardised NIH quality score below the mean, and not majority of the studies were single blinded or blinding unclear. Review authors rated quality of papers with 14-item NIH instrument which covers randomisation, blinding, drop out rates etc. Only the standardised z-score was reported no details provided about exact scores or domains of biases.

b. Inconsistency: I^2 = 22.928%, considered low heterogeneity (I^2<25%)

c. Indirectness: population, intervention, outcomes and comparisons are relevant. Only RCTs included, only populations meeting MCI criteria were used, mixed populations excluded. Comparisons were to active or inactive controls and outcomes were primarily accepted measures of cognition.

d. Imprecision: Results were reasonably precise with reported variance small (0.005) and CIs narrow Hedge's g= 0.216 (0.076, 0.0356). While sample size were small across all studies (n < 201) results were reasonably precise and effect size small.

e. Review states "[there was] a very small adjusted point estimate reflective of probable publication bias (Adjusted point estimate = 0.073; 95% CI [−0.087, 0.233]; Q = 44.231)"

f. Risk of bias: Downgraded once as primary study limitations were unclear and review lacks formal assessment of risk of bias.

g. Inconsistency: Downgraded once the two studies showed conflicting results, one study found that intervention group had a lower rate of incident dementia while the other study found that the intervention group had a higher rate of incident dementia. No meta-analysis was conducted and no data on CIs, I2 or effect sizes were available.

h. Indirectness: population, intervention, outcomes and comparisons are relevant. Only CTs and RCTs included in populations with MCI, comparisons were sham, waitlist or inactive control, Quality of life measured.

i. Imprecision: Downgraded once as one study had a small sample size (N = 20) and a large event rate (50% and 0%), while the other study had a large sample size (N = 127) but a small event rate (6.7% and 11.9%).

j. Publication bias: Downgraded once as only published records in English were included, grey literature was not searched and no formal assessment of publication bias was carried out.

k. Includes 9 RCT, 2 CT

l. Risk of bias: Downgraded once review lacks assessment of bias. Additionally, 2 trials lacked random allocation.

m. Inconsistency: tau squared was small <0.00, representing negligible heterogeneity.

n. Indirectness: Downgraded once as some of the control groups were active controls (i.e. engaged in alternative treatment)

o. Publication bias: Begg and Mazumdar's rank correlation non-significant (0.10, p=0.43) indicating no bias

p. Includes 18 RCT, 2 CT

q. Inconsistency: tau squared was small (0.09), representing little heterogeneity.

r. Indirectness: population, intervention, outcomes and comparisons are relevant. Only CTs and RCTs included in populations with MCI, comparisons were sham, waitlist or inactive control, ALDs

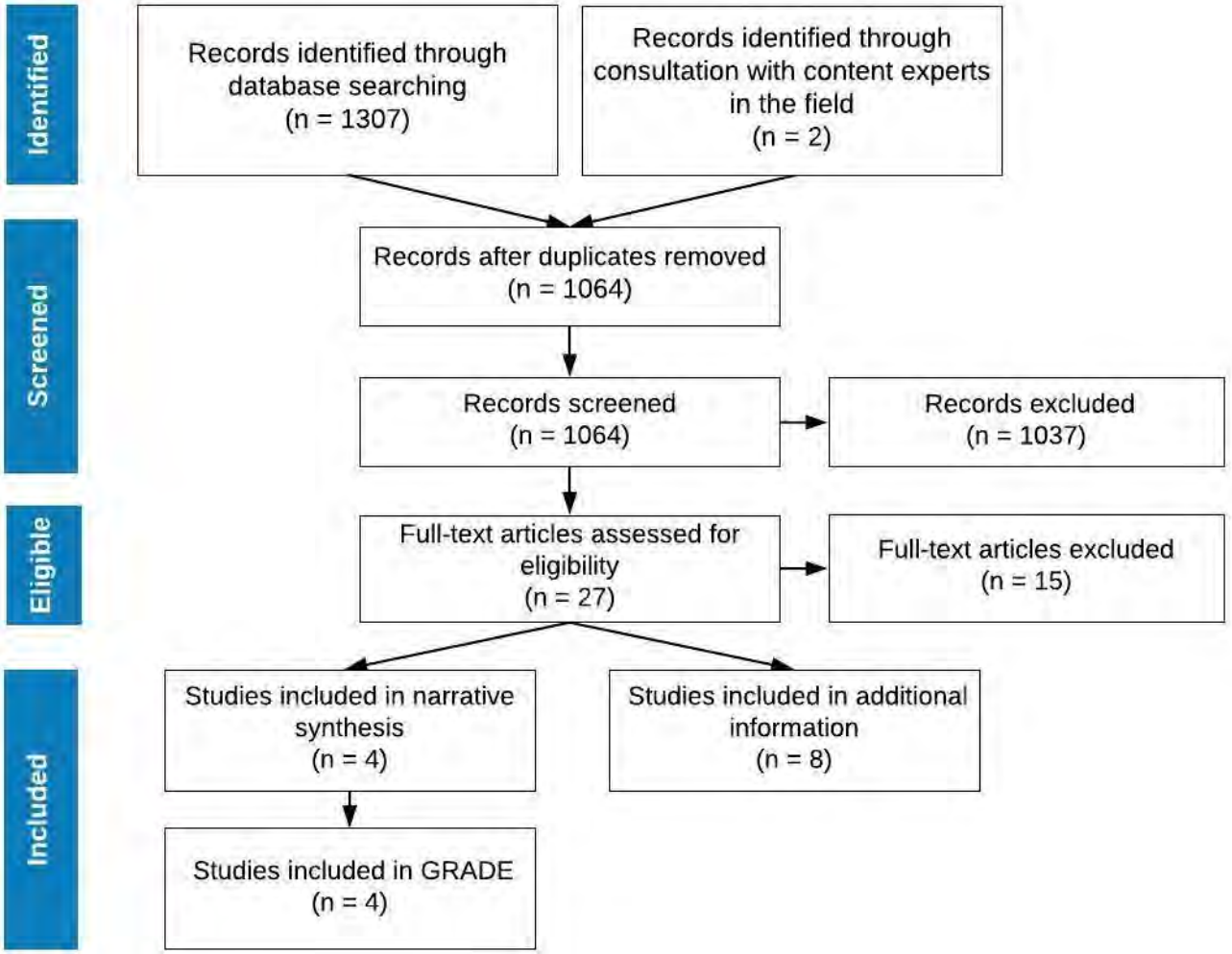
s. Publication bias: Begg and Mazumdar's rank correlation non-significant (-0.11, p=0.66) indicating no bias

References

1. Sherman, D. S., Mauser, J., Nuno, M., & Sherzai, D. (2017). The Efficacy of Cognitive Intervention in Mild Cognitive Impairment (MCI): a Meta-Analysis of Outcomes on Neuropsychological Measures. Neuropsychology review, 1-45.

2. Chandler, M. J., Parks, A. C., Marsiske, M., Rotblatt, L. J., & Smith, G. E. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: a systematic review and meta-analysis. Neuropsychology review, 26(3), 225-251

Annex: PRISMA[1] flow diagram for systematic review of reviews – cognitive stimulation and training



[1] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*, *6*(7), e1000097.

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Evidence-to-decision table

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds(1) Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. Studies have shown that increased cognitive activity can have a buffering effect against rapid cognitive decline(2).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	*Desirable effects* **Cognitive stimulation versus usual care or no intervention in healthy older adults** Only cognitive function reported as a critical outcome. No evidence on dementia or mild cognitive impairment (MCI). For cognitive function, the volume of evidence is moderate (10 RCTs)(3) and quality of evidence is very low. No meta-analysis was conducted. The review narratively reported that 50% of studies showed cognitive stimulation in healthy older adults improved cognitive outcomes in at least one cognitive domain (executive function, attention, memory, language and/or processing speed). **Cognitive training versus usual care or no intervention in healthy older adults** Only cognitive function reported as a critical outcome. No evidence on dementia or MCI. For cognitive function, the volume of evidence is moderate (14 RCTs)(4) and quality of evidence is low. The review conducted a meta-analysis which showed that cognitive training in	Kane et al.(7) and Butler et al.(8) concluded that cognitive training in healthy older adults can improve cognitive function in the domain trained, but not in other domains. Mowszowski et al(9). found that 11 out of 13 trials found improvements in executive function (EF) after EF specific training in healthy older adults and some improvements in ADL. Santos et al reported that 47.6% of Brazilian cognitive raining studies showed positive results in favour of cognitive training in at least one cognitive domain. Shah et al.(10) concluded that some commercially available computerized brain training products can assist in promoting better cognitive function and Sala et al. (11)concluded that video game skills is weakly related cognitive ability.

	healthy older adults has a moderate positive effect on overall cognitive functioning (Hedges' g = 0.419; 95% CI = 0.205 to 0.634). **Cognitive stimulation versus usual care or no intervention in adults with MCI** No evidence available, inestimable. **Cognitive training versus usual care or no intervention in adults with MCI** No data was available for MCI. For cognitive function the volume of evidence is moderate (16 ACTs)(5) and the quality of evidence is low. The meta-analysis on this outcome showed that cognitive training in adults with MCI has a small positive effect on cognition (Hedges' g = 0.216; 95% CI 0.076 to 0.356). For incident dementia the volume of evidence is low (2 RCTs) and the quality of evidence is very low. The results were reported narratively for this outcome. The review reported that one study found that half of the control group, but none of the intervention group, developed dementia at the 8 month follow up while another found that 6.7% of the control group and 11.9% of the intervention group developed dementia at the 2 year follow up. For quality of life and functional level, the volume of evidence is moderate (11 RCTs for quality of life and 20 RCT for functional level) (6)and quality of evidence is low. The meta-analysis on these outcomes showed that cognitive training in adults with MCI has a small positive effect on ADLs (d = 0.32, 95% CI 0.16 to 0.47) but not QoL (d = 0.06, 95% CI -0.11 to 0.22).	Yang et al.(12) found that memory focused interventions improved memory-related performance in people with cognitive disorders. Hill et al.(13) reported that computerized cognitive training has a positive effect on global cognition and psychosocial functioning in adults with MCI. Butler et al. (8)concluded that cognitive training in adults with MCI has no effect on cognitive function.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	*Undesirable effects* No data on undesirable outcomes were reported (7) (6) (5) (4) (3).	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Cognitive stimulation versus usual care or no intervention in healthy older adults** **Findings:** There is limited low quality evidence which showed that cognitive stimulation improves cognitive function in healthy adults. No evidence for MCI or incident dementia was available. **Cognitive training versus usual care or no intervention in healthy older adults** **Findings:** Certainty of the evidence is low for cognitive function which showed that cognitive training improves cognitive function in healthy adults. No evidence for MCI or incident dementia was available. **Cognitive stimulation versus usual care or no intervention in adults with MCI** No evidence available, inestimable. **Cognitive training versus usual care or no intervention in adults with MCI** **Findings:** There is low quality evidence to suggest that cognitive training improves cognitive functions and ADL in adults with MCI. There is very low quality of evidence that suggests cognitive training reduces incident dementia in adults with MCI. Low quality evidence suggests that cognitive training has no effect on QoL in adults with MCI. No evidence for effect of cognitive training on incident MCI is available.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	A review conducted by Anderson et al 2009(14) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia(15) and the United Kingdom(16) (UK) and have shown a general trend of individuals being fearful of developing dementia. There is no evidence showing that individuals would oppose dementia risk reduction, or view cognitive decline favourably. Data from low and middle income countries is unavailable. There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	Additional sources like the Saga Survey(17)and Alzheimer's Research UK(18)have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Cognitive stimulation versus usual care or no intervention in healthy older adults** May favor the intervention (very low quality evidence), no adverse effects were reported **Cognitive training versus usual care or no intervention in healthy older adults** May favor the intervention (low quality evidence)**,** no adverse effects were reported **Cognitive stimulation versus usual care or no intervention in adults with MCI** No evidence available, inestimable. **Cognitive training versus usual care or no intervention in adults with MCI** May favor the intervention (low to very low quality evidence), no adverse effects were reported	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Wide variety of interventions used and no data favouring one over another. Resources required are inestimable at this stage as none of the included studies provided information on this. Further research is required to determine mode of learning (e.g. pen-and-paper or computerised), domain targeted, and duration of cognitive intervention which would be efficacious for the target outcomes. Issues of adherence is another factor to consider in resource requirements, whereby more oversight may be required to ensure compliance. With respect to resources required, the data is scarce and inconclusive.	The cognitive stimulation and interventions may be resource-intensive especially of they are administered by psychotherapists working in high-income countries. Some features of the interventions, however, such as duration or frequency, could be adapted to particular settings, and could be administered by suitably trained and supported non-specialists.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Uncertain as evidence is limited and inconclusive, and due to lack of data on costing in the included studies. Also the resource costs are variable depending upon type of intervention.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Uncertain due to lack of data in the included studies. No evidence available on cost effectiveness of cognitive interventions for reducing the risk of cognitive impairment and/or dementia.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons(19) studies health equities in England, They found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment, and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	No data on acceptability were reported by the systematic reviews described above. However, there are no apparent reasons for which the intervention would not be acceptable to key stakeholders.	A small randomized study examined the feasibility and acceptability of a computerized cognitive stimulation (CCS) program and a computerized cognitive engagement (CCE)

○ Yes ○ Varies ○ Don't know		program, and then compared their effects in older adults with MCI.(n=9 in CCS and n=10 in CCE). The patients attended a group weekly session for a duration of 3 months. All of the participants attended the 12 sessions and showed a high level of motivation. Attrition rate was very low (one dropout at M3 assessment). The authors concluded that both interventions were highly feasible and acceptable and allowed improvement in different aspects of cognitive and psychosocial functioning in subjects with MCI. However, this data is insufficiently robust and its findings cannot be generalized to the population at large.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Insufficient evidence to make a determination. Feasibility is depends on the cognitive training or stimulation intervention required for efficacious outcomes, for which further research is required.	See description of study above.

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Guidelines for risk reduction of cognitive decline and dementia

Evidence profile:
social activity for reducing the risk of cognitive decline and/or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment, is preserving and promoting a high level of social activity more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

Cognitive function is strongly correlated with functional status, quality of life and independence in older adults[1, 2]. While some declines in cognitive function is considered to be normal with ageing, the degree and severity of this trajectory has been shown to be modifiable. Importantly, certain lifestyle factors have been shown to be neuroprotective against cognitive decline and dementia. One such protective factor is social engagement[2].

Social engagement is an important predictor of wellbeing throughout life[3]. Social disengagement conversely, has been shown to place older individuals at increased risk of transitioning into cognitive impairment and dementia[4]. A systematic review and meta-analysis of longitudinal cohort studies showed that lower social participation (RR = 1.41; 95% CI 1.13 to 1.75), less frequent social contact (RR = 1.57; 95% CI 1.32 to 1.85) and loneliness (RR = 1.57; CI 1.32 to 1.85) was associated with higher rates of incident dementia[5].

Individuals often face barriers to the preservation of social activity, relationships and networks in later life. Age-related factors that contribute to diminished social engagement include but are not limited to retirement, driving cessation, reduced mobility, living alone, death of partners and loved ones, as well as health conditions that affect motor-cognitive status.

Better understanding of the relationship between social engagement and cognitive function is therefore critical to the maintenance of health and wellbeing of the ageing population. This review seeks to examine whether the promotion and preservation of social activity in late life is effective in reducing the risk of cognitive decline and dementia in older adults.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment, is preserving and promoting high level of social activity more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Populations

- Adults with normal cognition or mild cognitive impairment

Interventions

- Preservation and promotion of social activity[1] including community and family engagement

Comparison

- Care as usual or no intervention

Outcomes

- Critical:
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Incident Dementia
- Important:
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

[1] Social activities are varied and difficult to define, however they may include meeting friends, attending events or functions, volunteering or participating in occupational duties or group recreational activities.[6]

Search Strategy

Searches using the following strategies (or similar) were conducted as follows

- ("social interaction" or "social Networks" or "social processes" or "social behaviour" or "social behavior" or "community networks" or "social media" or family) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheime*) and (systemati* or meta-analys*)[2]

Searches were conducted in:

- Medline
- Cochrane
- PsycInfo
- Embase
- NICE
- Global index medicus/Global Health Library
    - WHO regional data base
    - WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth

List of systematic reviews identified by the search process

Included in GRADE[3] tables

- Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: A systematic review. *Systematic Reviews, 6 (1),* 259

[2] Dates searched were 1 May 2016 - 1 May 2018. Additionally, the 2016 AHRQ review(7) was consulted for relevant records which systematically searched the literature between Jan 2009 – Sept 2016. In combination, the search period spanned >9 years. All abstracts were screened by two independent reviewers and with any discrepancies resolved by discussion. Full text articles were read by the same two independent reviewers and any discrepancy resolved by discussion.

[3] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO table

	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Preservation and promotion of social activity including community and family engagement versus care as usual or no intervention	Cognitive function (or cognitive test results using validated instruments) • Global cognition measured by composite measures (ADAS-Cog, MMSE, MDRS)	Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: A systematic review. *Systematic Reviews, 6 (1),* 259.	Systematic review is relevant. Includes samples of adults with normal cognition who were administered social activity interventions. Cognitive outcomes were included. RCTs were included. AMSTAR 2[4] rating is Low.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident Dementia	No reviews identified.	No reviews identified.
		Quality of life	No reviews identified.	No reviews identified.
		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events	No reviews identified.	No reviews identified.
		Drop-out rates	No reviews identified.	No reviews identified.

[4] AMSTAR: A Measurement Tool to Assess Systematic Reviews. More information: https://amstar.ca/index.php

Narrative descriptions of the studies that went into the analysis

GRADE table 1: social activity versus usual care or no intervention

Kelly et al[6] conducted a systematic review to evaluate the impact of social factors, including social activity, networks and support, on cognitive function in community dwelling older adults with no known cognitive impairment. Their review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines[8] and was of low quality as rated on the AMSTAR-2 checklist[9]. They included randomised controlled trials (RCTs), twin studies and observational evidence in their search. Review findings were reported narratively. Three RCTs[10-12] which assessed the association between cognitive function and social activity were deemed eligible. Overall cognition was measured by varied composite measures of global cognition, including the ADAS-cog, MMSE, and MDRS. One of the three RCTs found social activity intervention to be significantly associated with improvements in cognitive function, $p = 0.023$[12]. The authors noted the primary studies did not report *p*-values for several comparisons, and this may be a reason for the absence of numerical data in the review results.

GRADE table 1: Preservation and promotion of social activity including community and family engagement versus usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Author(s): Nicole Ee, Ruth Peters
Date: May 2018
Question: Preserving and promoting high level of social activity compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia
Setting: Community
Bibliography: Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: A systematic review. Systematic Reviews, 6 (1), 259.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preserving and promoting high level of social activity	usual care or no intervention	Relative (95% CI)	Absolute (95% CI)		
Cognitive function (follow up: range 14 weeks to 12 months; assessed with: Global cognition: MMSE, ADAS-Cog, MDRS etc. (higher scores indicate better cognition))												
3	randomised trials	serious [a]	not serious [b]	serious [c]	very serious [d]	publication bias strongly suspected [e]	183	393	-	see comment[f]	⊕◯◯◯ VERY LOW	CRITICAL
Incident MCI - not measured												
-	-	-	-	-	-	-	No data available.				-	CRITICAL
Incident Dementia - not measured												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preserving and promoting high level of social activity**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
-	-	-	-	-	-	-	No data available.				-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	No data available.				-	IMPORTANT
Functional level (ADL, IADL) - not measured												
-	-	-	-	-	-	-	No data available.				-	IMPORTANT
Adverse events - not measured												
-	-	-	-	-	-	-	No data available.				-	IMPORTANT
Drop-out rates - not measured												
-	-	-	-	-	-	-	No data available.				-	IMPORTANT

CI: Confidence interval

Explanations

a. Risk of bias: Downgraded once as primary study limitations were unclear and review lacks formal assessment of risk of bias. Results not reported for all cognitive function comparisons in primary studies; possibility of confounding factors that may influence results.

b. Inconsistency: No meta-analysis conducted. No data on CIs or I^2 or effect sizes across primary studies but general finding were of no effect or small positive effects on certain domains of cognition.

c. Indirectness: Downgraded once as the review only provided details on measures of global cognition in one study population.

d. Imprecision: Downgraded twice as no numerical data provided on CIs or test scores. Only p-value for ADAS-cog provided, p = 0.0203, none for other measures of global cognition. Sample sizes were small (n=120-235).

e. Publication bias: Downgraded once as only published records in English were included; no formal assessment of publication bias was carried out.

f. Results were reported narratively

Additional evidence not mentioned in GRADE tables

Though the RCT evidence was sparse and of very low grade, the review by Kelly et al[6] also identified several observational studies which reported on the effects of social activity, networks on cognitive function. Cognitive function was primarily measured with the MMSE and results were reported narratively.

Social activity versus usual care or no intervention

In addition to RCT evidence, Kelly et al[6] identified 22 observational studies of social activity. They reported that social activity was significantly associated with higher baseline scores on five measures of global cognition in four studies. At follow-up, 12 of 14 studies found global cognition measures were positively associated with social activity.

Social networks versus usual care or no intervention

Kelly et al[6] identified nine observations studies which investigated the relationships between social network and cognition. They reported social network size and frequency of contact was associated with baseline measures of global cognition in two of five studies and six of nine studies at follow-up. Two studies found no association between global cognition and social network, and one found no association with social network size.

Other relevant guidelines

Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset: https://www.nice.org.uk/guidance/ng16

Part 2: From evidence to decisions

Summary of evidence

Preserving and promoting high level of social activity compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Patient or population: Adults with normal cognition or mild cognitive impairment

Setting: Community

Intervention: Preserving and promoting high level of social activity

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with preserving and promoting high level of social activity**				
Cognitive function assessed with: Global cognition: MMSE, ADAS-Cog, MDRS etc. (higher scores indicate better cognition) follow up: range 14 weeks to 12 months	The mean cognitive function was **0**	The mean cognitive function in the intervention group was 0 (0 to 0)	-	576 (3 RCTs)	⨁◯◯◯ VERY LOW a,b,c,d,e,f	
Incident MCI - not measured	No data available.			-	-	
Incident Dementia - not measured	No data available.			-	-	

Preserving and promoting high level of social activity compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Patient or population: Adults with normal cognition or mild cognitive impairment

Setting: Community

Intervention: Preserving and promoting high level of social activity

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with preserving and promoting high level of social activity**				
Quality of life - not measured	No data available.			-	-	
Functional level (ADL, IADL) - not measured	No data available.			-	-	
Adverse events - not measured	No data available.			-	-	
Drop-out rates - not measured	No data available.			-	-	

***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

Preserving and promoting high level of social activity compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Patient or population: Adults with normal cognition or mild cognitive impairment

Setting: Community

Intervention: Preserving and promoting high level of social activity

Comparison: Usual care or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	**Risk with preserving and promoting high level of social activity**				

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

Explanations

a. Risk of bias: Downgraded once as primary study limitations were unclear and review lacks formal assessment of risk of bias. Results not reported for all cognitive function comparisons in primary studies; possibility of confounding factors that may influence results.

b. Inconsistency: No meta-analysis conducted. No data on CIs or I^2 or effect sizes across primary studies but general finding were of no effect or small positive effects on certain domains of cognition.

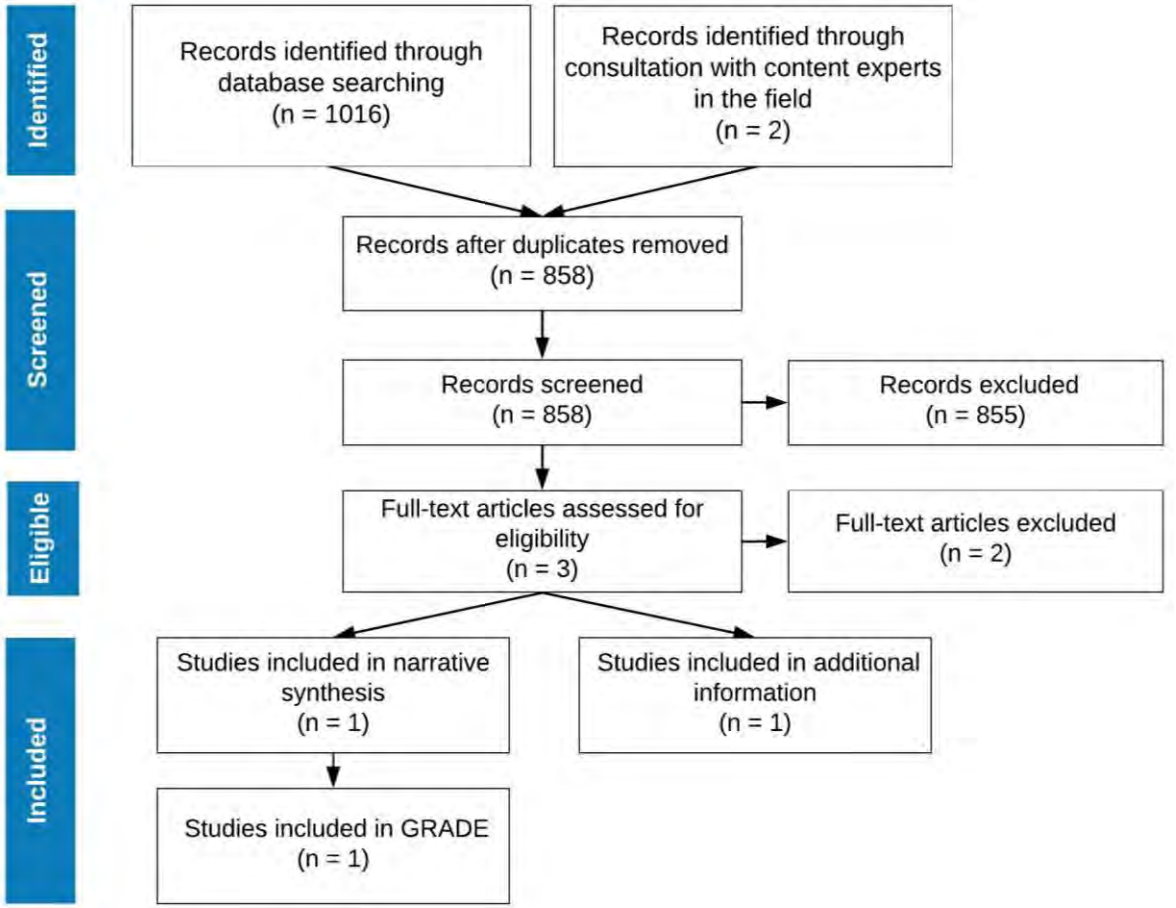
c. Indirectness: Downgraded once as the review only provided details on measures of global cognition in one study population.

d. Imprecision: Downgraded twice as no numerical data provided on CIs or test scores. Only p-value for ADAS-cog provided, p = 0.0203, none for other measures of global cognition. Sample sizes were small (n=120-235).

e. Publication bias: Downgraded once as only published records in English were included; no formal assessment of publication bias was carried out.

f. Results were reported narratively

Annex: PRISMA[1] flow diagram for systematic review of reviews – social activity for reducing risk of cognitive decline and/or dementia



Note. Kelly et al[6] was included both narrative syntheses/GRADE and additional information.

[1] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*, *6*(7), e1000097.

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Social activity for reducing the risk of cognitive decline and/or dementia

Evidence-to-decision table

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds (1) Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. Social engagement is an important predictor of wellbeing throughout life. Social disengagement conversely, has been shown to place older individuals at increased risk of transitioning into cognitive impairment and dementia (2)	A systematic review and meta-analysis of longitudinal cohort studies showed that lower social participation (RR = 1.41; 95% CI 1.13 to 1.75), less frequent social contact (RR = 1.57; 95% CI 1.32 to 1.85) and loneliness (RR = 1.57; CI 1.32 to 1.85) was associated with higher rates of incident dementia (3)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*Desirable outcomes;* For cognitive function, volume and quality of evidence is very low. No meta-analysis was conducted. Three RCTs of small to moderate sample size (n=120 to n=225) and follow-up (14 weeks to 12 months). No robust information was available on clinical significance. Only cognitive function reported as a critical outcome. No evidence on dementia or MCI.	Kelly et al. (4) also reported that observational studies found that social activity was significantly associated with global cognition in the majority of studies both at baseline and follow-up, and that social network size and frequency of contact was associated with the majority of studies at follow-up.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	*Undesirable outcomes:* No evidence on undesirable outcomes i.e. quality of life, functional level (ADL, IADL), adverse events, drop outs.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	For cognitive function, the certainty of evidence is very low. No evidence for MCI, dementia, quality of life, functional level (ADL, IADL), adverse events, drop outs.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	A review conducted by Anderson et al 2009 (5) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia (6) and the United Kingdom (7) (UK) and have shown a general trend of individuals being fearful of developing dementia. Data from low- and middle-income countries is unavailable. There is no evidence showing that individuals would oppose dementia risk reduction or view cognitive decline favourably. Hence, there is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	Additional sources like the Saga Survey (8) and Alzheimer's Research UK (9) have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%).

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Probably favours the intervention. No data on adverse effect available.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Wide variety of interventions used and no data favouring one over another. Resources required are inestimable at this stage. Further research is required to determine the type, form, and duration of social activity intervention which would be efficacious for the target outcomes. Issues of adherence is another factor to consider in resource requirements, whereby more oversight may be required to ensure compliance. With respect to resources required, the data is scarce and inconclusive.	Depends on the type of social activity intervention in question.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High	Uncertain as evidence is limited and inconclusive, and due to lack of data on costing in the included studies. Also, the resource costs are variable depending upon type of intervention.	

○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	No evidence available on cost effectiveness of social interventions.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons (10) studies health equities in England, they found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are no apparent reasons for which the intervention would not be acceptable to key stakeholders.	Acceptability could be determined via focus groups at a later stage when there is greater clarity on the type of social activity intervention required for efficacious outcomes.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Insufficient evidence to make a determination. Feasibility is depending on the social activity intervention required for efficacious outcomes, for which further research is required.	

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Risk reduction guidelines for cognitive decline and dementia

Evidence profile:
Weight reduction and cognitive decline or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment who are overweight or obese, are interventions for weight reduction (or control of obesity) more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

As the number of older adults increases worldwide, a rise in dementia and Alzheimer's disease (AD) has also been reported,[1] causing health, economic and social burdens.[2,3] In 2015, it has been estimated that there were 46.8 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050.[1] AD/dementia has been linked to modifiable, lifestyle-related, cardiovascular risk factors (CVRFs),[1-4] and since the management of CVD is still suboptimal in many countries, especially among older adults and no cure is available for AD, CVRFs management could be crucial in halting the rapid increase in the prevalence of dementia, as some projection models suggested.[5,6]

Overweight and obesity is one of the best characterised and established risk for a variety of non-communicable diseases, the cause of at least 2.8 million deaths each year world-wide, and of an estimated 35.8 million (2.3%) of global DALYs.[7] in 2008, 35% of adults aged 20+ were overweight (BMI ≥ 25 kg/m2) (34% men and 35% of women) with significantly variable prevalence among world areas, being the Americas, Europe, and the Eastern Mediterranean the regions with the highest concentration of overweight and obese people.[7] Overweight and obesity, in particular, has been linked to a number of medical complications such as type 2 diabetes,[8] cancer,[9] premature mortality,[10] and CVD,[11] both as a direct risk factor as well as a risk for other CVRFs, such as high cholesterol and hypertension.

Obesity has been steadily raising in the last few decades and in particular among older adults[12] and although an increasing body of evidence suggests that overweight (25< BMI < 30) in older adults could be more protective than normal weight in terms of overall mortality,[13] a link has also been established between excess of fat body mass and cognitive impairment.[14] A recent systematic review and meta-analysis of observational studies conducted on a total of about 600,000 individuals showed that obesity (but not overweight) at midlife increases the risk of dementia (RR, 1.33; 95% confidence interval [CI], 1.08-1.63).[15]

It has been suggested that weight loss could reduce indirectly the risk of dementia by improving a variety of metabolic factors linked with the pathogenesis of cognitive impairment and dementia (i.e. glucose tolerance, insulin sensitivity, blood pressure, oxidative stress, and inflammation).[16] However, a direct beneficial effect of weight reduction intervention is also plausible. Although, so far, evidence of potential cognitive benefits of weight loss seem to be strongly associated with increased physical activity,[17,18] in 2011 a systematic review on overweight obese people concluded that intentional weight loss can improve performance in some cognitive domains, at least in obese people.[19]

This review of systematic reviews was carried out to search, identify, and synthesise the evidence currently available on the efficacy of lifestyle/behavioural and/or pharmacological interventions aimed at weight loss in people overweight or obese in reducing the risk of dementia and/or cognitive impairment.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment who are overweight or obese, are interventions for weight reduction (or control of obesity) more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

- ✓ P: Adults with normal cognition or mild cognitive impairment who are overweight or obese
- ✓ I: Weight management
  - Non-pharmacological interventions: e.g. cognitive-behavioural intervention strategies, lifestyle interventions;
  - Pharmacological interventions: e.g. weight-loss medication (e.g. orlistat)
- ✓ C: Care as usual or no intervention
- ✓ O: *Critical*
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Dementia

  Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Date of search: 25th of April 2018

Search starting time: 31st December 2012

Full search terms

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Overweight OR Body weight or Body mass index OR weight loss OR Body weight changes) AND (Behavior OR behaviour OR drug therapy OR pharmacologic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment OR Appetite depressants)

Simplified search terms

(dementia OR MCI OR cognition OR Quality Of Life OR ADL OR Adverse Effects OR Drop-out) AND overweight AND weight reduction

*Searches were conducted in the following databases**:

- Cochrane
- Pubmed
- NICE Guidelines
- Embase
- PsycInfo
- Global Health Library (Including WHOLIS, PAHO, AIM, LILACS)
- Database of impact evaluations
- AFROLIB
- ArabPsycNet
- HERDIN NeON
- HrCak
- IndMED
- KoreaMed

- AJOL

* Please note that the EurasiaHealth database did not return any meaningful answer to the search.

List of systemic reviews identified by the search process

Included in GRADE[1] tables:

Comparison: Behavioural and/or lifestyle intervention vs usual care or no intervention

Veronese N, Facchini S, Stubbs B, Luchini C, Solmi M, Manzato E, Sergi G, Maggi S, Cosco T, Fontana L. Weight Loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2017 Jan;72:87-94.

Comparison: Pharmacological intervention vs placebo or no intervention

No Reviews nor individual RCTs of pharmacological-based interventions, which also included outcomes related to dementia and/or cognitive decline, were identified.

[1] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Lifestyle intervention vs. usual care or no intervention	Incidence of dementia	No relevant systematic review available.	N/A
		MCI	No relevant systematic review available.	N/A
		Cognitive function	Veronese N, Facchini S, Stubbs B, Luchini C, Solmi M, Manzato E, Sergi G, Maggi S, Cosco T, Fontana L. Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2017 Jan;72:87-94.	Very Recent (2017), moderate quality systematic review assessing the effect of intentional weight loss on cognitive outcomes and meta-analysis on RCTs testing the effect of lifestyle intervention aimed at weight loss on 5 cognitive domains
		Quality of Life	No relevant systematic review available.	N/A
		Functional levels (ADL)	No relevant systematic review available.	N/A
		Adverse events	No relevant systematic review available.	N/A
		Dropout Rates	No relevant systematic review available.	N/A
2	Pharmacological intervention vs. placebo or no intervention	Incidence of dementia	No relevant systematic review available.	N/A
		MCI	No relevant systematic review available.	N/A
		Cognitive function	No relevant systematic review available.	N/A
		Quality of Life	No relevant systematic review available.	N/A
		Functional levels (ADL)	No relevant systematic review available.	N/A
		Adverse events	No relevant systematic review available.	N/A
		Dropout Rates	No relevant systematic review available.	N/A

Narrative descriptions of the studies that went into the analysis

GRADE table 1

Based on the hypothesis that weight loss could improve cognition in obese or overweight individuals, Veronese et al.[20] carried out a systematic review and meta-analysis aimed to investigate the effect of intentional weight loss on cognitive status in this population across observational and interventional studies. Extensive search and screening of the literature, which included several major healthcare databases, was conducted by two authors (Veronese N and Facchini S) independently from inception to 02.01.2016. The review included only studies that: included participants with a BMI of at least 25; reported only about intentional weight loss; assessed cognition through validated scales; reported at least 2 kg of weight loss (i.e. clinically significant weight loss[19]) in the treated group between follow-up and baseline; and included only a lifestyle/beahvioural intervention (pharmacological treatments were not included).

Data extraction was also carried out by two authors (SM and LC) independently and the results at follow-up evaluation of any cognitive tests assessed through validated scales were used as outcomes. Cognitive tests were categorised in five domains: attention; executive function; memory; motor speed; language domains.

After screening and assessment of the 1250 records obtained, seven randomised controlled trials (RCTs) were considered eligible and included in the meta-analysis.[21-27] The studies included a total of 328 participants randomised to treated groups (262 in a dietary intervention group, 26 treated with physical activity, and 40 with both intervention components). In particular, the RCTs had a variety of interventions: four were based on diet alone,[21,22,25,26] one on diet and physical activity,[24] one on caloric restriction and physical activity,[23] and one on caloric restriction or unsaturated fatty acid enhancement (in two different arms).[27] Participants were followed up for a median of 20 weeks (range: 8–48). Based on the neuropsychological tests administered in each trial, the meta-analysis for each of the cognitive domains was included a sub-group of the seven RCTs selected. In the review a formal and quantitative assessment of both heterogeneity (Q^2 and I^2 statistics) and publication bias (Egger's test) was conducted.

In the meta-analysis a significant improvement of the *attention* domain (four studies included)[21,22,24,25] was reported (SMD = 0.44; 95%CI: 0.26–0.62, p < 0.0001) and the Egger's test did not detect any publication bias. Heterogeneity, however, results high (I2= 60%). A significant improvement was also found in the *memory* domain (6 studies included[21-23,24-26]; SMD = 0.35; 95%CI: 0.12–0.57, p = 0.002). However heterogeneity was also high (I2= 64%) and significant publication bias detected (Egger's test = 3.72 ± 0.68; p = 0.004), likely due to the inclusion of studies reporting negative findings. After a trim and fill procedure, the SMD increased to 0.61 (95%CI: 0.37-0.86). *Language* was the last cognitive domain to provide significant results (SMD = 0.21; 95%CI:0.05–0.37, p = 0.009). However, the highest heterogeneity rate was detected among the four studies included[21,24-26] in this meta-analysis (I2= 73%) and publication bias was also detected, but in this case the trim and fill procedure did not change the results (SMD = 0.32; 95%CI:0.03–0.61). Two domains did not show any significant results: *executive function* and *motor speed* (SMD = -0.00; 95%CI: -0.30–0.37, p < 0.97; and SMD = 0.17; 95%CI: -0.14–0.48, p < 0.28, respectively). Both analysis were carried out on 2 studies (although the authors did not provide information on what specific studies were included) and although no high heterogeneity was identified (I^2=41% and 12%, respectively) quantitative analysis of publication bias was not possible.

Main limitations of the studies were related to publication bias and heterogeneity (moderate to high), as well as a small sample size for the assessment of two outcomes. Furthermore, the mean duration of the intervention was relatively short and no formal assessment of dropout rates and/or adverse events was identified. The authors also

reported that the effect of weight loss on cognition appeared to be not moderated by the baseline BMI, suggesting that a beneficial effect of weight loss in both overweight and obese people. Lack of studies and RCTs that the impact of weight loss on dementia and Alzheimer's disease outcomes was identified.

Additional Evidence

The evidence (low to moderate quality), obtained from the analysis of the systematic review, indicates a small, but nonetheless significant, beneficial effect of lifestyle interventions aimed at weight reduction, in both overweight and obese people, on cognition in the attention, memory, and language domains, in particular.

The evidence included in GRADE is partially confirmed by an older (2011) systematic review and meta-analysis, published by Siervo and colleagues,[28] aimed at assessing the effect of intentional weight loss reported on cognitive function in overweight and obese people. Twelve trials (seven randomised and five non-randomised) were included in this study. Key inclusion criteria were: 1. statistically significant and intentional weight loss greater than 2 kg (considered as clinically meaningful) and likely association with improvements in metabolic and vascular functions; and 2. reported assessment of cognitive function before and after weight loss through standardised and validated neuropsychological tests. A small size significant effect of weight loss was found for memory (SMD 0.13, 95% CI 0.00–0.26, P = 0.04) and attention/executive functioning (SMD 0.14, 95% CI 0.01–0.27, P < 0.001). However, the association between weight loss and cognitive improvements was identified only in obese but not in overweight individuals. The quality of the evidence was mostly limited by heterogeneity and publication bias both formally assessed with standardised tests.

In addition to this, a body of observational evidence generally supports a role for overweight and obesity in increasing the risk of cognitive impairment, and highlight age-based difference on such effect.

In 2014, Prickett et al. examined the relationship between obesity and cognitive function in a systematic review of cross-sectional and/ or prospective studies.[29] The review included studies on adults between 18 and 65 years of age, with a BMI of at least 30, with concurrent assessment of cognitive function. Evidence from the 17 studies that were identified and included showed a significant association between obesity and cognitive impairment across almost all the cognitive domains investigated (complex attention, verbal and visual memory, decision making). However the quality of the evidence was hampered by methodological limitations identified in the studies considered (e.g. matching or handling of confounders, variability in the study design, use of appropriate comparison groups, incomplete investigation of the cognitive domains) as well as publication bias due to challenges in publishing non-significant results.

On the following year, Xu and colleagues published a Meta-analysis on risk and protective factors for Alzheimer's disease (AD).[30] PubMed and the Cochrane database of systematic reviews were systematically searched from inception to July 2014 for cohort studies and retrospective case–control studies reporting on risk factors for AD and dementia. Studies were included if: they reported original data concerning odds ratio (OR) or risk ratio (RR) of AD using a longitudinal cohort study or retrospective case–control study design; the study population was representative of the general population and; modifiable risk factors were included. A total of 323 papers were included in the meta-analysis. Concerning BMI, Grade I evidence indicated that its influences the risk of AD are complex and depend on age: high BMI in mid-life would increase the risk of the disease while high BMI in late life would be protective.

Pedditizzi et al. (2016) conducted a systematic review of epidemiological longitudinal studies, published from inception since September 2014[31] that reported on incidence of AD/dementia and cognitive function, as well as data related to overweight and obesity. The search was conducted on a range of relevant databases and studies had at least 2 years follow up and included an assessment of incident dementia and 21 studies met the selection criteria. The meta-analysis, which included 13 studies, showed

that obesity below the age of 65 was associated with a higher risk of dementia (RR 1.41, 95% CI 1.20–1.66), but the opposite was seen in those aged 65 and over (RR 0.83, CI: 0.74–0.94).

In the same year, Lafortune et al carried out a rapid systematic review on the midlife risk factors associated with dementia.[32] Longitudinal cohort studies were searched in several relevant databases starting from 2000 and 164 were included in the qualitative synthesis. Weight change/weight cycling was one of the risk factors considered, but the authors identified only limited evidence suggesting that weight changes (in both directions) in midlife is associated with an increase of dementia.

Finally, in 2017 Hersi et al. published a systematic review and qualitative synthesis of risk factors associated with progression to AD.[33] The authors searched for both primary observational studies and systematic reviews. Eleven systematic reviews and six primary studies that reported on the association between obesity and body mass index (BMI) with risk of AD, were identified. Overall the evidence from the synthesis of the included publications was inconclusive, although differences based on age were identified.

WHO guidelines for general population

The WHO guidance on overweight and obesity as per the "Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (2012)" (http://www.who.int/nmh/publications/phc2012/en/)

- Advise overweight patients to reduce weight by following a balanced diet.
- Advise patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise patients to reduce sedentary behaviour and practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).

GRADE Tables

GRADE table 1

Author(s): Mariagnese Barbera; Jenni Kulmala
Date:
Question: Behavioural and/or lifestyle interventions for weight reduction (or control of obesity) compared to usual care or no intervention for reducing risk of dementia and/or cognitive decline
Setting:
Bibliography: Veronese N, Facchini S, Stubbs B, Luchini C, Solmi M, Manzato E, Sergi G, Maggi S, Cosco T, Fontana L. Weight Loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2017 Jan;72:87-94.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognition Attention (follow up: mean 20 weeks; assessed with: a range of neurpsychological tests; Scale from: N/A to N/A)[1]												
4	randomised trials	not serious	serious [a]	not serious	not serious	none	222	104	-	SMD **0.44 SD higher** (0.26 higher to 0.62 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Cognition Executive Function (follow up: range 12 weeks to 48 weeks; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A)												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	99	56	-	SMD **0 SD** (0.38 lower to 0.37 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Cognition Memory (follow up: mean 14 weeks; assessed with: a range of neuropsychological tests; Scale from: N/A to N/A)[2]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)**	**usual care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
6	randomised trials	not serious	serious [c]	not serious	not serious	publication bias strongly suspected [d]	236	113	-	SMD **0.35 SD higher** (0.12 higher to 0.57 higher)	⨁⨁◯◯ LOW	CRITICAL
Cognition Motor Speed (follow up: N/A; assessed with: a range of neurpsychological tests; Scale from: N/A to N/A)[3]												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	117	50	-	SMD **0.17 SD higher** (0.14 lower to 0.48 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Cognition Language (follow up: mean 22 weeks; assessed with: a range of neuropsychological tests)[4]												
4	randomised trials	not serious	serious [e]	not serious	not serious	publication bias strongly suspected [f]	222	104	-	SMD **0.21 SD higher** (0.05 higher to 0.37 higher)	⨁⨁◯◯ LOW	CRITICAL

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

Explanations

a. Downgraded due to high heterogeneity (I2=60).

b. Downgraded due to small sample size.

c. Downgraded due to high heterogeneity (I2=64).

d. Downgraded due to publication bias identified through Egger's test likely due to the inclusion of studies reporting negative findings. A trim and fill procedure increased the SMD to 0.61 (95%CI: 0.37-0.86) with 3 studies trimmed.

e. Downgraded due to high heterogeneity (I2=75).

f. Downgraded due to publication bias identified through Egger's test. In this case, the trim and fill procedure did not change the results (SMD = 0.32; 95%CI:0.03–0.61).

Definition of interventions

1. Four studies included: three = diet-based interventions; one = diet + physical activity intervention
2. Two studies included both with diet-based interventions
3. Six studies included: four = diet-based interventions; one = caloric restriction + physical activity intervention; one = caloric restriction OR unsaturated fatty acid intervention
4. Two studies included: one = diet based intervention; one = diet + physical activity intervention
5. Four studies included: three = diet-based interventions; one = diet + physical activity intervention

Part 2: From evidence to recommendations

Summary of Findings

Behavioural and/or lifestyle interventions for weight reduction (or control of obesity) compared to usual care or no intervention for reducing risk of dementia and/or cognitive decline

Patient or population: reducing risk of dementia and/or cognitive decline
Setting:
Intervention: Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)
Comparison: usual care or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	Risk with Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)				
Cognition Attention (Attention) assessed with: a range of neuropsychological tests Scale from: N/A to N/A follow up: mean 20 weeks	-	SMD **0.44 SD higher** (0.26 higher to 0.62 higher)	-	326 (4 RCTs) [1]	⨁⨁⨁◯ MODERATE [a]	Weight reduction (or control of obesity) seems to improve attention.
Cognition Executive Function (Executive Function) assessed with: a range of neuropsychological tests Scale from: N/A to N/A follow up: range 12 weeks to 48 weeks	-	SMD **0 SD** (0.38 lower to 0.37 higher)	-	155 (2 RCTs) [2]	⨁⨁⨁◯ MODERATE [b]	Weight reduction (or control of obesity) does not seem to improve executive function.

Behavioural and/or lifestyle interventions for weight reduction (or control of obesity) compared to usual care or no intervention for reducing risk of dementia and/or cognitive decline

Patient or population: reducing risk of dementia and/or cognitive decline
Setting:
Intervention: Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)
Comparison: usual care or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	Risk with Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)				
Cognition Memory (Memory) assessed with: a range of neuropsychological tests Scale from: N/A to N/A follow up: mean 14 weeks	-	SMD **0.35 SD higher** (0.12 higher to 0.57 higher)	-	349 (6 RCTs) [3]	⨁⨁◯◯ LOW [c,d]	Weight reduction (or control of obesity) seems to improve memory.
Cognition Motor Speed (Motor Speed) assessed with: a range of neuropsychological tests Scale from: N/A to N/A follow up: N/A	-	SMD **0.17 SD higher** (0.14 lower to 0.48 higher)	-	167 (2 RCTs) [4]	⨁⨁⨁◯ MODERATE [b]	Weight reduction (or control of obesity) does not seem to improve motor speed.
Cognition Language (Language) assessed with: a range of neuropsychological tests follow up: mean 22 weeks	-	SMD **0.21 SD higher** (0.05 higher to 0.37 higher)	-	326 (4 RCTs) [5]	⨁⨁◯◯ LOW [e,f]	Weight reduction (or control of obesity) seems to improve language.

Behavioural and/or lifestyle interventions for weight reduction (or control of obesity) compared to usual care or no intervention for reducing risk of dementia and/or cognitive decline

Patient or population: reducing risk of dementia and/or cognitive decline
Setting:
Intervention: Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)
Comparison: usual care or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care or no intervention	Risk with Behavioural and/or lifestyle interventions for weight reduction (or control of obesity)				

*__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). **Higher SMD = better cognitive performance**.
CI: Confidence interval; **SMD:** Standardised mean difference

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

Explanations
a. Downgraded due to high heterogeneity (I2=60).
b. Downgraded due to small sample size.
c. Downgraded due to high heterogeneity (I2=64).
d. Downgraded due to publication bias identified through Egger's test likely due to the inclusion of studies reporting negative findings. A trim and fill procedure increased the SMD to 0.61 (95%CI: 0.37-0.86) with 3 studies trimmed.
e. Downgraded due to high heterogeneity (I2=75).
f. Downgraded due to publication bias identified through Egger's test. In this case, the trim and fill procedure did not change the results (SMD = 0.32; 95%CI:0.03–0.61).
Definition of interventions
1. Four studies included: three = diet-based interventions; one = diet + physical activity intervention

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5. Four studies included: three = diet-based interventions; one = diet + physical activity intervention

Evidence to Decision Table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ●Yes ○ Varies ○ Don't know	Worldwide ageing of populations is strongly associated with dementia, causing major health, economic and social burdens. In 2015, it has been estimated that there were 50 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 82 million in 2030 and 152 million in 2050.[1] Since no cure is available for Alzheimer's disease, the main cause of dementia, prevention could be crucial in halting the rapid increase in the prevalence of this condition and international experts have called upon world-wide governments to make prevention of dementia one of their key health priorities.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There is low to moderate evidence that lifestyle interventions aimed at weight reduction in both overweight and obese people could improve cognitive function in the attention, memory and language domains. No evidence was found related to the dementia and MCI outcomes nor to pharmacologic interventions. Interventions that are based on both diet and physical activity strategy showed better results.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ●Trivial ○ Varies ○ Don't know	Concerning lifestyle intervention no evidence of adverse events was identified. Very rare adverse events have been reported for pharmacological treatment with Orlistat mostly to the liver and kidney.[34]	

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The quality of the evidence ranges from low to moderate. Studies of various level of quality were included although no serious risk of bias was identified. However, publication bias was suspected for two of the outcomes that showed improvement upon intervention, mean duration of the intervention was relatively short, and heterogeneity among the studies was moderate/high.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cognitive impairment and dementia can have a major impact in the life not only of the person affected but also of the close network of family and friends, as well as caregivers and health professional in general.[35,36] Functional ability and dependency are playing are the major component of this effect. Furthermore, dementia, the main cause of disability and institutionalization among older adults[1], therefore reducing or delaying the onset of dementia could results in lower costs for public healthcare services. Patients, caregivers, and policy makers are likely to be the people who will value the most these recommendation.	
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No evidence was identified related to adverse events of the intervention. However the evidence include RCTs where intentional weigh loss programmes were conducted under professional supervision. Therefore, it is plausible to suppose that undesirable effect would be negligible and in any case out-weighted by the benefits. Rare but serious adverse events have been reported for treatment with orlistat, therefore the balance probably favours the comparison specifically for lifestyle interventions.	
Resources required How large are the resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ●Varies ○ Don't know	Resources will depend of the type of intervention (diet, physical exercise, pharmacological, multicomponent) and by the degree of supervision and support that should be provided by the healthcare professionals. A meta- and cost- effective analysis of commercial weight loss strategies estimated that the average cost per kilogram of weight lost ranged from $155 (95% CI: $110-$218) for lifestyle counselling-supported intervention to $546 (95% CI: $390-$736) for Orlistat.[37]	For more information: 'Best buys' and other recommended interventions to address noncommunicable diseases (NCDs) http://apps.who.int/iris/bitstream/handle/10665/259232/WHO-NMH-NVI-17.9-eng.pdf?sequence=1
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Interventions for weight-loss can be extremely variable, include several component such as: diet, physical activity, counselling and the costs will vary depending on the actual design.	
Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ●No included studies	Obesity has been steadily raising in the last few decades and in particular among older adults[12]. Although the evidence is not of high quality, if such intervention on a large scale had similar effects to that shown by the evidence it is plausible to suppose that dementia could be prevented or at least postponed in a certain percentage of the population. Furthermore weight loss could reduce indirectly the risk of dementia by improving a variety of metabolic factors linked with the pathogenesis of cognitive impairment and dementia (i.e. glucose tolerance, insulin sensitivity, blood pressure, oxidative stress, and inflammation).[16] In general interventions for weight reduction are resource-intensive as they do in most cases require professional guidance and supervision. Group-based guidance and e-interventions are probably a way to reduce costs. REF maybe we can use this: A study by Leahey et al. 2016[38] showed that internet delivered approach to weight loss maintenance seems to be effective for long-term weight control. Using peer coaches to provide reinforcement may be a particularly economic alternative to professionals.	

	The general extent of indirect costs of overweight and obesity is substantial due to lost productivity among workers with obesity (Goettler et al 2017).[39] Finkelstein et al. (2014)[32] conducted a systematic review of RCTs estimating the incremental cost-effectiveness of clinically proven nonsurgical commercial weight loss strategies for those with BMIs between 25 and 40.Lifestyle programs (Weight Watchers and Vtrim), one meal replacement program (Jenny Craig), and three pharmaceutical products (Qsymia, Lorcaserin, and Orlistat) were included in the analysis. Average cost per kilogram of weight lost ranged from $155 (95% CI: $110-$218) for Weight Watchers to $546 (95% CI: $390-$736) for Orlistat. The incremental cost per QALY gained for Weight Watchers and Qsymia was $34,630 and $54,130, respectively. All other commercial interventions were prohibitively expensive or inferior in that weight loss could be achieved at a lower cost through one or a combination of the other strategies. Group-based guidance and e-interventions are probably a way to reduce costs.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Lower socioeconomic groups are more likely to have earlier onset of dementia than higher socioeconomic groups. Older people from lower socioeconomic backgrounds are also more likely to experience cognitive dysfunction at earlier stages of cognitive decline and cognitive impairment, and will have fewer resources to cope with the symptoms than their counterparts from higher socioeconomic groups People from lower socioeconomic groups are more likely to live, work and age in physical and economic environments that do not support social connectedness, physical activity or mental stimulation. this can increase the risk of cognitive impairment and dementia in later life.[40] Based on this it is believed that interventions to reduce risk of cognitive decline and dementia will increase equity in health. Furthermore, women are disproportionally affected with AD. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men.[41]	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Moderate quality evidence suggest that weight-loss through lifestyle interventions improve cognitive performance at least in some domains. A survey on 300 participants showed that behavioural program are rated the more acceptable than pharmacological. [42]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The interventions presented in the reported evidence are relatively short and mainly based on supporting lifestyle and behavioural (diet and physical activity) changes. Apart from the involvement of the stakeholders requires the support and supervision of healthcare professionals. The main barriers are costs, lack of motivation, lack of time, and physical limitations.	

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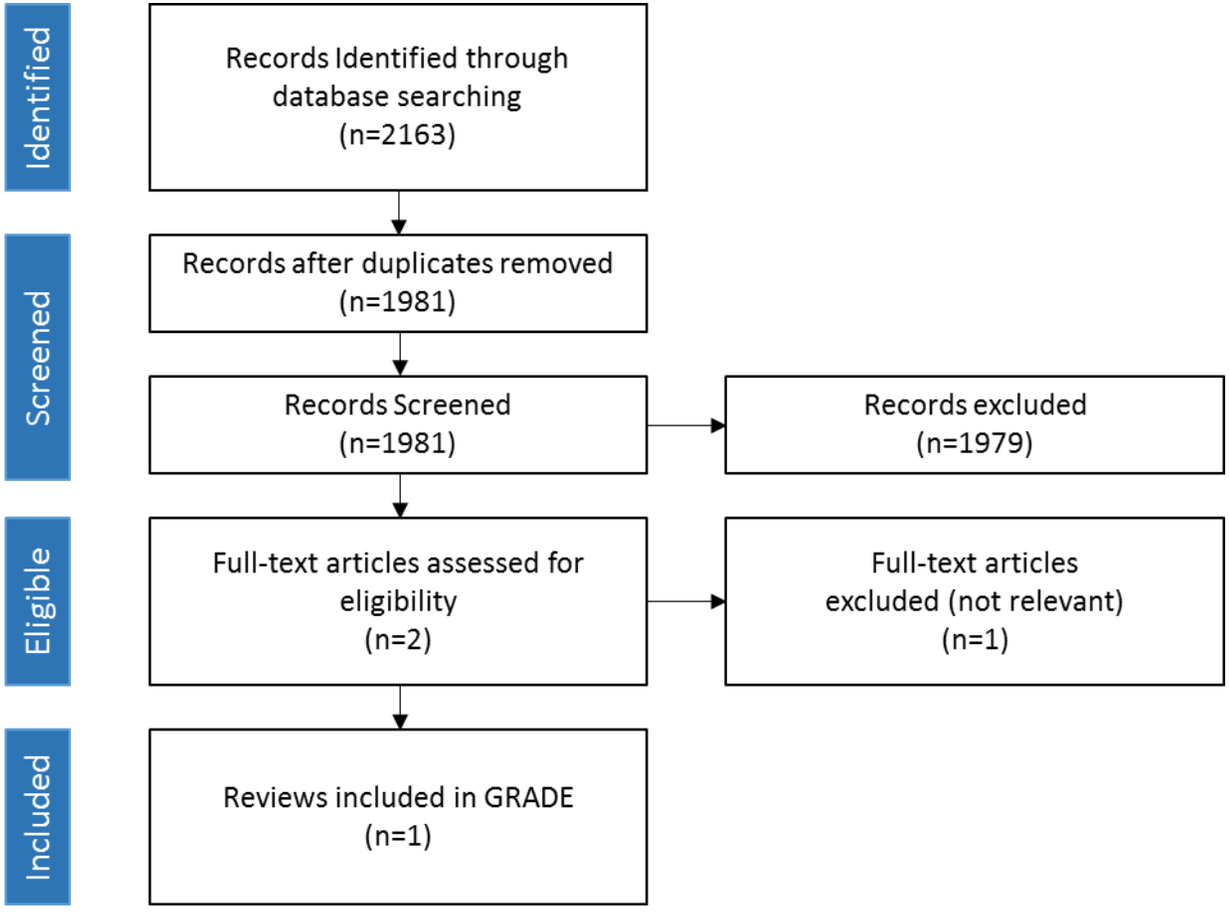
Annex: PRISMA[2] flow diagram for systematic review of the reviews – cognitive decline interventions[2]



[2] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For more information: http://www.prisma-statement.org

Guidelines for risk reduction of cognitive decline and dementia

Evidence profile:
treatment of hypertension for reducing risk of cognitive decline and/or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment and hypertension, is treatment of hypertension more effective than placebo/no intervention in reducing the risk of cognitive decline/dementia?

Background

Hypertension (also known as high or raised blood pressure) is an extremely common condition that is associated with an increased risk of heart attacks, heart failure, stroke and kidney failure. It occurs in approximately 40% of the adult population and its prevalence is known to increase with age[1].

Hypertension in midlife has been found to be associated with an increased risk of late-life dementia [2]. Specifically, hypertension has been shown to be related to decreases in integrity of the blood-brain barrier which can lead to protein extravasation and subsequent neural cell damage [3], increased risk of clinical and sub-clinical ischaemic events in the grey and white matter and may possibly increase risk of amyloid deposition [4]. In particular a pattern of increased blood pressure during mid-life followed by a rapid decrease in blood pressure later in life has been found in individuals who go on to develop dementia [2, 5, 6].

There is mixed evidence relating to the reduction of blood pressure in late midlife or late-life and subsequent cognitive decline or dementia, however, there is evidence to show that the reduction of hypertension can have substantial benefits in reducing cardiovascular morbidity and mortality and thus the improving overall health of the aging population [7].

Hypertension can be prevented through a range of lifestyle factors including eating a healthy diet, maintaining a healthy weight and participating in an adequate amount of physical activity. It can also be controlled through antihypertensive medication. However, the evidence for the effectiveness of blood-pressure lowering treatments in reducing dementia risk is mixed.

This review was conducted in order to synthesize the evidence on interventions for hypertension and their impact on reducing cognitive decline and dementia.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment and hypertension, is treatment of hypertension more effective than placebo/no intervention in reducing the risk of cognitive decline/dementia?

Populations

- Adults with normal cognition or mild cognitive impairment with hypertension

Interventions

- Antihypertensive medication
- Lifestyle interventions

Comparison

- Placebo/no intervention

Outcomes

- Critical:
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Incident Dementia
- Important:
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Searches using the following strategies (or similar) were conducted as follows

- (systemati* or meta-analys*) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheimer's or Alzheimer) and (behaviour or behavior or "drug therapy" or "pharmacologic therapy" or pharmacotherapy or "cognitive behavioural therapy" or "cognitive behavioral therapy" or "cognitive therapy" or "online therapy" or "anti-hypertensive" or antihypertensive or treatment) and (hypertension or "blood pressure" or systolic or diastolic or prehypertension)[1]

Searches were conducted in:

- Medline
- Cochrane
- PsycInfo
- Embase
- NICE
- Global index medicus/Global Health Library
    - WHO regional data base
    - WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth

[1] Dates searched were 1 May 2016 - 1 May 2018. Additionally, the 2016 AHRQ review(8) was consulted for relevant records which systematically searched the literature between Jan 2009 – Sept 2016. In combination, the search period spanned >9 years. All abstracts were screened by two independent reviewers and with any discrepancies resolved by discussion. Full text articles were read by the same two independent reviewers and any discrepancy resolved by discussion.

List of systematic reviews identified by the search process

Included in GRADE[2] tables

- Parsons, C., Murad, M. H., Andersen, S., Mookadam, F., & Labonte, H. (2016). The effect of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly: A meta-analysis. *Future Cardiology, 12*(2), 237-24
- Weiss, J., Kerfoot, A., Freeman, M., Motu'apuaka, M., Fu, R., Low, A., ... & Kansagara, D. (2016). Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis.

[2] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO table

	Intervention/ Comparison	Outcomes	Systematic reviews	Explanations
1	Treatment of hypertension vs placebo or no intervention	Cognitive function	Parsons, C., Murad, M. H., Andersen, S., Mookadam, F., & Labonte, H. (2016). The effect of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly: A meta-analysis. *Future Cardiology, 12*(2), 237-248.	Systematic review examining the impact of antihypertensive treatment on cognition. Includes meta-analysis of RCTs. AMSTAR 2[3] rating is Low.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident Dementia	Parsons, C., Murad, M. H., Andersen, S., Mookadam, F., & Labonte, H. (2016). The effect of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly: A meta-analysis. *Future Cardiology, 12*(2), 237-248.	Systematic review examining the impact of antihypertensive treatment on incident dementia. Includes meta-analysis of RCTs. AMSTAR 2[3] rating is Low.
		Quality of life	Weiss, J., Kerfoot, A., Freeman, M., Motu'apuaka, M., Fu, R., Low, A., ... & Kansagara, D. (2016). Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis.	Systematic review examining the impact of intensive blood pressure treatment on quality of life. No meta-analysis was conducted for this outcome but RCTs were included in the review. AMSTAR 2[3] rating is Low.
		Functional level (ADL, IADL)	Weiss, J., Kerfoot, A., Freeman, M., Motu'apuaka, M., Fu, R., Low, A., ... & Kansagara, D. (2016). Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis.	Systematic review examining the impact of intensive blood pressure treatment on functional level. No meta-analysis was conducted for this outcome but RCTs were included in the review. AMSTAR 2[3] rating is Low.

[3] AMSTAR: A Measurement Tool to Assess Systematic Reviews. More information: https://amstar.ca/index.php

		Adverse events	Weiss, J., Kerfoot, A., Freeman, M., Motu'apuaka, M., Fu, R., Low, A., ... & Kansagara, D. (2016). Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis.	Systematic review examining the impact of intensive blood pressure treatment and adverse events. No meta-analysis was conducted for this outcome but RCTs were included in the review. AMSTAR 2[3] rating is Low.
		Drop-out rates	No reviews identified.	No reviews identified.
2	Lifestyle interventions to treat hypertension vs placebo or no intervention	Cognitive function	No reviews identified.	No reviews identified.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident Dementia	No reviews identified.	No reviews identified.
		Quality of life	No reviews identified.	No reviews identified.
		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events	No reviews identified.	No reviews identified.
		Drop-out rates	No reviews identified.	No reviews identified.

Narrative descriptions of the studies that went into the analysis

GRADE table 1: Antihypertensive medication to treat hypertension compared with placebo/no intervention for reducing the risk of cognitive decline or dementia

Parsons et al [9] carried out a systematic review of randomised trials of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly. They reviewed the literature from 1990 to 2014. They performed two meta-analyses. The first one examined the outcome of cognitive decline and included three trials N = 13,900). The review reported a combined risk ratio of 0.96 (95% CI 0.87 to 1.06) towards antihypertensive use. The second meta-analysis examined the incidence of dementia and included four trials (N = 15,427). The review reported a combined risk ratio of 0.90 (95% CI 0.76 to 1.07) towards antihypertensives. The AMSTAR 2 rating for this review was low. The review had limitations in its search and data extraction methodologies.

Weiss et al [10] carried out a systematic review to examine the benefits and harms of intensive blood pressure treatment in adults aged 60 and over. The reported moderate strength evidence from sub-studies of four trials of antihypertensives (two trials were comparing treatment to placebo). The review concluded that antihypertensive therapy (to achieve moderate blood pressure control) was not associated with a deterioration in quality of life compared to less intensive controls. They also reported low strength evidence from one trial that moderate blood pressure control was not associated with deterioration in functional status compared with less intensive controls. They reported mixed results with regards to adverse events. The AMSTAR 2 rating for this review was low. The review had limitations in its search and data extraction methodologies.

GRADE table 2: Lifestyle interventions to treat hypertension versus placebo or no intervention for reducing the risk of cognitive decline or dementia

No reviews identified.

GRADE table 1: Antihypertensive medication to treat hypertension versus placebo or no intervention for reducing the risk of cognitive decline or dementia

Author(s): Nicole Ee, Ruth Peters, Lidan Zheng
Date: June 2018
Question: Antihypertensive medication compared to no treatment or placebo for reducing the risk of cognitive decline or dementia in adults with normal cognition or mild cognitive impairment and hypertension
Setting: Community
Bibliography: Parsons, C., Murad, M. H., Andersen, S., Mookadam, F., Labonte, H.. The effect of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly: A meta-analysis. Future Cardiology; March 2016.
Weiss, J., Kerfoot, A., Freeman, M., Motu'apuaka, M., Fu, R., Low, A., ... & Kansagara, D. (2016). Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antihypertensive medication**	**no treatment or placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognitive function (assessed with: MMSE, short-CARE (higher score indicates better cognition))												
3	randomised trials [1]	serious [a]	not serious [b]	not serious [c]	not serious [d]	publication bias strongly suspected [e]	[f]	[f]	**RR 0.96** (0.87 to 1.06)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
Incident MCI - not measured												
-	-	-	-	-	-	-	No data available				-	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antihypertensive medication**	**no treatment or placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Incident Dementia												
4	randomised trials [1]	serious [a]	not serious [b]	not serious [c]	not serious [d]	publication bias strongly suspected [e]	[f]	[f]	**RR 0.90** (0.76 to 1.07)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (assessed with: Varied including various QoL questionnaries, PGWB, SIP, SSA-P EuroQOL)												
4	randomised trials [2]	serious [g]	not serious [b]	serious [h]	not serious [i]	publication bias strongly suspected [e]	Review states "we found moderate strength evidence from prospective substudies of 4 large low risk of bias trials that use of antihypertensive therapy to achieve moderate BP control (SBP 140-150 mmHg) (two were comparing treatment to placebo) was not associated with deterioration in quality of life compared to less intensive blood pressure control did not affect QOL". [2]				⨁◯◯◯ VERY LOW	IMPORTANT
Functional level (follow up: mean 5 years; assessed with: ADLs)												
1	randomised trials [2]	very serious [j]	not serious [k]	serious [l]	not serious [m]	publication bias strongly suspected [e]	Review states "we found low strength evidence from one large low risk of bias trial that moderate blood pressure control was not associated with deterioration in functional status compared to less intensive control" [2]				⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events - not measured												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**antihypertensive medication**	**no treatment or placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
19	randomised trials [2]	not serious [n]	serious [o]	serious [p]	not serious [q]	publication bias strongly suspected [e]	Review states: "Two trials found a trend towards increased adverse events in the intervention group, while 4 trials found the intervention group had the same or lower risk of adverse events. One trial found a nearly two-fold increase risk of serious adverse events possibly or definitely related to the intervention. The specific types of adverse events reported varied among trials, though cough or hypotension were among the more frequently reported events. There was higher rate of syncope among those assigned to more aggressive treatment in 2 trials, but not in a third" [2]				⨁◯◯◯ VERY LOW	IMPORTANT
Drop-out rates - not measured												
-	-	-	-	-	-	-	No data available [r]				-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Risk of bias: Downgraded once as two studies had unclear methodology regarding random allocation; review lacks formal assessment of risk of bias.

b. Inconsistency: CIs similar, overlapping and effects non-significant across primary studies. No data on I^2.

c. Indirectness: all trials were placebo controlled, with two on diuretics and one on ARBs. Comparisons, populations, outcomes and interventions were relevant.

d. Imprecision: CIs similar across trials, all non-significant, reasonable sample size (n>1200).

e. Publication bias: Downgraded once as only published records in English were included; no formal assessment of publication bias was carried out.

f. No details on meta-analysis calculation given

g. Risk of bias: Downgraded once as the sub-populations used to assess quality of life outcomes were not assessed risk of bias; study limitations with respect to this sample were unclear.

h. Indirectness: Downgraded once as of the four trials, two were placebo controlled, one allowed active treatment in the placebo arm part way through the trial and one was comparing levels of achieved blood pressure.

i. Imprecision: Downgraded once because quality of life comparison ranged significant to non-significant from (reported p-values: <.00 to .76=0); uncertainty present. CIs, not reported for all studies. Sample size reasonable (n>2000)

j. Risk of bias: Downgraded once as only 1 RCT available for this outcome, results are limited in generalisability and need replication.

k. Inconsistency: Not applicable; only one primary study.

l. Indirectness: Only one study for which population, intervention, outcomes and comparisons were relevant.

m. Imprecision: One large study (N = 4756), no CI's given.

n. Risk of bias: The majority of studies (18 out of 19), had a low risk of bias. One study had a high risk of bias.

o. Inconsistency: Downgraded once as 2 trials found a trend towards increased adverse events, while 4 trials found the same or lower risk of adverse events in the intervention group. No meta-analysis conducted. No numerical data on CIs or I2 or effect sizes across primary studies.

p. Indirectness: Downgraded once as only 10 out of the 19 trials compared antihypertensive intervention to placebo (the other 8 trials compared levels of achieved blood pressure and 1 was a drug-drug comparison).

q. Imprecision: sample size large (n> 98,964), no CI's provided, event rate varied across trials.

r. Only withdrawal rates due to adverse events were reported. No meta-analysis was conducted as report states “heterogeneity of treatment effects was excessive”.

References

1. Parsons, C., Murad, M. H., Andersen, S., Mookadam, F., Labonte, H.. The effect of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly: A meta-analysis. Future Cardiology; March 2016.

2. Weiss, J., Kerfoot, A., Freeman, M., Motu'apuaka, M., Fu, R., Low, A., ... & Kansagara, D. (2016). Benefits and Harms of Treating Blood Pressure in Older Adults: A Systematic Review and Meta-analysis.

GRADE table 2: Lifestyle interventions to treat hypertension versus placebo or no intervention for reducing the risk of cognitive decline or dementia

Author(s): Ruth Peters, Nicole Ee, Lidan Zheng
Date: May 2018
Question: Lifestyle interventions to treat hypertension compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension
Setting: Community
Bibliography: -

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cognitive function - not reported									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident MCI - not reported									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident Dementia – not reported									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Quality of life - not reported									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Functional status (ADL IADL) - not reported									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Adverse events - not reported									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Drop-out rates - not reported									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT

CI: Confidence interval

Additional evidence not mentioned in GRADE tables

Diuretic versus placebo or other antihypertensives

Tully et al [11] carried out a systematic review and meta-analysis to look at the impact of diuretic use on incident dementia. They examined adults without dementia (at baseline) and included RCTs and observational studies where diuretic use was compared to no treatment, placebo or other antihypertensives. They included a total of 13 cohorts (of which four were placebo controlled trials of antihypertensives). For two of the cohorts, they reported contacting the authors for unpublished data relating to the dementia outcomes. In total there were 52,559 participants and 3444 incident dementia cases. The median duration of follow up was 6.1 years (standard deviation 2.2). The results of the meta-analysis for incident dementia (which combined adjusted published and unpublished data) showed a combined hazard ratio of 0.83 (95% CI 0.76 to 0.91) in favour of diuretic treatment. When stratified by length of follow-up, the combined HRs were 0.74 (95% CI 0.75to 0.94) for those with <5 year follow up and HR0.81 (95% CI 0.71 to 0.92) for those with >5 year follow up. They do not report separate results by baseline cognitive function (MCI or normal cognition) or by baseline presence of hypertension.

Calcium channel blockers versus placebo or other antihypertensives

Hussain et al [12] carried out a systematic review and meta-analysis to look at the impact of calcium channel blocker use on incident dementia. They examined adults aged over 60 years with hypertension and without dementia at baseline. The review included RCTs and observational studies and where calcium channel blocker use was compared to no treatment, placebo or other antihypertensives. They identified 5 articles when searching medical databases and sourced another five from an earlier review of calcium channel blocker use and incident dementia[12]. They included 10 cohorts with a total of 75,239 participants and a median follow up of 8.2 years (standard deviation not provided). They carried out a meta-analysis including all 10 cohorts and reported a combined risk ratio of 0.70 (95% CI 0.58 to 0.85) for incident dementia in favour of calcium channel blocker use. They do not report separate results by baseline cognitive function (MCI or normal cognition) or by baseline presence of hypertension.

Varied antihypertensive classes versus placebo or other antihypertensive treatment

Kane et al [8] carried out a peer reviewed systematic review of interventions to prevent age-related cognitive decline, mild cognitive impairment and clinical Alzheimer's type dementia. The review was prepared for the United States Agency for Healthcare Research and Quality (AHRQ). The authors reviewed the literature from Jan 09 to Sept 2016 and for evidence published prior to Jan 2009 they drew on a prior version of the review also prepared for the AHRQ. The review was rigorous. It rates as a moderate quality review when rated using the AMSTAR 2 quality rating only losing points for a lack of information related to excluded articles and a lack of detail as to the funding sources for each included study. The review focused on populations who were cognitively normal or may have age-related changes or MCI but do not yet have dementia. The review did not include dementia due to specific, identifiable conditions such as Lewy body, infectious diseases, frontotemporal,

and traumatic brain injury. The review included studies addressing vascular components of mixed dementia, but clear post-stroke dementia was out of scope.

For hypertension and use of antihypertensives the review reported low strength evidence that 3 to 4.7 years of antihypertensive treatment versus placebo appears to have no benefit on cognitive test performance in adults with normal cognition. They also reported that the results for dementia were inconsistent. There was insufficient evidence to draw conclusions (only one study) in adults with MCI. The review reports no statistically significant difference in brief cognitive test performance with beta blocker versus placebo (n=3228, up to 3.9 years follow up), or ARB vs placebo (n=10,863, up to 56 months), or ACE and thiazide combination vs placebo (n=14,985 up to 4.3 years).

For combination therapy (type not specified) vs placebo the review reports statistically significant difference in dementia diagnoses favouring combination therapy versus placebo (n=3228, up to 3.9 years follow up). No meta-analysis data provided. For ACE and Thiazide combination vs placebo the review states no statistically significant difference in dementia diagnoses for treatment vs placebo (n=14,985, up to 4.3 years). For ARB vs placebo the review states no statistically significant difference in dementia diagnoses for ARB vs placebo (n=4937, 44 months).

Stuhec et al [13] carried out a systematic review of RCTs examining a population aged (on average) 65 years or older, without dementia and who were taking antihypertensive medication. They included 15 RCTs that compared antihypertensive drugs to other antihypertensive drug regimens or placebo. 8 were double blind, one was single blind and one was a crossover trial. Outcomes included cognitive testing on a variety of cognitive tools. There were no numerical results provided for each constituent study and no meta-analysis was performed. The authors did not report separate results by baseline cognitive function (MCI or normal cognition) or by baseline presence of hypertension. The review reports that Angiotensin II receptor blockers improved cognitive functioning in the elderly, especially with regards to episodic memory, however the other antihypertensive drugs did not improve cognition.

Fink et al [14] carried out a systematic review which examined randomised and non-randomised controlled trials in those without dementia. They reviewed the literature from 2009 to 2017 and included earlier studies from a 2010 Agency for Healthcare Research and Quality (AHRQ) report on interventions for preventing Alzheimer Disease and cognitive decline. They identified 51 trials that studied dementia medications, antihypertensives, diabetes medications, nonsteroidal anti-inflammatory drugs [NSAIDs] or aspirin, hormones, and lipid-lowering agents. The primary outcomes included cognitive diagnoses of Mild Cognitive Impairment (MCI) or dementia (Alzheimer disease or unspecified type, but excluding other specific causes, such as dementia solely attributable to a clinically recognized stroke). The authors concluded that pharmacologic treatments neither improved nor slowed decline in cognitive test performance.

Hernandorena et al [15] carried out a systematic search and presented a narrative review discussing the observational studies and clinical trials that have reported on the use of antihypertensives and outcomes of cognitive function, hippocampal atrophy and dementia. They concluded that most observational studies have suggested a potential preventive effect of antihypertensive therapies, however RCTs and meta-analyses provide more conflicting results.

Any antihypertensive class vs no treatment/placebo

Peters et al[16] conducted a meta-analysis of prospective longitudinal studies and trials of antihypertensives and reported that, in RCTs with a ≥5 year follow up, antihypertensive treatment overall was associated with a 35% reduced risk of dementia in individuals aged >65 years (OR =0.65; 95% CI 0.51 to 0.83). However, no significant associations were found between antihypertensive use and incident dementia or cognitive decline in cohort studies or RCTs with a ≥1 year follow up.

Antihypertensive control vs placebo (less/more intensive control)

In the systematic review conducted by Weiss et al [10], they also examined cognitive function and reported moderate strength evidence that the use of antihypertensive treatment to achieve moderately strict blood pressure control for up to five years does not worsen cognitive outcomes compared to less strict blood pressure control.

Intensive vs standard blood pressure control

Preliminary results from the Sprint Mind Trial[17] reported that there was a significantly lower rate of incident MCI (HR=0.81, 95% CI 0.70 to 0.95) and a nonsignificant reduction in probable dementia (HR=0.83; 95% CI 0.67 to 1.04) in the intensive treatment group (SBP target of <120 mmHg) versus the standard treatment group (SBP target of <140 mmHg).

Other relevant guidelines

The WHO guidelines Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010): http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset: https://www.nice.org.uk/guidance/ng16

Part 2: From evidence to recommendations

Summary of evidence table 1

Antihypertensive medication compared to no treatment or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension

Patient or population: Adults with normal cognition or mild cognitive impairment and hypertension

Setting: Community

Intervention: Antihypertensive medication

Comparison: No treatment or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment or placebo	Risk with antihypertensive medication				
Cognitive function assessed with: MMSE, short-CARE (higher score indicates better cognition)	0 per 1,000 [a]	**0 per 1,000** (0 to 0) [a]	**RR 0.96** (0.87 to 1.06)	(3 RCTs) [1]	⨁⨁◯◯ LOW [b,c,d,e,f]	
Incident MCI - not measured	No data available			-	-	
Incident Dementia	0 per 1,000 [a]	**0 per 1,000** (0 to 0) [a]	**RR 0.90** (0.76 to 1.07)	(4 RCTs) [1]	⨁⨁◯◯ LOW [b,c,d,e,f]	

Antihypertensive medication compared to no treatment or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension

Patient or population: Adults with normal cognition or mild cognitive impairment and hypertension

Setting: Community

Intervention: Antihypertensive medication

Comparison: No treatment or placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment or placebo	**Risk with antihypertensive medication**				
Quality of life assessed with: Varied including various QoL questionnaires, PGWB, SIP, SSA-P EuroQOL	Review states "we found moderate strength evidence from prospective substudies of 4 large low risk of bias trials that use of antihypertensive therapy to achieve moderate BP control (SBP 140-150 mmHg) (two were comparing treatment to placebo) was not associated with deterioration in quality of life compared to less intensive blood pressure control did not affect QOL". [2]			(4 RCTs) [2]	⨁◯◯◯ VERY LOW c,f,g,h,i	
Functional status assessed with: ADLs follow up: mean 5 years	Review states "we found low strength evidence from one large low risk of bias trial that moderate blood pressure control was not associated with deterioration in functional status compared to less intensive control" [2]			(1 RCT) [2]	⨁◯◯◯ VERY LOW f,j,k,l,m	

Antihypertensive medication compared to no treatment or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension

Patient or population: Adults with normal cognition or mild cognitive impairment and hypertension

Setting: Community

Intervention: Antihypertensive medication

Comparison: No treatment or placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment or placebo	**Risk with antihypertensive medication**				
Adverse events	Review states: "Two trials found a trend towards increased adverse events in the intervention group, while 4 trials found the intervention group had the same or lower risk of adverse events. One trial found a nearly two-fold increase risk of serious adverse events possibly or definitely related to the intervention. The specific types of adverse events reported varied among trials, though cough or hypotension were among the more frequently reported events. There was higher rate of syncope among those assigned to more aggressive treatment in 2 trials, but not in a third." [2]			(19 RCTs) [2]	⨁◯◯◯ VERY LOW [f,n,o,p,q]	
Drop-out rates - not measured	No data available			-	- [r]	

***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; **RR:** Risk ratio

Antihypertensive medication compared to no treatment or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension

Patient or population: Adults with normal cognition or mild cognitive impairment and hypertension

Setting: Community

Intervention: Antihypertensive medication

Comparison: No treatment or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment or placebo	Risk with antihypertensive medication				

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

Explanations

a. Risk of bias: Downgraded once as two studies had unclear methodology regarding random allocation; review lacks formal assessment of risk of bias.

b. Inconsistency: CIs similar, overlapping and effects non-significant across primary studies. No data on I^2.

c. Indirectness: all trials were placebo controlled, with two on diuretics and one on ARBs. Comparisons, populations, outcomes and interventions were relevant.

d. Imprecision: CIs similar across trials, all non-significant, reasonable sample size (n>1200).

e. Publication bias: Downgraded once as only published records in English were included; no formal assessment of publication bias was carried out.

f. No details on meta-analysis calculation given

g. Risk of bias: Downgraded once as the sub-populations used to assess quality of life outcomes were not assessed risk of bias; study limitations with respect to this sample were unclear.

h. Indirectness: Downgraded once as of the four trials, two were placebo controlled, one allowed active treatment in the placebo arm part way through the trial and one was comparing levels of achieved blood pressure.

i. Imprecision: Downgraded once because quality of life comparison ranged significant to non-significant from (reported p-values: <.00 to .76=0); uncertainty present. CIs, not reported for all studies. Sample size reasonable (n>2000)

j. Risk of bias: Downgraded once as only 1 RCT available for this outcome, results are limited in generalisability and need replication.

k. Inconsistency: Not applicable; only one primary study.

l. Indirectness: Only one study for which population, intervention, outcomes and comparisons were relevant.

m. Imprecision: One large study (N = 4756), no CI's given.

n. Risk of bias: The majority of studies (18 out of 19), had a low risk of bias. One study had a high risk of bias.

o. Inconsistency: Downgraded once as 2 trials found a trend towards increased adverse events, while 4 trials found the same or lower risk of adverse events in the intervention group. No meta-analysis conducted. No numerical data on CIs or I2 or effect sizes across primary studies.

p. Indirectness: Downgraded once as only 10 out of the 19 trials compared antihypertensive intervention to placebo (the other 8 trials compared levels of achieved blood pressure and 1 was a drug-drug comparison).

q. Imprecision: sample size large (n> 98,964), no CI's provided, event rate varied across trials.

r. Only withdrawal rates due to adverse events were reported. No meta-analysis was conducted as report states “heterogeneity of treatment effects was excessive”.

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Summary of evidence table 2

Lifestyle interventions to treat hypertension compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension

Patient or population: Adults with normal cognition or mild cognitive impairment and hypertension

Setting: Community

Intervention: Lifestyle interventions to treat hypertension

Comparison: Usual care or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Cognitive function - not reported	No data available.	-	-
Incident MCI - not reported	No data available.	-	-
Incident dementia - not reported	No data available.	-	-
Quality of life - not reported	No data available.	-	-
Functional status (ADL IADL) - not reported	No data available.	-	-
Adverse events - not reported	No data available.	-	-
Drop-out rates - not reported	No data available.	-	-

Lifestyle interventions to treat hypertension compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hypertension

Patient or population: Adults with normal cognition or mild cognitive impairment and hypertension

Setting: Community

Intervention: Lifestyle interventions to treat hypertension

Comparison: Usual care or no intervention

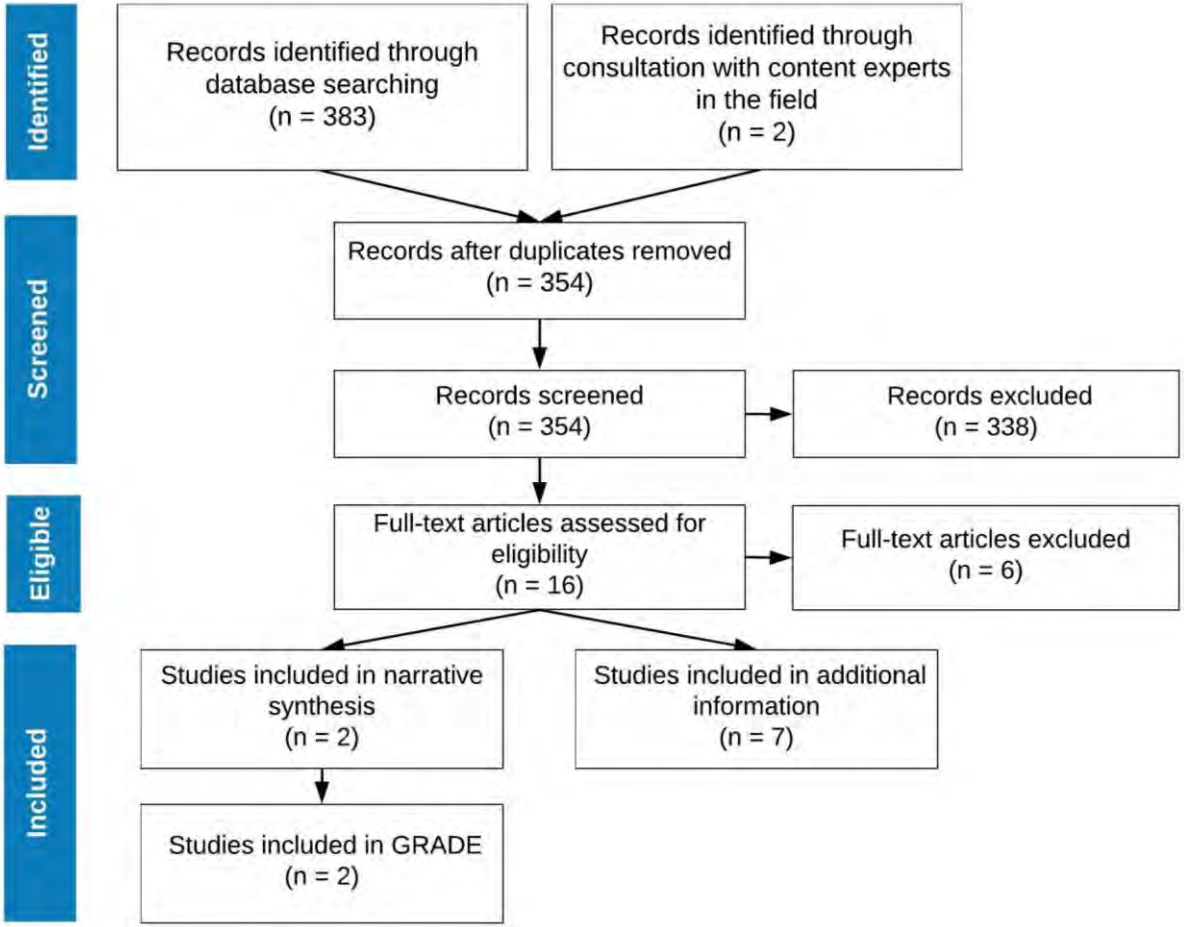
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

***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

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

Annex: PRISMA[1] flow diagram for systematic review of reviews – treatment of hypertension



Note. Weiss et al[10] is included in the narrative synthesis and GRADE for quality of life outcomes, as well as in additional information for cognitive function outcomes.

[1] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*, *6*(7), e1000097.

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Treatment of hypertension for reducing risk of cognitive decline and/or dementia

Evidence-to-recommendation table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds(1). Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. Hypertension is an extremely common condition that is associated with an increased risk of heart attacks, heart failure, stroke and kidney failure. **Hypertension in midlife has been found to be associated with an increased risk of late-life dementia(2).**	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	*Desirable effects* **Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention** No data was available for MCI. For cognitive function and incident dementia the volume of evidence is low (3 RCTs for cognitive function and 4 RCT for dementia) and quality of evidence is low for both. The review conducted two meta-analyses and reported that the use of antihypertensive's did not significantly reduce cognitive decline (RR 0.96, 95% CI 0.87 to 1.06) or incidence of dementia (RR 0.90, 95% CI 0.76 to 1.07). **Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention** No data	New information presented at the Alzheimer's Association International Conference (AAIC) July 2018 is in agreement with previous findings. Peters et al (3)carried out a systematic review and meta-analysis and found no difference by antihypertensive classes for cognitive function but reported an OR0.65 (0.51:0.83) for incident dementia in favour of antihypertensive treatment compared to placebo in clinical trial populations aged >65 years with ≥5 year follow up. Williamson et al (4)reported preliminary results from the Sprint Mind Trial showing a significantly lower rate of incident MCI (HR=0.81, 95% CI 0.70 to 0.95)

		and a nonsignificant reduction in probable dementia (HR=0.83; 95% CI 0.67 to 1.04) in the intensive treatment group (SBP target of <120 mmHg) versus the standard treatment group (SBP target of <140 mmHg). Tully et al (5)carried out a systematic review and meta-analysis to look at the impact of diuretic use on incident dementia. The results of the meta-analysis for incident dementia (which combined adjusted published and unpublished data) showed a combined hazard ratio of 0.83 (95% CI 0.76 to 0.91) in favour of diuretic treatment Hussain et al (6)carried out a systematic review and meta-analysis to look at the impact of calcium channel blocker use on incident dementia. They carried out a meta-analysis including all 10 cohorts and reported a combined risk ratio of 0.70 (95% CI 0.58 to 0.85) for incident dementia in favour of calcium channel blocker use. Kane et al (7)carried out a peer reviewed systematic review of interventions to prevent age-related cognitive decline, mild cognitive impairment and clinical Alzheimer's type dementia. For hypertension and use of antihypertensives the review reported low strength evidence that 3 to 4.7 years of antihypertensive treatment versus placebo appears to have no benefit on cognitive test performance in adults with normal cognition. They also reported that the results for dementia were inconsistent. There was insufficient evidence to draw conclusions (only one study) in adults with MCI. For combination therapy (type not specified) vs placebo the review reports statistically significant difference in dementia diagnoses favouring combination therapy versus placebo (n=3228, up to 3.9 years follow up). No meta-analysis data provided Stuhec et al (8)carried out a systematic review of RCTs examining a population aged (on average) 65

		years or older, without dementia and who were taking antihypertensive medication. The review reports that Angiotensin II receptor blockers improved cognitive functioning in the elderly, especially with regards to episodic memory, however the other antihypertensive drugs did not improve cognition. Fink et al carried out a systematic review which examined randomised and non-randomised controlled trials in those without dementia. The authors concluded that pharmacologic treatments neither improved nor slowed decline in cognitive test performance. Hernandorena et al(9) carried out a systematic search and presented a narrative review discussing the observational studies and clinical trials that have reported on the use of antihypertensives and outcomes of cognitive function, hippocampal atrophy and dementia. They concluded that most observational studies have suggested a potential preventive effect of antihypertensive therapies, however RCTs and meta-analyses provide more conflicting results. Weiss et al (10)carried out a systematic review to examine the benefits and harms of intensive blood pressure treatment in adults aged 60 and over and reported moderate strength evidence that the use of antihypertensive treatment to achieve moderately strict blood pressure control for up to five years does not worsen cognitive outcomes compared to less strict blood pressure control.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	*Undesirable effects* **Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention** For quality of life, the volume of evidence (4 RCTs) and quality of evidence is very low. For functional level, the volume of evidence is low (1 RCT) and the quality of evidence is very low. No meta-analyses were conducted. For quality of life, the review states "we found moderate strength evidence that use of antihypertensive therapy to achieve moderate BP control (SBP 140-150 mmHg) was not associated with deterioration in quality of life compared to less intensive blood pressure control". For functional level, the review states "we found low strength evidence from one large low risk of bias trial that moderate blood pressure control was not associated with deterioration in functional status compared to less intensive control." For adverse events the volume of evidence is moderate (19 RCTs) and the quality of evidence is very low. The review reports a wide range of adverse events (but cough and hypotension were most frequently reported) and mixed findings regarding whether antihypertensive intervention increases the frequency of adverse events. Overall drop out rates were not reported. **Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention** No data adverse events, quality of life, functional levels, or dropouts.	Adverse effects are highly dependant on the medication administered. See American Heart Association website for list of possible side effects for each class of antihypertensives (link: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/MakeChangesThatMatter/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention** **Findings:** Certainty of the evidence is low for both cognitive function and incident dementia, which showed that antihypertensive therapy has no effect on cognitive decline or incidence of dementia. The certainty of evidence for adverse events is very low showing that antihypertensive therapy does not decrease quality of life or functional level. The certainly of evidence is very low showing mixed findings with regards to antihypertensive and adverse events. No evidence for MCI was available. No evidence on overall drop out rates. **Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention** **Findings:**	

	No data available, inestimable.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	A review conducted by Anderson et al 2009(11) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia(12) and the United Kingdom(13) (UK) and have shown a general trend of individuals being fearful of developing dementia. There is no evidence showing that individuals would oppose dementia risk reduction, of view cognitive decline favourably. Data from low and middle income countries is unavailable. There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	Additional sources like the Saga Survey(14) and Alzheimer's Research UK(15) have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	**Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention** Does not favor either the intervention or the comparison (low quality evidence suggests no effect of antihypertensive therapy on cognitive decline or dementia, but intervention also does not lower quality of life or functional level, mixed results regarding adverse effects). **Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention** No data available, inestimable.	There is consistent indirect evidence in favour of these interventions. Drug specific adverse events may require change of one drug for another.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Various medications can be used to treat hypertension and costs are dependent the drug administered (see additional considerations). No data on resources required were reported by the systematic reviews described above.	The WHO(16)recommendations for antihypertensive medications are listed below. The prices are taken from the International Drug Price Indicator Guide(17) and are listed as price per unit. · Amlodipine Tablet: 5 mg (as maleate, mesylate or besylate); Median Price US$ (Supplier/Buyer) = 0.0252/0.0094 · Bisoprolol (includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years)

		Tablet: 1.25 mg (price not listed); 5 mg; Median Price US$ (Supplier/Buyer) = not listed/0.0660 · Enalapril Tablet: 2.5 mg (price not listed); 5 mg (as hydrogen maleate); Median Price US$ (Supplier/Buyer) = 0.0165/0.0095 · Hydralazine (Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines). Powder for injection: 20 mg (hydrochloride) in ampoule; Median Price US$ (Supplier/Buyer) = 4.6717/4.1600 Tablet: 25 mg; Median Price US$ (Supplier/Buyer) = 0.0378/0.0475; 50 mg (hydrochloride); Median Price US$ (Supplier/Buyer) = 0.1485/0.0557 · Hydrochlorothiazide Oral liquid: 50 mg/5 mL (price not listed) Solid oral dosage form: 12.5 mg; Median Price US$ (Supplier/Buyer) = not listed/0.0087; 25 mg; Median Price US$ (Supplier/Buyer) = 0.0043/0.0094 · Methyldopa (Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines). Tablet: 250 mg; Median Price US$ (Supplier/Buyer) = 0.0313/0.0436 · Losartan

		Tablet: 25 mg (price not listed); 50 mg; Median Price US$ (Supplier/Buyer) = not listed/0.0202 100 mg (price not listed). *Complementary List* · Sodium nitroprusside Powder for infusion: 50 mg in ampoule. Lifestyle interventions to reduce blood pressure (eg change in diet or physical activity) would require different resources with variable cost depending on the level of intervention (eg societal, individual) and on local circumstances.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Antihypertensive medication is commonly prescribed as a treatment option for hypertension. They are included in the WHO model list of essential medicines(16)and their costs are listed in the International Drug Price Indicator Guide(17)	The WHO(18) brief on hypertension states that: “Not all patients diagnosed with hypertension require medication, but those at medium to high risk will need one or more of eight essential medicines to lower their cardiovascular risk (a thiazide diuretic, an angiotensin converting enzyme inhibitor, a long-acting calcium channel blocker, a beta blocker, metformin, insulin, a statin and aspirin). The cost of implementing such a programme is low, at less than US$ 1 per head in low-income countries, less than US$ 1.50 per head in lower middle-income countries and US$ 2.50 in upper middle-income countries.”

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Various medications can be used to treat hypertension and costs are dependent the drug administered, however there is evidence to show that antihypertensives can be cost-effective in the treatment of hypertension8 (see additional considerations). No data on cost effectiveness were reported by the systematic reviews described above.	The cost effectiveness of stroke and ischemic and hypertensive heart disease interventions in adults (retrieved from the WHO guidelines Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010) p.64(19)): · Intervention = Combination treatment with aspirin, betablocker, thiazide, ACE inhibitor and statin in district hospital à Cost Effectiveness = 2128 US$/DALY Retrieved from the Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition(20): "[A] way to address the availability and affordability of medications for hypertension and dyslipidemia is to use a combination of generic CVD medications or a polypill for all adults with significant risk for CVD. This single intervention could reduce IHD events by as much as 50 percent."

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons(21) studies health equities in England, They found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment, and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	Health inequity in hypertensive treatment should be addressed

● Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Varies; Drug-related side effects are a key consideration in acceptability of the intervention. There is no other apparent reasons for which pharmacological interventions for hypertension to reduce the risk of cognitive decline and/or dementia would not be acceptable to key stakeholders.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, medication already available and used in individuals with hypertension.	Feasibility for lifestyle interventions to reduce blood pressure may limited by local circumstances

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Guidelines for risk reduction of cognitive decline and dementia

Evidence profile:
treatment of diabetes for reducing the risk of cognitive decline and/or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment and diabetes mellitus, is treatment of diabetes more effective than placebo/no intervention in reducing the risk of cognitive decline and/or dementia?

Background

Diabetes mellitus is a chronic condition that occurs in approximately 8.5% of the adult population and its prevalence increases with age[1-3]. Diabetes occurs in two forms (type 1 and type 2), however the majority of people with diabetes are diagnosed with type 2 diabetes which occurs as a result of lifestyle factors such as poor diet, lack of physical exercise, obesity, excessive alcohol consumption and smoking.

The presence of late-life diabetes has been found to be linked to an increased risk of dementia [4-6]. However, the mechanism by which this occurs is unclear. Poor glucose control, in particular hypoglycaemia, has been associated with lower cognitive functioning and greater cognitive decline [7]. In addition, the complications associated with diabetes such as nephropathy (kidney damage) retinopathy (eye damage), hearing impairment and cardiovascular disease have all been found to increase the risk of dementia [8, 9].

The literature examining interventions that aim to improve glycaemic control shows mixed findings with regards to cognitive outcomes [10, 11]. In addition, the evidence on the effectiveness of medicated treatments for diabetes in reducing dementia risk is inconsistent [12-14]. There is some evidence to suggest the treating the cardiovascular comorbidities associated with diabetes such as high cholesterol and hypertension may mediate the risk for dementia [12, 15]. However overall, the exact relationship between diabetes and dementia is still poorly understood.

The following review provides a summary of the literature examining the effectiveness of diabetes interventions in reducing dementia risk.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment and diabetes mellitus, is treatment of diabetes more effective than placebo/no intervention in reducing the risk of cognitive decline and/or dementia?

Populations

- Adults with normal cognition or mild cognitive impairment and diabetes mellitus

Interventions

- Medications for glycaemic control
- Diet and lifestyle interventions

Comparison

- Placebo/no intervention

Outcomes

- Critical:
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Incident Dementia
- Important:
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Searches using the following strategies (or similar) were conducted as follows

- (systemati* or meta-analys*) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheime*)).ab. and diabetes.af. and ("hypoglycemic agents" or treatment or therapy or pharmacotherapy or behaviour or behavior)[1]

Searches were conducted in:

- Medline
- Cochrane
- PsycInfo
- Embase
- NICE
- Global index medicus/Global Health Library
    - WHO regional data base
    - WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth

[1] Dates searched were 1 May 2016 - 1 May 2018. Additionally, the 2016 AHRQ review(16) was consulted for relevant records which systematically searched the literature between Jan 2009 – Sept 2016. In combination, the search period spanned >9 years. All abstracts were screened by two independent reviewers and with any discrepancies resolved by discussion. Full text articles were read by the same two independent reviewers and any discrepancy resolved by discussion.

List of systematic reviews identified by the search process

Included in GRADE[2] tables

- Areosa Sastre, A., Vernooij, R. W., Gonzalez-Colaco Harmand, M., & Martinez, G. (2017). Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev, 6*, Cd003804. doi:10.1002/14651858.CD003804.pub2
- Podolski, N., Brixius, K., Predel, H. G., & Brinkmann, C. (2017). Effects of Regular Physical Activity on the Cognitive Performance of Type 2 Diabetic Patients: A Systematic Review. *Metab Syndr Relat Disord, 15*(10), 481-493. doi:10.1089/met.2

[2] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO table

	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Medications for glycaemic control versus placebo/no intervention	Cognitive function • Mini-Mental State Exam (MMSE)	Areosa Sastre, A., Vernooij, R. W., Gonzalez-Colaco Harmand, M., & Martinez, G. (2017). Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev, 6*, Cd003804. doi:10.1002/14651858.CD003804.pub2	Systematic review relevant to the area. Includes samples of adults with normal cognition and diabetes who were treated with medications for intensive glycaemic control. Global cognitive outcomes were included. RCTs were included. AMSTAR 2[3] rating is Moderate.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident Dementia	Areosa Sastre, A., Vernooij, R. W., Gonzalez-Colaco Harmand, M., & Martinez, G. (2017). Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev, 6*, Cd003804. doi:10.1002/14651858.CD003804.pub2	Systematic review relevant to the area. Includes samples of adults with normal cognition and diabetes who were treated with medications for intensive glycaemic control. Incidence of dementia is included. RCTs were included. AMSTAR 2[3] rating is Moderate.
		Quality of life	No reviews identified.	No reviews identified.
		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events • Hypoglycaemia	Areosa Sastre, A., Vernooij, R. W., Gonzalez-Colaco Harmand, M., & Martinez, G. (2017). Effect of the treatment of Type 2 diabetes mellitus	Systematic review relevant to the area. Includes samples of adults with normal cognition and diabetes who were treated with medications for

[3] AMSTAR: A Measurement Tool to Assess Systematic Reviews. More information: https://amstar.ca/index.php

			on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev, 6*, Cd003804. doi:10.1002/14651858.CD003804.pub2	intensive glycaemic control. Adverse events are included. Meta-analysis on RCTs was included. AMSTAR 2[3] rating is Moderate.
		Drop-out rates	No reviews identified.	No reviews identified.
2	Diet and lifestyle interventions versus placebo/no intervention • physical activity	Cognitive function • MMSE	Podolski, N., Brixius, K., Predel, H. G., & Brinkmann, C. (2017). Effects of Regular Physical Activity on the Cognitive Performance of Type 2 Diabetic Patients: A Systematic Review. *Metab Syndr Relat Disord, 15*(10), 481-493. doi:10.1089/met.201	Systematic review relevant to the area. Includes samples of adults with diabetes who attended physical training intervention. Global cognitive outcomes were included. No meta-analysis conducted, however RCTs were included in the review. AMSTAR 2[3] rating is Critically Low*. *Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident Dementia	No reviews identified.	No reviews identified.
		Quality of life	No reviews identified.	No reviews identified.
		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events	No reviews identified.	No reviews identified.
		Drop-out rates	No reviews identified.	No reviews identified.

Narrative descriptions of the studies that went into the analysis

GRADE table 1: medications for glycaemic control versus to placebo or no intervention

Areosa et al.[17] conducted a COCHRANE systematic review investigating the effects of different types of treatment for type 2 diabetes on the development of cognitive impairment and dementia. The review only included randomised control trials which compared two or more different treatments for Type 2 diabetes. Cognitive function was measured at baseline and post-treatment. Two authors independently extracted the data and assessed the quality of the studies using the GRADE method. The authors included four studies in their analysis. Two of the studies[10, 18] (combined N = 13 934) compared intensive glycaemic control to standard glycaemic control and the other two studies[19, 20] compared different pharmacological treatments to each other. One study[10] was at high risk of performance and detection bias and all four studies had unclear risk of bias across at least two domains. Both of the intensive vs standard glycaemic control studies[10, 18] used MMSE to measure outcome, were of moderate quality and found no difference between the groups in global cognitive functioning measures at follow-up. One study measured MMSE score after 40 months (MD = -0.01, 95% CI -0.18 to -0.16, p = NS) and the other measured the number of participants who declined in 3 or more MMSE points after 5 years (RR 0.98, 95% CI 0.87 to 1.85, p = NS). There was also low quality evidence from one study that there was little to no difference between the treatment groups in incidence of dementia (RR 1.27, 95% CI 0.87 to 1.85, p = NS). The review concluded that was no good evidence across any of the studies that the intensity of glycaemic control or differences in pharmacological treatments for diabetes had any effect on preventing or delaying cognitive impairment. However, there is moderate quality evidence that participants exposed to intensive glycaemic control may experience more episodes of severe hypoglycaemia (RR 2.18, 95% CI 1.52 to 3.14, p <0.001). The AMSTAR 2 rating of this review was moderate.

GRADE table 2: diet and lifestyle interventions versus placebo or no intervention

Podolski et al.[21] conducted a systematic review examining the effects of regular physical activity on cognitive function in individuals with type 2 diabetes. The review included four cross-sectional studies, one longitudinal study and nine intervention studies. No numerical results were reported and no meta-analysis was conducted. Out of the nine physical training intervention studies, only three compared the outcomes of an intervention group to a group that was not receiving any intervention and/or participating in a different program and only two of these were randomised trials. One of the RCTs[22] found higher global cognitive scores in the intervention group compared to the control group after 2 years while the other RCT[23] found no difference in cognitive functioning scores between the two groups after 10-13 years. The AMSTAR 2 rating of this review was critically low. No risk of bias assessment was conducted.

GRADE table 1: Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention for reducing the risk of cognitive decline and/or dementia

Author(s): Nicole Ee, Lidan Zheng, Ruth Peters
Date: May 2018
Question: Treatment for diabetes in the form of medications for glycaemic control compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and diabetes mellitus
Setting: Community
Bibliography: Areosa, S. A., & Grimley, E. V. (2002). Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia. The Cochrane database of systematic reviews, (4), CD003804-CD003804.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**treatment for diabetes in the form of medications for glycaemic control**	**placebo or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognitive function (follow up: range 40 months to 60 months; assessed with: MMSE (higher scores indicate better cognition))												
2	randomised trials	serious [a]	not serious [b]	not serious [c]	not serious [d]	none [e]	Review states "We found moderate-quality evidence to suggest that there is probably little or no difference between intensive and standard treatment regimes on global cognitive function measured with the MMSE." [f]				⊕⊕⊕◯ MODERATE	CRITICAL
Incident MCI - not measured												
-	-	-	-	-	-	-	No data available				-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**treatment for diabetes in the form of medications for glycaemic control**	**placebo or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Incident Dementia (follow up: median 5 years)												
1	randomised trials	serious [g]	not serious [h]	not serious [i]	very serious [j]	none [e]	61/5571 (1.1%)	48/5569 (0.9%)	**RR 1.27** (0.87 to 1.85)	**2 more per 1,000** (from 1 fewer to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT
Functional level - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT
Adverse Events (assessed with: rate of hypoglycaemic events)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**treatment for diabetes in the form of medications for glycaemic control**	**placebo or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	very serious [k]	serious [l]	not serious [m]	serious [n]	none [e]	226/6463 (3.5%)	108/6468 (1.7%)	**RR 2.18** (1.52 to 3.14)	**20 more per 1,000** (from 9 more to 36 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Drop-out rates - not measured												
-	-	-	-	-	-	-	No data available				-	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Risk of bias: Downgraded once as both studies had high or unclear risk of bias for blinding (performance and detection bias) and blinding of participants and personnel (performance bias) and additional unclear blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias) in one study.

b. Inconsistency: No meta-analysis conducted thus no I^2 heterogeneity measure available. Both studies had evidence of non-significant difference between intensive and standard glycaemic control. CI (RR=0.98; CI: 0.88-1.08) only available for one study which defined global function as reduction of at least 3 MMSE points, other study reported mean MMSE score as .01 lower. Slight inconsistency in measure but no reason to believe this would have substantial impact on conclusions.

c. Indirectness: population, intervention, outcomes and comparisons are relevant. Populations were drawn from 215 clinical centres across 20 different countries and in 52 outpatient clinics, and both trials had 2x2 factorial design, with global cognition as outcomes, and compared intensive to standard glycaemic control.

d. Imprecision: sample sizes were large (n>2700), CIs only reported for one trial.

e. Publication bias: Grey literature and trial registries were searched, ALOIS used to ensure search was up to date and as comprehensive as possible; not enough trials to explore reporting bias formally, but no reason to believe bias is present.

f. Data could not be pooled because one study reported MMSE results as the number of participants who showed a 3 or more point decline in MMSE.

g. Risk of bias: Downgraded once unclear risk of bias for blinding (performance and detection bias) and blinding of participants and personnel (performance bias) in the one study included.

h. Inconsistency: not applicable as only one study for this outcome.

i. Indirectness: relevant population, interventions, outcomes and comparisons. population drawn from 20 veteran affairs medical centres in the USA, compared standard to intense glycaemic control, measured incident dementia.

j. Imprecision: Downgraded twice as (review states) "Event rate low" and RR ranges from benefit to harm.

k. Risk of bias: Downgraded once as both studies had unclear risk of bias for blinding (performance and detection bias) and blinding of participants and personnel (performance bias) and additional unclear random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias), and other bias in one study.

l. Inconsistency: Downgraded once as heterogeneity is present and substantial; I^2 = 54%; CIs overlapped RR= 1.87 (1.43, 2.45); RR= 2.74 (1.79, 4.18).

m. Indirectness: population, intervention, outcomes and comparisons are relevant. Studies conducted in 20 veteran affairs medical centres in the USA, and 215 clinical centres in 20 different countries. One trial had 2x2 factorial design, and the other single intervention and control group design. Both compared intensive to standard glycaemic control, and measured hypoglycaemic events as the outcome. Variability is limited and would not substantially affect results.

n. Imprecision: Downgraded once as (review states) "Wide 95% confidence interval around the pooled estimate of effect." RR=2.18 (1.52, 3.14). Sample size were reasonable (n>12 000).

GRADE table 2: Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention for reducing the risk of cognitive decline and/or dementia

Author(s): Nicole Ee, Lidan Zheng, Ruth Peters
Date: June 2018
Question: Treatment for diabetes in the form of diet and lifestyle interventions compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and diabetes mellitus
Setting: Community
Bibliography: Podolski, N., Brixius, K., Predel, H. G., & Brinkmann, C. (2017). Effects of Regular Physical Activity on the Cognitive Performance of Type 2 Diabetic Patients: A Systematic Review. Metabolic syndrome and related disorders, 15(10), 481-493.

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cognitive function (follow up: range 2 years to 13 years; assessed with: 3ME (higher scores indicate better cognition))									
2	randomised trials	serious [a]	not serious [b]	not serious [c]	serious [d]	publication bias strongly suspected [e]	The review only searched pubmed and no numerical results were provided. The review narratively reported the results of one RCT that found higher 3ME scores indicating better function at follow-up in the intervention group compared to the control group (N = 415) and another RCT that found no differences between the two groups at follow-up (N = 3751).	⨁◯◯◯ VERY LOW	CRITICAL
Incident MCI - not measured									
-	-	-	-	-	-	-	No data available	-	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Incident Dementia - not measured									
-	-	-	-	-	-	-	No data available	-	CRITICAL
Quality of life - not measured									
-	-	-	-	-	-	-	No data avaliable	-	IMPORTANT
Functional level (ADL, IADL) - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Adverse events - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT
Drop-out rates - not measured									
-	-	-	-	-	-	-	No data available	-	IMPORTANT

CI: Confidence interval

Explanations

a. Risk of bias: Downgraded once as one of the two studies was of low quality as rated by reviewers. OCEBM scale was used to rate studies classifying evidence into levels level 1b (RCTs with high methodological quality), 2b (RCTs with low methodological quality) and 4 (non-RCTs with or without controls). One study obtained a 1b rating and the other a 4.

b. Inconsistency: Downgraded once. No meta-analysis conducted. No data on CIs or I^2 or effect sizes across primary studies. One study found significance of effect while the other found no effect.

c. Indirectness: Downgraded once as one of the trials did not have control group. Population, intervention, outcomes, are relevant. Population as of T2DM patients included ages 35-65, with lifestyle intervention in the form of exercise. Cognitive function measured with accepted measure (3ME).

d. Imprecision: Downgraded once as sample sizes were small or unclear (n=64; NR). No numerical results or data reported on CIs or effects.

e. Publication bias: Downgraded once as only published records in English were included, only one database was used, no grey literature or trial registry searches were conducted, and no formal assessment of publication bias was carried out.

Additional evidence not mentioned in GRADE table

Antidiabetic treatments versus placebo

Kane et al.[16] carried out a peer reviewed systematic review of interventions to prevent age-related cognitive decline, mild cognitive impairment and clinical Alzheimer's type dementia. The review was prepared for the United States Agency for Healthcare Research and Quality (AHRQ). The authors reviewed the literature from Jan 09 to Sept 2016 and for evidence published prior to Jan 2009, they drew on a prior version of the review also prepared for the AHRQ. The review was rigorous. It rates as a moderate quality review when rated using the AMSTAR 2 quality rating only losing points for a lack of information related to excluded articles and a lack of detail as to the funding sources for each included study. The review focused on populations who were cognitively normal or may have age-related changes or MCI but do not yet have dementia. The review did not include dementia due to specific, identifiable conditions such as Lewy body, infectious diseases, frontotemporal, and traumatic brain injury.

In the section regarding medicated treatments for diabetes, five studies were examined. These five studies were separated into two categories. The first category consisted of studies examining antidiabetic interventions for adults with normal cognition. Specifically, these studies examined interventions that promoted intense glycaemic control in adults with diabetes versus standard glycaemic control or usual care. The review reported that intense versus standard glycaemic control had no effect on cognitive performance in middle-aged adults with normal cognition. The second category consisted of studies examining antidiabetic interventions in adults with MCI. Specifically, these studies examined pharmacological monotherapy interventions (Pioglitzaone and Metformin) versus placebo in obese adults without diabetes and/or with untreated diabetes. The review reported that minimal differences were found between the treatment and placebo groups with regards to cognitive outcomes. Overall the review concluded that there was a lack of evidence showing that treatments for diabetes had an impact on the incidence of MCI or dementia. While some of the studies included the development of dementia as an outcome variable, the criteria they used to measure this outcome was not reliable.

Intensive vs standard glycaemic control

Tuligenga[24] conducted a meta-analysis of RCTs comparing intensive versus standard glycaemic control and reported that there was no statistically significant difference in cognitive decline between the intensive glycaemic control group and the standard glycaemic control group (SDM = 0.02; 95% CI -0.03 to 0.08). They also noted that there was significant heterogeneity across individual studies (I^2 = 68%).

Physical activity intervention (cross-sectional and longitudinal studies)

The cross-sectional studies in the Podolski et al.[21] review all found positive correlations between amount of physical activity and scores across a range of cognitive measures in participants with type 2 diabetes. The longitudinal study had an observational period of 10 years and found that individuals with diabetes with lower levels of

physical activity in their daily lives and had a higher risk of developing cognitive impairments and dementia compared to individuals that had higher levels of physical activity. Out of the nine physical training intervention studies, improvements in cognitive functioning between pre-and post-intervention were found across six studies. Two studies found no changes in cognitive functioning and one study found negative changes in cognitive test scores. The authors remarked that the quality of most the training studies was low due to small sample sizes and/or missing control groups. Overall, the review concluded that there is some evidence to show that physical training may help improve the cognitive outcomes of individuals with type 2 diabetes.

Other relevant guidelines

The WHO guidelines Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010): http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset: https://www.nice.org.uk/guidance/ng16

Part 2: From evidence to recommendations

Summary of evidence table 1

Treatment for diabetes in the form of medications for glycaemic control compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and diabetes mellitus

Patient or population: Adults with normal cognition or mild cognitive impairment and diabetes mellitus

Setting:

Intervention: Treatment for diabetes in the form of medications for glycaemic control

Comparison: Placebo or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	**Risk with treatment for diabetes in the form of medications for glycaemic control**				
Cognitive function assessed with: MMSE (higher scores indicate better cognition) follow up: range 40 months to 60 months	Review states "We found moderate-quality evidence to suggest that there is probably little or no difference between intensive and standard treatment regimes on global cognitive function measured with the MMSE." [a]			(2 RCTs)	⨁⨁⨁◯ MODERATE [b,c,d,e,f]	
Incident MCI - not measured	No data available			-	-	
Incident Dementia follow up: median 5 years	9 per 1,000	**11 per 1,000** (7 to 16)	**RR 1.27** (0.87 to 1.85)	11140 (1 RCT)	⨁◯◯◯ VERY LOW [f,g,h,i,j]	

Treatment for diabetes in the form of medications for glycaemic control compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and diabetes mellitus

Patient or population: Adults with normal cognition or mild cognitive impairment and diabetes mellitus

Setting:

Intervention: Treatment for diabetes in the form of medications for glycaemic control

Comparison: Placebo or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	**Risk with treatment for diabetes in the form of medications for glycaemic control**				
Quality of life - not measured	No data available			-	-	
Functional level - not measured	No data available			-	-	
Adverse Events assessed with: rate of hypoglycaemic events	17 per 1,000	**36 per 1,000** (25 to 52)	**RR 2.18** (1.52 to 3.14)	12931 (2 RCTs)	⨁◯◯◯ VERY LOW [f,k,l,m,n]	
Drop-out rates - not measured	No data available			-	-	

***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; **RR:** Risk ratio

Treatment for diabetes in the form of medications for glycaemic control compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and diabetes mellitus

Patient or population: Adults with normal cognition or mild cognitive impairment and diabetes mellitus

Setting:

Intervention: Treatment for diabetes in the form of medications for glycaemic control

Comparison: Placebo or no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	**Risk with treatment for diabetes in the form of medications for glycaemic control**				

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

Explanations

a. Risk of bias: Downgraded once as both studies had high or unclear risk of bias for blinding (performance and detection bias) and blinding of participants and personnel (performance bias) and additional unclear blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias) in one study.

b. Inconsistency: No meta-analysis conducted thus no I^2 heterogeneity measure available. Both studies had evidence of non-significant difference between intensive and standard glycaemic control. CI (RR=0.98; CI: 0.88-1.08) only available for one study which defined global function as reduction of at least 3 MMSE points, other study reported mean MMSE score as .01 lower. Slight inconsistency in measure but no reason to believe this would had substantial impact on conclusions.

c. Indirectness: population, intervention, outcomes and comparisons are relevant. Populations were drawn from 215 clinical centres across 20 different countries and in 52 outpatient clinics, and both trials had 2x2 factorial design, with global cognition as outcomes, and compared intensive to standard glycaemic control.

d. Imprecision: sample sizes were large (n>2700), CIs only reported for one trial CIs.

e. Publication bias: Grey literature and trial registries were searched, ALOIS used to ensure search was up to date and as comprehensive as possible; not enough trials to explore reporting bias formally, but no reason to believe bias is present.

f. Data could not be pooled because one study reported MMSE results as the number of participants who showed a 3 or more point decline in MMSE.

g. Risk of bias: Downgraded once unclear risk of bias for blinding (performance and detection bias) and blinding of participants and personnel (performance bias) in the one study included.

h. Inconsistency: not applicable as only one study for this outcome.

i. Indirectness: relevant population, interventions, outcomes and comparisons. population drawn from 20 veteran affairs medical centres in the USA, compared standard to intense glycaemic control, measured incident dementia.

j. Imprecision: Downgraded twice as (review states) "Event rate low" and RR ranges from benefit to harm.

k. Risk of bias: Downgraded once as both studies had unclear risk of bias for blinding (performance and detection bias) and blinding of participants and personnel (performance bias) and additional unclear random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias) and incomplete outcome data (attrition bias), and other bias in one study.

l. Inconsistency: Downgraded once as heterogeneity is present and substantial; I^2 = 54%; CIs overlapped RR= 1.87 (1.43, 2.45); RR= 2.74 (1.79, 4.18).

m. Indirectness: population, intervention, outcomes and comparisons are relevant. Studies conducted in 20 veteran affairs medical centres in the USA, and 215 clinical centres in 20 different countries. One trial had 2x2 factorial design, and the other single intervention and control group design. Both compared intensive to standard glycaemic control, and measured hypoglycaemic events as the outcome. Variability is limited and would not substantially affect results.

n. Imprecision: Downgraded once as (review states) "Wide 95% confidence interval around the pooled estimate of effect." RR=2.18 (1.52, 3.14). Sample size were reasonable (n>12 000).

Summary of evidence table 2

Treatment for diabetes in the form of diet and lifestyle interventions compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment with diabetes mellitus

Patient or population: Adults with normal cognition or mild cognitive impairment and diabetes mellitus

Setting:

Intervention: Treatment for diabetes in the form of diet and lifestyle interventions

Comparison: Placebo or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Cognitive function assessed with: 3ME (higher scores indicate better cognition) follow up: range 2 years to 13 years	The review only searched pubmed and no numerical results were provided. The review narratively reported the results of one RCT that found higher 3ME scores at follow-up in the intervention group compared to the control group (N = 415) and another RCT that found no differences between the two groups at follow-up (N = 3751).	(2 RCTs)	⨁◯◯◯ VERY LOW [a],[b],[c],[d],[e]
Incident MCI - not measured	No data available	-	-
Incident Dementia - not measured	No data available	-	-
Quality of life - not measured	No data avaliable	-	-
Functional level (ADL, IADL) - not measured	No data available	-	-

Treatment for diabetes in the form of diet and lifestyle interventions compared to placebo or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment with diabetes mellitus

Patient or population: Adults with normal cognition or mild cognitive impairment and diabetes mellitus

Setting:

Intervention: Treatment for diabetes in the form of diet and lifestyle interventions

Comparison: Placebo or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Adverse events - not measured	No data available	-	-
Drop-out rates - not measured	No data available	-	-

***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

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

Explanations

a. Risk of bias: Downgraded once as one of the two studies was of low quality as rated by reviewers. OCEBM scale was used to rate studies classifying evidence into levels level 1b (RCTs with high methodological quality), 2b (RCTs with low methodological quality) and 4 (non-RCTs with or without controls). One study obtained a 1b rating and the other a 4.

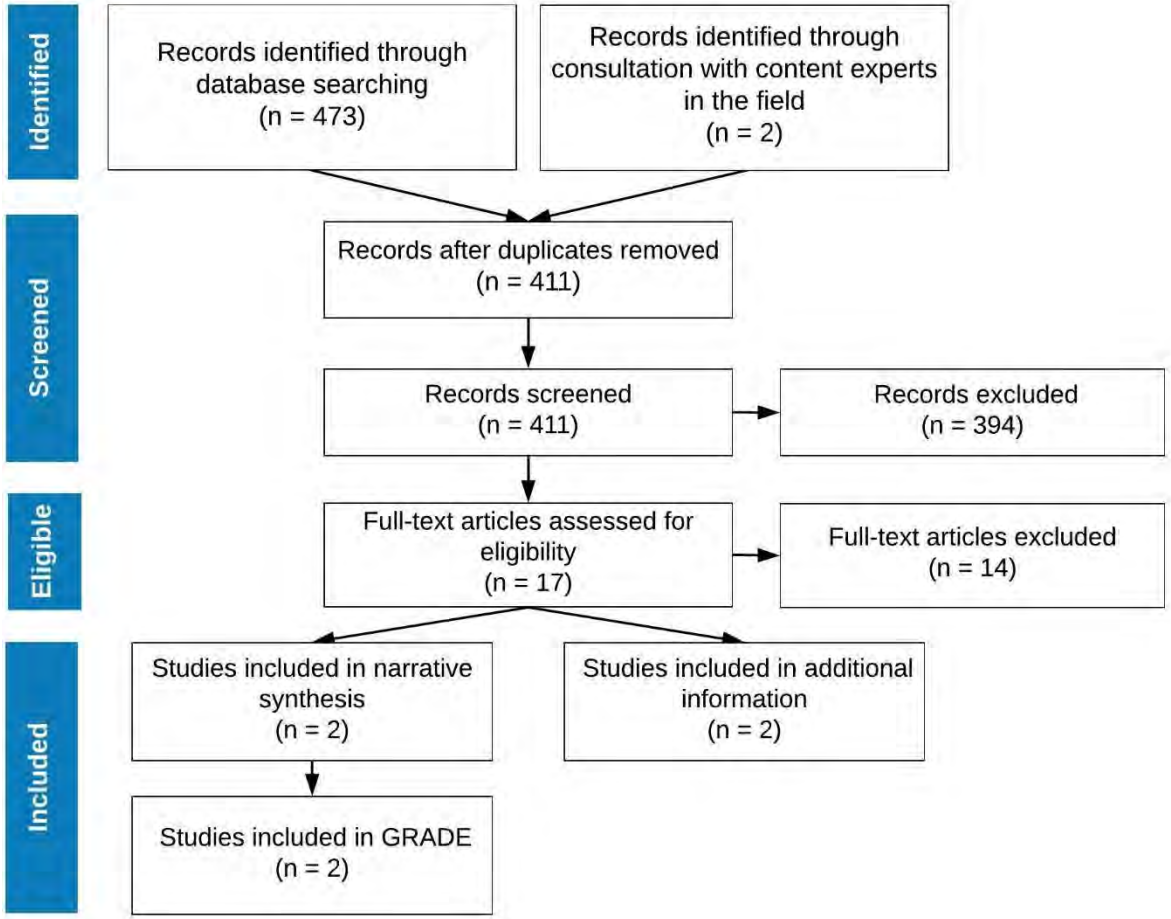
b. Inconsistency: Downgraded once. No meta-analysis conducted. No data on CIs or I^2 or effect sizes across primary studies. One study found significance of effect while the other found no effect.

c. Indirectness: Downgraded once as one of the trials did not have control group. Population, intervention, outcomes, are relevant. Population as of T2DM patients included ages 35-65, with lifestyle intervention in the form of exercise. Cognitive function measured with accepted measure (3ME).

d. Imprecision: Downgraded once as sample sizes were small or unclear (n=64; NR). No numerical results or data reported on CIs or effects.

e. Publication bias: Downgraded once as only published records in English were included, only one database was used, no grey literature or trial registry searches were conducted, and no formal assessment of publication bias was carried out.

Annex: PRISMA[1] flow diagram for systematic review of reviews – treatment for diabetes



Note. The same record (Podolski et al.[(21)]) was included both narrative syntheses/GRADE and additional information.

[1] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*, *6*(7), e1000

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Treatment of diabetes for reducing the risk of cognitive decline and/or dementia

Evidence-to-recommendation table

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds(1). Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. Diabetes mellitus is a chronic condition that occurs in approximately 8.5% of the adult population and its prevalence increases with age. The presence of late-life diabetes has been found to be linked to an increased risk of dementia(2)	Diabetes is a well established risk factor for cognitive decline and dementia
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention** *Desirable effects* No data was available for MCI. For cognitive function the volume of evidence is low (2 RCTs) and the quality of evidence is moderate. For incident dementia the volume of evidence is low (1 RCT) and the quality of evidence is very low. No meta-analyses were conducted. For cognitive function, the review states “little to no difference between intensive and standard treatment regimens on the MMSE” but no numerical data is provided. For incident dementia, the review reports a non-significant effect of intense glycaemic control (RR = 1.27, 95% CI .087 to 1.85). An average of 500 patients would have to receive intensive glycaemic control for treatment of diabetes instead of standard care for one additional patient to develop dementia. Number to harm (NNH) = 500	Tuligenga(3) conducted a meta-analysis of RCTs comparing intensive versus standard glycaemic control and reported that there was no statistically significant difference in cognitive decline between the intensive glycaemic control group and the standard glycaemic control group (SDM = 0.02; 95% CI -0.03 to 0.08). They also noted that there was significant heterogeneity across individual studies (I2 = 68%). Aresoa et al. (4)narratively reported there was no good evidence that the intensity of glycaemic control or differences in pharmacological treatments for diabetes had any effect on preventing or delaying cognitive impairment.

	Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention *Desirable effects* No data for MCI, incident dementia. For cognitive function, volume of evidence is low, quality of evidence is very low and the findings were mixed. No meta-analysis was conducted, and there was no robust data on clinical significance.	With regards to lifestyle interventions, one review (5) found mixed results regarding the impact of physical activity on cognitive functioning in adults with diabetes. The AHRQ report (6) concluded that overall, there was a lack of evidence showing that treatments for diabetes had an impact on the incidence of MCI or dementia. A review of cross-sectional and longitudinal studies (5) found that physical training may help improve the cognitive outcomes of individuals with type 2 diabetes.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention** *Undesirable effects:* No evidence on quality of life, functional level or drop outs. For adverse events the volume of evidence is low with two RCTs reporting hypoglycaemia. Quality of evidence is very low. There were more hypoglycaemic episodes in the intensively treated group RR = 2.18 (1.52 to 3.14). On average 55.6 patients would have to receive intensive glycaemic control for treatment of diabetes instead of standard care for one additional patient to have a hypoglycaemic episode. NNH = 55.6. **Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention** *Undesirable effects:* No data adverse events, functional levels, or dropouts.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention** **Findings:** Certainty of the evidence is moderate for cognitive function and very low for incident dementia, which showed intensive as opposed to standard glycaemic control has an unclear effect on cognitive function and no effect on dementia. The certainty of evidence for adverse events is very low, showing intensive glycaemic control Increases risk of hypoglycaemic events. No evidence for MCI was available. No evidence on quality of life or functional outcomes or drop-out rates. **Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention** **Findings:** Certainty of evidence is very low. The effect of physical activity on cognitive function is unclear: No evidence for MCI or dementia. No adverse events for diet and lifestyle.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	A review conducted by Anderson et al 2009(7) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia(8)and the United Kingdom(9)(UK) and have shown a general trend of individuals being fearful of developing dementia. There is no evidence showing that individuals would oppose dementia risk reduction, of view cognitive decline favourably.	Additional sources like the Saga Survey(10) and Alzheimer's Research UK(11) have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)

	Data from low and middle income countries is unavailable. There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	**Treatment for diabetes in the form of medications for glycaemic control versus placebo or no intervention:** May favour standard glycaemic control because intense glycaemic control has no effect on cognitive function but may result in increased episodes of hypoglycaemia. **Treatment for diabetes in the form of diet and lifestyle interventions versus placebo or no intervention** Unable to make conclusive comment due to mixed findings and very low quality evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	For the treatment of diabetes in the form of medications for glycaemic, no additional resources are needed because the evidence favours standard care over intensive glycaemic control. However, see additional considerations for a list of medications can be used to treat diabetes. The costs are dependent the drug used. For the treatment of diabetes in the form of diet and lifestyle interventions, only one review was included and it examined the effects of regular physical activity on the cognitive performance of patients with type II diabetes. No data on resources required were reported.	The WHO(12)recommendations for antidiabetic medicines are listed below. The prices are taken from the International Drug Price Indicator Guide (http://mshpriceguide.org/en/home/) and are listed as price per unit. · Gliclazide (glibenclamide not suitable above 60 years) è Solid oral dosage form: (controlled-release tablets) 30 mg; Median Price US$ (Supplier/Buyer) = not listed/0.0350; 60 mg (price not listed);80 mg; Median Price US$ (Supplier/Buyer) = 0.0591/0.0455. · Glucagon è Injection: 1 mg/ mL.; Median Price US$ (Supplier/Buyer) = not listed/25.7458 · Insulin injection (soluble) è Injection: 40 IU/ mL in 10- mL vial; Median Price US$ (Supplier/Buyer) = not listed/0.2600; 100 IU/ mL in 10- mL vial; Median Price US$ (Supplier/Buyer) = 0.8834/0.4919 · Intermediate-acting insulin è Injection: 40 IU/ mL in 10- mL vial; Median Price US$ (Supplier/Buyer) = not listed/0.2600; 100 IU/ mL in 10- mL vial (as compound insulin zinc suspension or isophane insulin); Median Price US$ (Supplier/Buyer) = 0.8834/0.3603 · Metformin è Tablet: 500 mg (hydrochloride); Median Price US$ (Supplier/Buyer) = 0.0169/0.0262 *Complementary List* · Metformin Tablet: 500 mg (hydrochloride)
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Antidiabetic medication and physical activity are already being recommended as treatment option for patients with diabetes. Antidiabetic medications are included in the WHO model list of essential medicines(12) and their costs are listed in the International Drug Price Indicator Guide(13). Physical activity interventions are not well defined and their costs can vary depending on a range of factors (e.g. equipment needed, length of intervention, guided vs unguided etc).	The WHO factsheet on diabetes (http://www.who.int/en/news-room/fact-sheets/detail/diabetes) states that: "Treatment of diabetes involves diet and physical activity along with lowering blood glucose and the levels of other known risk factors that damage blood vessels. Tobacco use cessation is also important to avoid complications. Interventions that are both cost-saving and feasible in developing countries include: · blood glucose control, particularly in type 1 diabetes. People with type 1 diabetes require insulin, people with type 2 diabetes can be treated with oral medication, but may also require insulin; · blood pressure control; and foot care. Other cost saving interventions include: · screening and treatment for retinopathy (which causes blindness) · blood lipid control (to regulate cholesterol levels) · screening for early signs of diabetes-related kidney disease and treatment."
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Various medicinal and diet/lifestyle interventions can be used to treat diabetes and costs are dependent the intervention administered. However there is evidence to show that antidiabetic interventions can be cost-effective in the treatment of diabetes6 (see additional considerations). No data on cost effectiveness were reported by the systematic reviews described above.	The cost effectiveness of antidiabetic interventions in adults (retrieved from the WHO guidelines Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010)(14) p.64): · Intervention = Life style intervention for type 2 diabetes Cost Effectiveness = 60 US$/QALY · Intervention = Optimal Glycemic control in clinic Cost Effectiveness = 1810 US$/QALY (SSA) · Intervention = ACE inhibitor for blood pressure control Cost Effectiveness = 620 US$/QALY (EAP) For more information: 'Best buys' and other recommended interventions to address noncommunicable diseases (NCDs) http://apps.who.int/iris/bitstream/handle/10665/259232/WHO-NMH-NVI-17.9-eng.pdf?sequence=1

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons(15)studies health equities in England, They found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment, and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	Depends on access to treatment especially in low- and middle-income countries

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Both antidiabetic medication and physical activity are already being used as treatment options for patients with diabetes. The evidence reviewed here shows that treatment for diabetes in the form of medications for glycaemic control has an unclear effect on cognitive function, no effect on dementia and increases risk of hypoglycaemic events. As such, the acceptability of antidiabetic medication interventions for reducing the risk of and cognitive decline and/or dementia may vary across stakeholders.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, both standard care and intensive glycaemic control are already being used in diabetic populations currently. Physical activity is also already being recommended as a treatment option for diabetes.	

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Risk reduction guidelines for cognitive decline and dementia

Evidence profile:
Treatment of dyslipidaemia and cognitive decline or dementia

Scoping question:

For adults with normal cognition or mild cognitive impairment and dyslipidaemia, is control of dyslipidaemia more effective than placebo or no intervention in reducing reduce the risk of cognitive decline and/or dementia?

Background

As the number of older adults increases worldwide, a rise in dementia and Alzheimer's disease (AD) has also been reported,[1] causing health, economic and social burdens.[2,3] In 2015, it has been estimated that there were 46.8 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050.[1] AD/dementia has been linked to modifiable, lifestyle-related, cardiovascular risk factors (CVRFs),[1-4] and since the management of CVD is still suboptimal in many countries, especially among older adults and no cure is available for AD, CVRFs management could be crucial in halting the rapid increase in the prevalence of dementia, as some projection models suggested.[5,6]

Elevated serum cholesterol is one of the key modifiable CVRFs. A third of ischaemic heart disease world-wide is attributable to dyslipidemia and it is estimated to be the cause of 2.6 million deaths (4.5% of total) per year, as well as a considerable proportion of disability.[7] The prevalence of raised total cholesterol among countries seems to correlate with wealth: in high-income countries, more than 50% of adults have elevated total cholesterol level, more than double of the rate in low-income countries.[7]

The idea that raised level of blood cholesterol could be related with an increased risk of dementia was already introduced in the mid-1970s.[8] Since then, a number of epidemiological studies have demonstrated a close relationship between high serum cholesterol levels and the onset of AD/dementia,[9-11] but results have been inconsistent, with other studies showing no or negative correlation.[12,13] Nonetheless, the best establish genetic factor[14] that increase susceptibility to sporadic, late-onset AD is the ϵ4 allele of apolipoprotein E (ApoE), a protein playing a key role in lipid metabolism and closely involved in the transport of cholesterol in the brain.

Based on the severity of the dyslipidemia, lifestyle or pharmacological approaches can be undertaken to reduce blood cholesterol. Weight reduction and decrease of saturated fats in the diet (decreasing the consumption of food of animal origin) are the most common and effective lifestyle recommendations.[15] However, dyslipidemia is often controlled and managed pharmacologically, with statins being the drugs of first choice. Several observational studies have investigated the possible beneficial effect of statins therapy in preventing dementia, but bias and heterogeneity hampered the overall quality of the evidence.[16-18] Recently, a re-analysis of statin use in AD patients from failed clinical trials suggested by trend that use of simvastatin may slow the progression of cognitive decline, and to a greater extent in people homozygotes for ApoE4.[19]

This review of systematic reviews was carried out to search, identify, and synthesise the evidence currently available on the efficacy of lifestyle and/or pharmacological interventions aimed at decreasing dyslipidemia in reducing the risk of dementia and/or cognitive impairment.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment and dyslipidemia, is treatment of dyslipidemia more effective than placebo or no intervention in reducing reduce the risk of cognitive decline and/or dementia?

- ✓ P: Adults with normal cognition or mild cognitive impairment with dyslipidemia
- ✓ I: Statins
  Lifestyle Intervention
- ✓ C: Placebo or no intervention
- ✓ O: *Critical*
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Dementia

  Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Date of search: 27th of April 2018

Search starting time: 31st December 2012

Full search terms

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Cholesterol OR Hypercholesterolemia OR lipoproteins OR HDL cholesterol OR LDL cholesterol OR triglycerides) AND (Behavior OR behaviour OR drug therapy OR pharmacologic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment OR statins OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Anticholesteremic agents)

Simplified search terms

(dementia OR MCI OR cognition OR Quality of Life OR ADL OR Adverse Effects OR Drop-out) AND cholesterol AND cholesterol lowering therapy

*Searches were conducted in the following databases**:

- Cochrane
- PubMed
- NICE Guidelines
- Embase
- PsycInfo
- Global Health Library (Including WHOLIS, PAHO, AIM, LILACS)
- Database of impact evaluations
- AFROLIB
- ArabPsycNet
- HERDIN NeON
- HrCak
- IndMED
- KoreaMed

- AJOL

* Please note that the EurasiaHealth database did not return any meaningful answer to the search.

List of systemic reviews identified by the search process

Included in GRADE[1] tables:

Comparison: Statins vs Placebo

McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016 Jan 4;(1):CD003160. doi: 10.1002/14651858.CD003160.pub3.

Comparison: Lifestyle Intervention vs No intervention

No systematic reviews were identified. The search focused also on identifying potential single trial publications focused on lifestyle interventions for the management of cholesterol reduction, but no intervention study specifically aimed at reducing cholesterol through lifestyle, which also included outcomes related to dementia and/or cognitive impairment, was identified.

[1] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO Table

Serial Number	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Justification for systematic review used
1	Statin treatment vs. placebo	Incidence of dementia	McGuinness B, et al. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016 Jan 4;(1):CD003160. doi: 10.1002/14651858.CD003160.pub3. Review.	Most recent (2-year-old) moderate quality, systematic review (Cochrane) assessing effect of statins on dementia incidence
		MCI	No relevant systematic review available.	N/A
		Cognitive function	McGuinness B, et al. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016 Jan 4;(1):CD003160. doi: 10.1002/14651858.CD003160.pub3. Review	Most recent (2-year-old) moderate quality, systematic review (Cochrane) assessing effect of statins on cognitive outcomes
		Quality of Life	No relevant systematic review available.	N/A
		Functional levels (ADL)	No relevant systematic review available.	N/A
		Adverse events	McGuinness B, et al. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016 Jan 4;(1):CD003160. doi: 10.1002/14651858.CD003160.pub3. Review	Most recent (2-year-old) moderate quality, systematic review (Cochrane) assessing adverse events
		Dropout Rates	McGuinness B, et al. Statins for the prevention of dementia. Cochrane Database Syst Rev. 2016 Jan 4;(1):CD003160. doi: 10.1002/14651858.CD003160.pub3. Review	Most recent (2-year-old) moderate quality, systematic review (Cochrane) assessing adverse events
2	Lifestyle intervention vs. no intervention	Incidence of dementia	No relevant systematic review available.	N/A
		MCI	No relevant systematic review available.	N/A
		Cognitive function	No relevant systematic review available.	N/A
		Quality of Life	No relevant systematic review available.	N/A
		Functional levels (ADL)	No relevant systematic review available.	N/A
		Adverse events	No relevant systematic review available.	N/A
		Dropout Rates	No relevant systematic review available.	N/A

Narrative descriptions of the studies that went into the analysis

GRADE table 1

McGuinnes et al.[20] carried out a systematic review to evaluate the efficacy and safety of statins for the prevention of dementia in people at risk of dementia due to their age (65-year-old or more). Extensive search and screening of the literature, which included several major healthcare databases, trial registers as well as grey literature, was conducted by two authors (McGuinness B and Passmore P) independently. The search included randomised, double-blind, placebo-controlled trials in which a statin was given for at least 12 months; trials comparing two different statins without a placebo.

The following outcome measures were considered in the systematic review.
Primary: objective diagnosis of dementia; objective diagnosis of AD according to standard criteria; objective diagnosis of VaD according to standard criteria; change in Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog) or other accepted objective and standardised tests of cognitive performance in people at risk of AD/VaD on treatment with statins; incidence and severity of adverse effects.
Secondary: change in cognitive status accounting for prior cholesterol level, ApoE genotype and cognitive level; participant-perceived quality of life; change in ADLs; change in behaviour.

Of the 346 references retrieved, 8 studies were potentially eligible after screening and finally 2 studies completely fulfilled the selection criteria set by the authors (the reason for exclusion of studies was described in detail). The two studies identified, HPS 2002[21] and PROSPER,[22] included 20,536 and 5,804 participants, had a mean follow-up time of 5 and 3.2 years, respectively, and were both deemed at low risk of bias for all the criteria considered (sequence generation, allocation, blinding, attrition, and publication). Although the two trials had either dementia and/or cognition as outcomes (as secondary outcomes), they were assessed through different measurement, therefore the authors could conduct the meta-analysis only on the outcome reporting about dropout rate due to adverse events.

Incidence of dementia was assessed only in the HPS2002 trial[21], where the treatment with statins did not show to have any effect on the number of developing dementia (OR 1.0 95% CI: -0.61 to 1.65). In the same study *cognition* was assessed through a Modified Telephone Interview for Cognitive Status (TIC-m, the output is a score ranging from 0 to 39, where the lower is the score the worse is the cognitive performance)[23] and the results were consistent with the dementia outcome showing no effect of the statin treatment on the cognitive performance (Mean Difference 0.02 95% CI: -0.12 to 0.16). The PROSPER study[22] only included cognitive outcomes measured through four different tests: *Mini Mental State Examination* (MMSE, score ranging from 0 to 30, the lower is the score the worse is the cognitive performance); *Stroop Colour Word Test* (measuring attention, the output is the total number of seconds required to complete the test); *Picture-Word Learning Test* (it measures immediate and delayed recall, the score ranges from 0 to 15 and the lower is the score the worse is the cognitive performance); and *Letter Digit Coding Test* (it measures processing speed and the output records the total number of correct entries completed in 60 seconds). Consistently with the first study, also in the PROSPER trials the treatment with statins showed no effect on cognitive performance (MMSE Mean Difference 0.06 95% CI: -0.04 to 0.16; Stroop test Mean Difference 0.8 95% CI: -0.4 to 2.0; Picture-Word Learning Test Mean Difference 0.02 95% CI: -0.12 to 0.16; and Letter Digit Coding test Mean Difference 0.01 95% CI: -0.24 to 0.23). The meta-analysis assessing *adverse events leading to drop-out* there was no evidence of a difference in withdrawal rates between arms (OR 0.94 95% CI 0.83 to 1.05).

Both studies were assessed for bias and deemed at low risk. However, the quality of the evidence was hampered by some key methodological limitations. First of all, cognitive outcomes were among the tertiary endpoint in both studies. HPS 2002[22] had no baseline cognitive data, and assessed cognition using only one cognitive test (TICS-m);[23] the study had dementia has an outcome but did not explain clearly the diagnostic criteria and event rates were very low, making the estimate for the effect of statin treatment on incidence of dementia imprecise. Furthermore, although PROSPER[22] used four different cognitive tests as outcomes, they were administered at different time points, and incidence of dementia was not included among the outcomes. Finally, the study was conducted on a selected population at high risk of dementia due to age, but neither study systematically assessed dementia at baseline, therefore, despite both attempted to exclude participants with pre-existing dementia or significant cognitive impairment, there is no guarantee that only dementia-free individuals were included. For this last reason the evidence was further downgraded from the quality level determined in the systematic review.

Additional Evidence

The evidence (low to moderate quality) retrieved from the analysis of the systematic review presented here above showed that statins treatment, in people with dyslipidemia and high risk of dementia due to age, seems to not have an effect on dementia incidence and/or cognition. However, a large body of observational evidence is available correlating high cholesterol with an increased and risk of dementia and, vice-versa, linking cholesterol lowering therapies with decreased risk.

In 2013, a meta-analysis[16] of prospective cohort studies including statins as main intervention, having dementia risk as outcome, which had to be expressed in as relative risk (RR) and corresponding 95% Cl, and identified until July 2011, was published. The search yielded eight studies (N=2851) that were included in the meta-analysis; studies were also formally assessed for heterogeneity (I^2- and Q-statistics) and publication bias (Begg rank correlation test). The results showed a significant association between statin use and reduction of dementia risk (RR 0.62; 95%Cl 0.43-0.81). No publication bias was detected, however the authors reported statistically significant heterogeneity (I^2 = 70.8% p = 0.001). The treatment with statins was associated with even lower risk of dementia in subgroup analysis that included studies with a longer mean follow-up (≥ 4 years; RR 0.56; 95% Cl 0.39-0.79), but in this case heterogeneity was still significant (I^2 = 76.3% p = 0.005); or studies with a larger sample size (≥350; RR 0.52; 95% Cl 0.36-0.67), in this case no significant heterogeneity was reported (I^2 = 27.6% p = 0.246).

In the same year, a systematic review was published[24] with the aim of describe the current molecular, epidemiological and genetic evidence of a link between dyslipidaemia and AD. The search identified 22 longitudinal studies on the association between serum lipid levels and development of AD later in life. Overall inconsistency was reported in the results, mostly due to discrepancies in the study design and in the parameters used for the assessment of dyslipidaemia (total cholesterol, HDL, LDL, triglycerides). However, the highest degree of inconsistency was shown in studies where the timespan between the serum lipid and the brain function assessments was the shortest, that is studies with a shorter follow-up and that measured cholesterolemia at older age. Instead, the studies that assessed the level of serum cholesterol at middle age and that, therefore, had a longer follow-up period showed a much stronger correlation between dyslipidemia and increased risk of AD.

More recently, a systematic review of the evidence related to risk factors associated with the onset and progression of AD was carried.[25] The search included: systematic reviews reporting on risk factors for disease onset; systematic reviews reporting on risk factors for disease; and primary studies reporting on non-genetic risk factors for disease onset. A total of 136 systematic reviews and 432 studies relevant for the range of risk factors considered were identified; of these, seven systematic reviews (five

deemed of sufficient quality to be included in the evidence) and three primary studies were identified to investigate the association between cholesterol and/or dyslipidemia and AD. Overall, evidence summarized in the identified systematic reviews suggested that elevated midlife total serum cholesterol was associated with an increased risk of AD. None of the primary studies, however, identified a statistically significant association between cholesterol and risk of AD.

Finally, Geifman and colleagues[19] investigated the effect of statins treatment on AD progression and cognitive decline. The main analysis was conducted on a dataset of integrated AD clinical trials. However, validation of the primary findings was conducted on two research cohorts (N=2570) which included participants without AD diagnosis at baseline.[26,27] In this dataset, statin use was associated with a lower risk of AD (HR = 0.8; 95% CI 0.68, 0.95; $p < 0.01$) and the prevalence of AD, at the end of follow-up, was significantly lower in subjects using statins compared to subjects with no known use of statins at baseline or throughout follow-up (24.8% vs 30.7%; $p < 0.0005$).

In conclusion, although evidence from RCTs in older adults seems to show that statin treatment does not have an effect on cognition (in either directions), a large body of observational evidence links dyslipidemia (especially at mid age) with an increased risk of dementia and supports a protective role of statin treatment on cognition and dementia incidence.

No evidence related to lifestyle interventions aimed at reducing dyslipidemia and dementia and/or cognitive outcomes was identified either at a systematic review or at a single RCT level.

WHO guidelines for general population

The WHO's Prevention and control of noncommunicable diseases: Guidelines for primary health care in low-resource settings (WHO PEN, 2012). http://www.who.int/nmh/publications/phc2012/en/ includes relevant recommendations for the general population for the prevention of myocardial infarction and stroke[35].

Package of Essential Noncommunicable (PEN) Disease Interventions for Primary Health Care in Low-Resource Settings Geneva, WHO, 2010. http://www.who.int/cardiovascular_diseases/publications/pen2010/en/

Primary prevention of heart attacks and strokes:

- Tobacco cessation, Regular physical activity 30 minutes a day, Reduced intake of salt <5 g per day, Fruits and vegetables at least 400g per day
- Aspirin, statins and antihypertensives for people with 10-year cardiovascular risk >30%
- Antihypertensives for people with blood pressure ≥160/100
- Antihypertensives for people with persistent blood pressure ≥140/90 and 10-year cardiovascular risk >20% unable to lower blood pressure through life style measures

Secondary prevention (post myocardial infarction):

- Tobacco cessation, healthy diet and regular physical activity

- Aspirin, angiotensin-converting enzyme inhibitor, beta-blocker, statin

Secondary prevention (post stroke):

- Tobacco cessation, healthy diet and regular physical activity.
- Aspirin, antihypertensive (low dose thiazide, angiotensin-converting enzyme inhibitor), and statin

GRADE Tables

GRADE table 1

Author(s): Mariagnese Barbera; Jenni Kulmala
Date: 04.06.2018
Question: ***Control of dyslipidemia through statin treatment compared to placebo for reducing risk of cognitive decline and/or dementia***
Setting: Community; randomised controlled trials
Bibliography: McGuinness B, Craig D, Bullock R, and Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Re. 2016 Jan :(1):CD003160. doi: 10.1002/14651858.CD003160.pub3.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**control of dyslipidemia**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Dementia (follow-up: mean 5 years; assessed with: Incident dementia)												
1	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	serious [1,b]	none	31/10269 (0.3%)	31/10267 (0.3%)	**OR 1.00** (0.61 to 1.65)	**0 fewer per 1,000** (from 1 fewer to 2 more)	⊕⊕◯◯ LOW	CRITICAL
Cognitive function (follow-up: mean 42 months; assessed with: MMSE; Scale from: 0 to 30, higher score = better outcome)												
1	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	not serious	none	2891	2913	-	MD **0.06 points higher** (-0.04 lower to 0.16 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognitive function (follow-up: mean 42 months; assessed with: Stroop colour word test; measured as time in seconds required to repeat the colour sequence, lower score = better outcome)												
1	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	not serious	none	2891	2913	-	MD **0.8 seconds higher** (-0.4 lower to 2 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**control of dyslipidemia**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Cognitive function (follow-up: mean 42 months; assessed with: Picture-word learning test; Scale from: 0 to 15, higher score = better outcome)												
1	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	not serious	none	2891	2913	-	MD **0.02 words higher** (-0.12 lower to 0.16 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognitive function (follow-up: mean 42 months; assessed with: Letter digit coding test; total number of correct entries completed in 30 seconds, higher score = better outcome)												
1	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	not serious	none	2891	2913	-	MD **0.01 correct entries lower** (-0.24 lower to 0.23 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Cognitive function (assessed with: Telephone Interview for Cognitive Status Score; Scale from: 0 to 39, higher score = better outcome)												
1	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	not serious	none	10269	10267	-	MD **0.02 points higher** (-0.12 lower to 0.16 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Dropouts due to adverse events (assessed with: Number of dropouts due to adverse events)												
2	randomised trials	not serious Figure two of systematic review[1]	not serious	serious [a]	not serious	none	600/13160 (4.6%)	641/13180 (4.9%)	**OR 0.94** (0.83 to 1.05)	**3 fewer per 1,000** (from 2 more to 8 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

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

Explanations

a. Downgraded due to review conducted on a selected population at high risk of cognitive decline.

b. Downgraded in the Cochrane review due to Imprecision. The study does not specify how the diagnosis of dementia was carried out and the event rate was very low.

References

1. McGuinness B, Craig D,Bullock R,Passmore P.. Statins for the prevention of dementia. Cochrane Database Syst Rev.; 2016.

Part 2: From evidence to decisions

Summary of Findings

Control of dyslipidemia through treatment with statins compared to placebo for reducing risk of cognitive decline and/or dementia

Patient or population: reducing risk of cognitive decline and/or dementia
Setting: Community
Intervention: Control of dyslipidemia through treatment with statins
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Control of dyslipidemia through treatment with statins**				
Incidence of dementia (Dementia) assessed with: Incidence of dementia follow-up: mean 5 years	**3 per 1,000**	**3 per 1,000**	**OR 1.00** (0.61 to 1.65)	20536 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Control of dyslipidemia through treatment with statins does not seem to reduce incidence of dementia.
Cognitive function (Cognition) assessed with: MMSE Scale from: 0 to 30 follow-up: mean 42 months	N/A	The mean cognitive function in the intervention group was **0.06 points higher** (0.04 lower to 0.16 higher)	-	5804 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Control of dyslipidemia through treatment with statins likely does not seem to improve cognitive function.

Control of dyslipidemia through treatment with statins compared to placebo for reducing risk of cognitive decline and/or dementia

Patient or population: reducing risk of cognitive decline and/or dementia
Setting: Community
Intervention: Control of dyslipidemia through treatment with statins
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Control of dyslipidemia through treatment with statins**				
Cognitive function (Cognition) assessed with: Stroop colour word test Scale from: - to - follow-up: mean 42 months	N/A	The mean cognitive function in the intervention group was **0.8 words higher** (0.4 lower to 0.2 higher)	-	5804 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Control of dyslipidemia through treatment with statins does not seem to improve cognitive function.
Cognitive function (Cognition) assessed with: Picture-word learning test Scale from: 0 to 15 follow-up: mean 42 months	N/A	The mean cognitive function in the intervention group was **0.02 words higher** (0.12 lower to 0.16 higher)	-	5804 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Control of dyslipidemia through treatment with statins does not seem to improve cognitive function.
Cognitive function (Cognition) assessed with: Letter digit coding test follow-up: mean 42 months	N/A	The mean cognitive function in the intervention group was **0.01 correct entries lower** (0.24 lower to 0.23 higher)	-	5804 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Control of dyslipidemia through treatment with statins does not seem to improve cognitive function.

Control of dyslipidemia through treatment with statins compared to placebo for reducing risk of cognitive decline and/or dementia

Patient or population: reducing risk of cognitive decline and/or dementia
Setting: Community
Intervention: Control of dyslipidemia through treatment with statins
Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Control of dyslipidemia through treatment with statins**				
Cognitive function (Cognition) assessed with: Telephone interview for cognitive status score Scale from: 0 to 39	N/A	The mean cognitive function in the intervention **group was 0.02 points higher** (0.12 lower to 0.16 higher)	-	5804 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Control of dyslipidemia through treatment with statins does not seem to improve cognitive function.
Dropouts due to adverse events (Dropouts/AEs) assessed with: Number of study discontinuations due to adverse events	**49 per 1,000**	**46 per 1,000**	**OR 0.94** (0.83 to 1.05)	26340 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Control of dyslipidemia through treatment with statins does not seem to have an effect on drop-out rates due to adverse events.

***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; **OR:** Odds ratio; **MD:** Mean difference

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

Evidence-to-Decision Table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Worldwide ageing of populations is strongly associated with dementia, causing major health, economic and social burdens. In 2015, it has been estimated that there were 50 million people with dementia in the world, and the number is predicted to double every 20 years, reaching 82 million in 2030 and 152 million in 2050.[1] Since no cure is available for Alzheimer's disease, the main cause of dementia, prevention could be crucial in halting the rapid increase in the prevalence of this condition and international experts have called upon world-wide governments to make prevention of dementia one of their key health priorities.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	There is evidence showing that the treatment with statins does not affect the risk of dementia (low quality) and/or cognitive decline (moderate quality). In the systematic review considered[20] only two RCTs were identified that investigated the effect of statins treatment on dementia and cognitive outcomes. Although both studies benefitted from quite large populations (more than 26000 participants in total), data related to diagnosis of dementia and cognitive performance were not pooled, due to differences in study design. Limitations due to indirectness were identified as the review specifically focused on individuals at high risk of dementia and/or cognitive decline (due to age). However, a large body of observational evidence has linked dyslipidemia to an increased risk of dementia and/or cognitive decline and found an association between control of dyslipidemia and reduction of dementia and/or cognitive decline risk. Indirect evidence suggests that managing dyslipidaemia in mid-life can help reducing the risk of cognitive decline and/or dementia.	Life-course perspective is crucial since there is no evidence of an effect in late-life, but in mid-life. Detecting dyslipidaemia earlier in life could have beneficial effects and that is why the timing of the intervention is particularly important.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is moderate quality evidence that the treatment with statins does not increase the incidence of serious adverse events that led to the discontinuation of the trials compared to the placebo. In this case, data from the 2 RCTs were pooled[20] and no difference between the intervention and control (placebo) group was identified.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The evidence gathered suggest that controlling dyslipidemia through statin treatment in older adults (65-year-old or more) does not seem to have an effect on the incidence of dementia (low quality evidence) and/or cognitive decline (moderate quality evidence). However the studies included suffer from several limitations, the most important being: 1. no clear criteria to define the diagnosis of dementia as outcomes where provided; 2. cognitive performance was not among the primary outcomes; 3. the evidence rated to the incidence of dementia was deemed of low quality due to the very small number of cases identified (3/1000); and 4. both studies were conducted on a selected population of individual at high risk of developing dementia but neither ascertained dementia at baseline in a systematic fashion, although in both cases attempted were made to exclude people with pre-existing dementia or significant cognitive impairment. However, the observational evidence clearly points towards a beneficial effect of reduction of dyslipidemia on the risk of dementia and/or cognitive decline. There is a complex association between blood lipids and risk of cognitive decline and/or dementia especially in relation to age. The evidence are mostly observational and pharmaco-epidemiological.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Cognitive impairment and dementia can have a major impact in the life not only of the person affected but also of the close network of family and friends, as well as caregivers and health professional in general.[28,29] Functional ability and dependency are playing are the major component of this effect. Furthermore, dementia, the main cause of disability and institutionalization among older adults[1], therefore reducing or delaying the onset of dementia could results in lower costs for public healthcare services. Patients, caregivers, and policy makers are likely to be the people who will value these recommendations the most.	
Balance of effects		

Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ● Varies ○ Don't know	Based on evidence from both observational and intervention studies the balance of the effect is towards the intervention as statin treatment showed negligible effect on adverse events and observational evidence links dyslipidemia control to reduction of dementia and/or cognitive decline. Complex relationship between blood lipids and risk of cognitive decline and/or dementia. Using statins in midlife to manage dyslipidaemia may have beneficial effects on the risk of cognitive decline and dementia.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The main costs of the intervention are related to the medication. Very recently, it has been estimated that about 400 USD is the annual cost for a statin treatment (all fills).[30] Lifestyle interventions to control dyslipidemia generally include weight-loss, healthy diet patterns and physical activity components. These interventions can therefore be cost-intensive depending how much supervision and support is required from healthcare professionals. However, no specific evidence on lifestyle interventions are available.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Statins are the most common medications regularly used for cholesterol lowering therapies. They are well established, and cost are well known.[30]	
Cost effectiveness Does the cost-effectiveness of the intervention favour the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Statin treatment in older adults (75-94 years old) is projected to be cost-effective for primary prevention of cardiovascular disease.[31] No evidence was found directly for the prevention of dementia and/or cognitive decline. If other outcomes, such as cardiovascular disease, are considered, statins treatment is cost-effective.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Lower socioeconomic groups are more likely to have earlier onset of dementia than higher socioeconomic groups. Older people from lower socioeconomic backgrounds are also more likely to experience cognitive dysfunction at earlier stages of cognitive decline and cognitive impairment, and will have fewer resources to cope with the symptoms than their counterparts from higher socioeconomic groups People from lower socioeconomic groups are more likely to live, work and age in physical and economic environments that do not support social connectedness, physical activity or mental stimulation. this can increase the risk of cognitive impairment and dementia in later life.[32] Based on this it is believed that interventions to reduce risk of cognitive decline and dementia will increase equity in health. Furthermore, women are disproportionally affected with AD. The larger proportion of older women who have AD and other dementias is explained primarily by the fact that women live longer, on average, than men.[33] Finally, low socioeconomic position (SEP) was associated with overall and rapidly increasing statin nonadherence among men. Conversely, in women, associations between SEP and nonadherence were weak and inconsistent. Group-based trajectory modelling provided insight into the dynamics of statin adherence and its association with SEP.[34]	
Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Although relatively safe, statins are known to have adverse events, being headache, altered liver-function tests, paraesthesia, and gastrointestinal effects, including abdominal pain, some of the most commonly reported. No evidence was available for lifestyle interventions. Acceptability could vary among countries and stakeholders. Lifestyle interventions may be more acceptable than statin treatment.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Prescription of statins is common and can be done by GPs in many countries. Cost represent the main barrier. Lifestyle interventions to control dyslipidemia generally include weight-loss, healthy diet patterns and physical activity. The main barriers for these types of intervention are costs, lack of motivation, lack of time, and physical limitations.	

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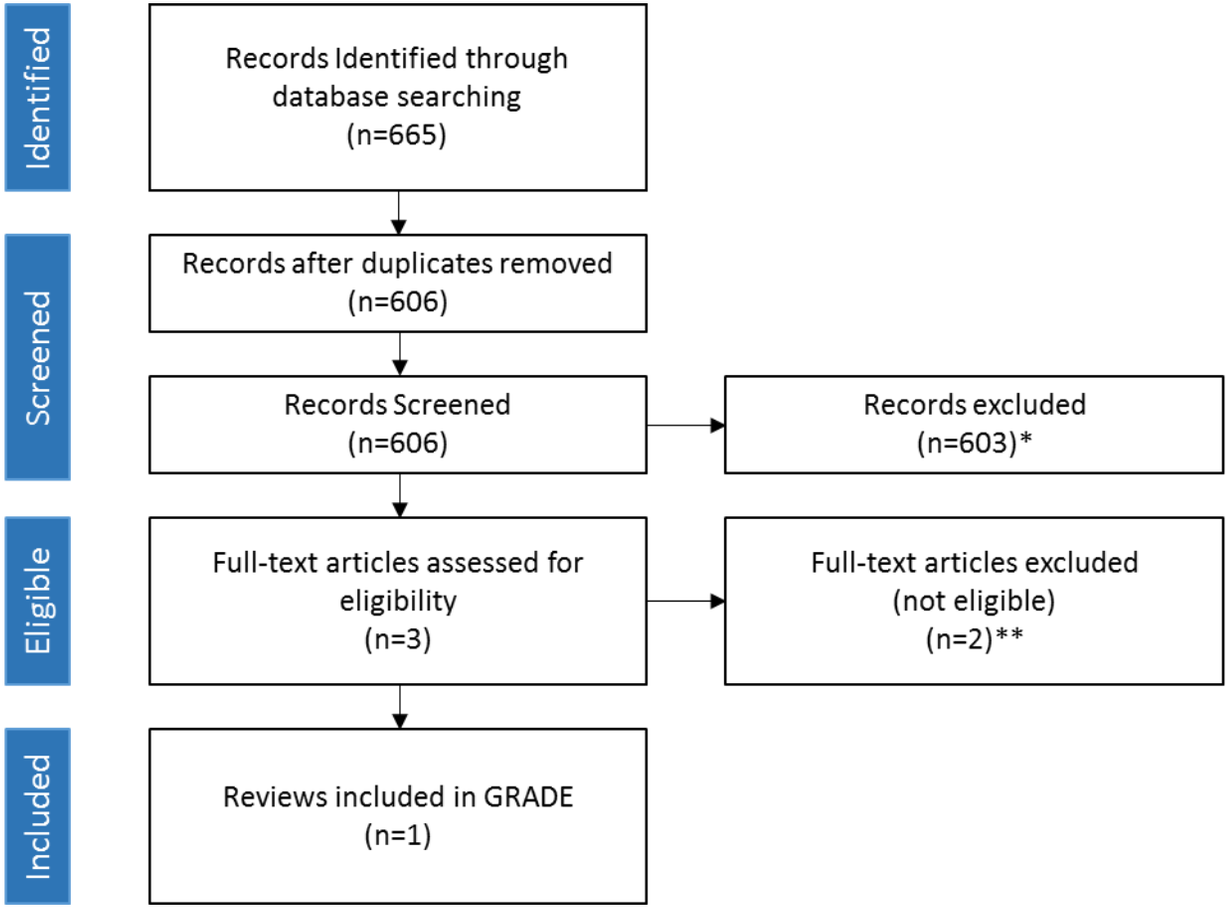
Annex: PRISMA[2] flow diagram for systematic review of the reviews – cognitive decline interventions[2]



* A meta-analysis of prospective cohort studies, a systematic review, and a systematic review of systematic reviews of observational evidence were included in the "Additional" Evidence section.

** One article, an observational study on a nulti-cohort dataset, was included in the "Additional Evidence" Section

[2] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). For more information: http://www.prisma-statement.org

Evidence profile:
treatment of depression for reducing the risk of and cognitive decline and/or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment and depressive disorder, is treatment of depression more effective than usual care, placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

There is a substantial body of evidence linking depression to cognitive decline and dementia. A review carried out as part of the World Alzheimer Report in 2014 combined 32 studies into a meta-analysis which looked at the effect of depression on the risk of incident dementia. This involved 62,568 participants with a median follow-up of five years (range 2 to 17). The review reported that the presence of depression nearly doubled the risk of dementia (pooled effect size = 1.97, 95% CI 1.67 to 2.32)[1].

The authors also carried out a meta-regression looking at follow-up time. They reported a trend toward smaller effect sizes in studies with longer follow-up suggesting that depression may have a prodromal role in dementia.

There are several potential explanations for the link between depression and cognitive impairment or dementia. Some of these include associations between depression, noradrenergic changes and white matter lesions, depression which stems from insight into impairment at early stages of decline, depression highlighting underlying deficits i.e. by reducing motivation and bringing its own cognitive deficits[2-5].

Currently, it is unclear whether treatment for depression reduces risk of dementia, although it has been suggested that some antidepressants may reduce incidence through decreasing amyloid production[6]. The following review provides a summary of the literature examining the effectiveness of treatment for depression in reducing dementia risk.

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment and moderate to severe depressive disorder, is treatment of depression more effective than usual care, placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

Populations

- Adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Interventions

- Pharmacological interventions to treat depression (antidepressant medication)
- Psychological interventions to treat depression (e.g. cognitive behavioural therapy, problem-solving therapy, interpersonal therapy, behavioural activation)

Comparison

- Care as usual or placebo or no intervention

Outcomes

- Critical:
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Incident Dementia
- Important:
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Searches using the following strategies (or similar) were conducted as follows

- (depression or depressive) and (systemati* or meta-analys*) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheimer's or Alzheimer*) and (treatment or therapy or pharmacotherapy or antidepressan* or antidepressiv*)[1]

Searches were conducted in:

- Medline
- Cochrane
- PsycInfo
- Embase
- NICE
- Global index medicus/Global Health Library
    - WHO regional data base
    - WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth

List of systematic reviews identified by the search process

Included in GRADE[2] tables

- Baune BT, Brignone M, Larsen KG. A Network Meta-Analysis Comparing Effects of Various Antidepressant Classes on the Digit Symbol Substitution Test (DSST) as a Measure of Cognitive Dysfunction in Patients with Major Depressive Disorder. The international journal of neuropsychopharmacology. 2018;21(2):97-107.

[1] Dates searched were 1 May 2016 - 1 May 2018. Additionally, the 2016 AHRQ review(7) was consulted for relevant records which systematically searched the literature between Jan 2009 – Sept 2016. In combination, the search period spanned >9 years. All abstracts were screened by two independent reviewers and with any discrepancies resolved by discussion. Full text articles were read by the same two independent reviewers and any discrepancy resolved by discussion.

[2] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO table

	Intervention/ Comparison	Outcomes	Systematic reviews	Explanations
1	Antidepressant versus placebo	Cognitive function • Global cognition (varied measures e.g. MMSE, ADAS-Cog, MDRS)	Baune BT, Brignone M, Larsen KG. A Network Meta-Analysis Comparing Effects of Various Antidepressant Classes on the Digit Symbol Substitution Test (DSST) as a Measure of Cognitive Dysfunction in Patients with Major Depressive Disorder. The international journal of neuropsychopharmacology. 2018;21(2):97-107.	Systematic review includes adults with major depressive disorder (unclear if they screened for MCI). Includes meta-analysis of RCTs. AMSTAR 2[3] rating is Critically Low*. *Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident dementia	No reviews identified.	No reviews identified.
		Quality of life	No reviews identified.	No reviews identified.
		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events	No reviews identified.	No reviews identified.

[3] AMSTAR: A Measurement Tool to Assess Systematic Reviews. More information: https://amstar.ca/index.php

		Drop-out rates	No reviews identified.	No reviews identified.
2	Psychological interventions to treat depression vs care as usual or no intervention	Cognitive function	No reviews identified.	No reviews identified.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident dementia	No reviews identified.	No reviews identified.
		Quality of life	No reviews identified.	No reviews identified.
		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events	No reviews identified.	No reviews identified.
		Drop-out rates	No reviews identified.	No reviews identified.

Narrative descriptions of the studies that went into the analysis

GRADE table 1: pharmacologic interventions to treat depression versus usual care or placebo

Baune et al[8] conducted a systematic review to appraise the current RCT evidence on pharmacological and non-pharmacological interventions for treating cognitive dysfunction in adults with Major Depressive Disorder (MDD). Screening and data-extraction were carried out by two independent reviewers and they state that studies were critically appraised using criteria based on the recommendations from the UK National Institute of Health and Care Excellence (NICE) guidelines. The authors state that there were 72 eligible trials, however, their focus was on the use of network meta-analysis and so they did not report details of the 72 trials or an assessment of bias. The authors reported that the Digit Symbol Substitution Test (DSST) was the most commonly used cognitive outcome and this was the basis for their meta-analysis (they used the standardised mean difference in DSST score as the common outcome). They report that the total number of patients in the trials where DSST was used as a primary or secondary cognitive endpoint ranged from 27 to 602 and that the time of DSST assessment varied from 3 to 24 weeks after baseline assessment. However, details of participant numbers, recruitment settings, length of follow-up etc are not provided separately for the constituent trials. The authors separate out the results by antidepressive drug rather than combining drugs. They report no non-pharmacological outcomes. For vortioxetine there were three trials included in the meta-analysis. Vortioxetine compared favourably to placebo in a random effects meta-analysis with a combined standardised mean difference of 0.34 (95% CI 0.18 to 0.49). For dulexetine (four trials) they reported a result of 0.13 (95% CI -0.03 to 0.28) and for sertraline, citalopram, escitaopram, phenelzine and nortripyline single trials, they reported results of -0.17 (95% CI -0.57 to 0.22), -0.04 (95% CI -0.33 to 0.26), -0.25 (95% CI -0.57 to 0.06), -0.02 (95% CI -0.52 to 0.48) and 0.01 (95% CI -0.56 to 0.58) respectively. The authors also report some drug-to-drug comparisons; however, it is unclear whether these represent usual care and so the results are not included here. The AMSTAR 2 rating of this review was Critically Low. It was missing details relating to individual studies and a discussion of the impact of bias on the outcomes reported.

GRADE table 2: psychological interventions versus usual care or no intervention

No systematic review was found.

GRADE table 1: Pharmacological interventions to treat depression versus usual care or placebo for reducing the risk of cognitive decline and/or dementia

Author(s): Ruth Peters, Nicole Ee, Lidan Zheng
Date: May 2018
Question: Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder
Setting: Community
Bibliography: Baune BT, Brignone M, Larsen KG. A Network Meta-Analysis Comparing Effects of Various Antidepressant Classes on the Digit Symbol Substitution Test (DSST) as a Measure of Cognitive Dysfunction in Patients with Major Depressive Disorder. The international journal of neuropsychopharmacology. 2018;21(2):97-107.

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Cognitive function (assessed with: Digit symbol substitution test (higher scores indicate better cognition))									
12	randomised trials	serious [a]	not serious [b]	serious [c]	serious [d]	none [e]	Outcome standardised mean difference in Digit Symbol Substitution Test (raw scores not provided) 3 studies are combined for vortioxetine vs placebo, result in favour of treatment SMD 0.34 (0.18:0.49). 4 studies are combined for duloxetine vs placebo NS result, SMD 0.13 (-0.03:0.28). Single studies vs placebo reported for sertraline -0.17 (-0.57:0.22), citalopram -0.04 (-0.33:0.26), escitalopram -0.25 (-0.57:0.06), phenelzine -0.02 (-0.52:0.48), nortryptyline 0.01 (-0.56:0.58)	⊕◯◯◯ VERY LOW[f]	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Incident MCI - not measured									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident Dementia - not measured									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Quality of life - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Functional level (ADL, IADL) - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Adverse events - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Drop-out rates - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT

CI: Confidence interval

Explanations

a. Risk of bias: Downgraded once as studies were critically appraised using NICE guidelines and the majority of studies had an unclear risk of bias or a high risk of bias in one or more of the 7 categories (statistical analyses, outcome selection and reporting, withdrawals, blinding, baseline comparability, allocation concealment and randomisation).

b. Inconsistency: Network meta-analysis conducted. Review authors reported risk of consistency was relatively small with only 2 potential loops identified in each of the by-treatment and by-class analysis. Vortioxetine was the only anti-depressant class with significant positive effects, all remaining were non-significant.

c. Indirectness: Downgraded once as only 9 of the 12 studies used placebo control; the review did not report on measures of global cognition and many of the pharmacological interventions included were single trials. Review authors report "large variability in cognitive outcomes" with DSST the only measure that would be appropriate for the analyses.

d. Imprecision: Downgraded once CIs for 4 classes of the anti-depressant classes were wide around the SMD. (However, CIs for Vortiozetine versus placebo and versus dulozetine were reasonable). Event rate not reported. Sample sizes generally small (n= 9 to 707)

e. Publication bias: No reason to believe bias is present, trial registries and unpublished literature was searched for relevant papers.

f. Although a meta-analysis was conducted, a combination of indirectness, imprecision and an unclear risk of bias resulted in a “Very Low” GRADE rating for this outcome.

GRADE table 2: Psychological interventions to treat depression versus usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Author(s): Ruth Peters, Nicole Ee, Lidan Zheng
Date: May 2018
Question: Psychological interventions versus usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or Mild Cognitive Impairment with moderate to severe depressive disorder
Setting: Community
Bibliography: -

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cognitive function									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident MCI									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident Dementia									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Quality of life									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Functional level (ADL, IADL)									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Adverse events									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Drop-out rates									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT

CI: Confidence interval

Additional evidence not mentioned in GRADE tables

Pharmacological, physical and psychological therapies

Salagre et al[9] conducted a systematic review with the aim of identifying articles assessing treatments which focused on the residual cognitive symptoms of MDD. Details of the screening and extraction process and assessment of bias are unclear. They included randomised and non-randomised studies of varied antidepressants with drug/drug and drug/placebo comparisons. They divide their results into pharmacological therapies (sub category antidepressant medication), physical therapies and psychological therapies. No meta-analyses were carried out.

Pharmacological treatment: In a narrative review of the 30 antidepressant studies, they conclude that the evidence supports a beneficial effect of Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Norepinephrine Reuptake Inhibitors (NRIs) or bupropion (a norepinephrine dopamine reuptake inhibitor) on cognition and suggest that Selective Serotonin Reuptake Inhibitors (SSRIs) would be especially useful in treating young patients. They conclude that special attention should be paid to vortioxetine and duloxertine whose action may be independent of effects on mood. Data on study design, number of participants, age (elderly or middle-aged), cognitive measures and main findings are reported however, no numerical results are given. The baseline status of the participants in the studies is also unclear as some were reported as having subjective cognitive complaints at baseline. The impact of bias is not evaluated.

Psychological treatment: The review included six randomised and non- randomised studies of cognitive remediation and one randomised trial of problem solving therapy in participants with MDD, treatment resistant depression and first episode depression. Comparator groups are unclear and mixed including healthy controls, drug treatment, other therapy and waiting list controls. Populations include in and out patients. Cognitive outcomes are mixed, no numerical data is provided and no meta-analysis was carried out. They conclude that preliminary evidence suggests precognitive effect of cognitive remediation. The impact of bias is not evaluated.

Antidepressants versus antidepressant with adjunctive treatment

Zheng et al[10] conducted a systematic review to look at the efficacy and safety of Huperzine A, a traditional Chinese medicine with acetyl cholinesterase inhibitory properties isolated from a genus of clubmosses (Huperzineserrta) in the treatment of MDD. Data screening and extraction was carried out independently by two authors and risk of bias was assessed using the Cochrane Risk of Bias scale. Two open label randomised controlled trials compared fluoxetine alone to fluoxetine with adjunctive huperzine A and reported cognitive outcomes (one reported results for memory using the Wechsler Memory Scale Revised Chinese version and the other for executive function using the Wisconsin Cart Sorting Test). Both trials reported in favour of huperzine A. The trials were reported as lasting 6 to 8 weeks and to have included 78 and 100 participants respectively. Both studies were considered to be at high risk of bias. No meta-analysis was carried out. One open label randomised controlled trial compared fluoxetine alone to fluoxetine with adjunctive huperzine A and reported both cognitive outcomes

(executive function) and quality of life using the general quality of life inventory of the World Health Organisation (WHOQOL-100). The results were in favour of Huperzine A. The trial was small (n=100) and of short duration and considered to be at high risk of bias

Cognitive Behavioural Therapy (CBT)

Simon et al[11] conducted a systematic review of the effectiveness of CBT on older adults with depression and cognitive deficits. They narratively reported that there is limited evidence regarding cognitive outcomes after CBT however there have been some reports of improved executive functioning[12] and problem solving skills[13, 14].

Other relevant guidelines

WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings: http://www.who.int/mental_health/mhgap/evidence/en/

Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset: https://www.nice.org.uk/guidance/ng16

Part 2: From evidence to decisions

Summary of evidence table 1

Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Patient or population: Adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Setting:

Intervention: Pharmacological interventions to treat depression (antidepressant medication)

Comparison: Usual care or placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Cognitive function assessed with: Digit symbol substitution test (higher scores indicate better cognition)	Outcome standardised mean difference in Digit Symbol Substitution Test (raw scores not provided) 3 studies are combined for vortioxetine vs placebo, result in favour of treatment SMD 0.34 (0.18:0.49). 4 studies are combined for duloxetine vs placebo NS result, SMD 0.13 (-0.03:0.28). Single studies vs placebo reported for sertraline -0.17 (-0.57:0.22), citalopram -0.04 (-0.33:0.26), escitalopram -0.25 (-0.57:0.06), phenelzine -0.02 (-0.52:0.48), nortryptyline 0.01 (-0.56:0.58)	(12 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d,e,f]
Incident MCI - not measured	No data available.	-	-

Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Patient or population: Adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Setting:

Intervention: Pharmacological interventions to treat depression (antidepressant medication)

Comparison: Usual care or placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Incident Dementia - not measured	No data available.	-	-
Quality of life - not measured	No data available.	-	-
Functional level (ADL, IADL) - not measured	No data available.	-	-
Adverse events - not measured	No data available.	-	-
Drop-out rates - not measured	No data available.	-	-

***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

Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Patient or population: Adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Setting:

Intervention: Pharmacological interventions to treat depression (antidepressant medication)

Comparison: Usual care or placebo

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

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

Explanations

a. Risk of bias: Downgraded once as studies were critically appraised using NICE guidelines and the majority of studies had an unclear risk of bias or a high risk of bias in one or more of the 7 categories (statistical analyses, outcome selection and reporting, withdrawals, blinding, baseline comparability, allocation concealment and randomisation).

b. Inconsistency: Network meta-analysis conducted. Review authors reported risk of consistency was relatively small with only 2 potential loops identified in each of the by-treatment and by-class analysis. Vortioxetine was the only anti-depressant class with significant positive effects, all remaining were non-significant.

c. Indirectness: Downgraded once as only 9 of the 12 studies used placebo control; the review did not report on measures of global cognition and many of the pharmacological interventions included were single trials. Review authors report "large variability in cognitive outcomes" with DSST the only measure that would be appropriate for the analyses.

d. Imprecision: Downgraded once CIs for 4 classes of the anti-depressant classes were wide around the SMD. (However, CIs for Vortiozetine versus placebo and versus dulozetine were reasonable). Event rate not reported. Sample sizes generally small (n= 9 to 707)

e. Publication bias: No reason to believe bias is present, trial registries and unpublished literature was searched for relevant papers.

f. Although a meta-analysis was conducted, a combination of indirectness, imprecision and an unclear risk of bias resulted in a “Very Low” GRADE rating for this outcome.

Summary of evidence table 2

Psychological interventions versus usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or Mild Cognitive Impairment with moderate to severe depressive disorder

Patient or population: Adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Setting: Community

Intervention: Psychological interventions to treat depression

Comparison: Usual care or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Cognitive function - not measured	No data available.	-	-
Incident MCI - not measured	No data available.	-	-
Incident Dementia - not measured	No data available.	-	-
Quality of life - not measured	No data available.	-	-
Functional level (ADL, IADL) - not measured	No data available.	-	-
Adverse events - not measured	No data available.	-	-
Drop-out rates - not measured	No data available.	-	-

Psychological interventions versus usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or Mild Cognitive Impairment with moderate to severe depressive disorder

Patient or population: Adults with normal cognition or mild cognitive impairment with moderate to severe depressive disorder

Setting: Community

Intervention: Psychological interventions to treat depression

Comparison: Usual care or no intervention

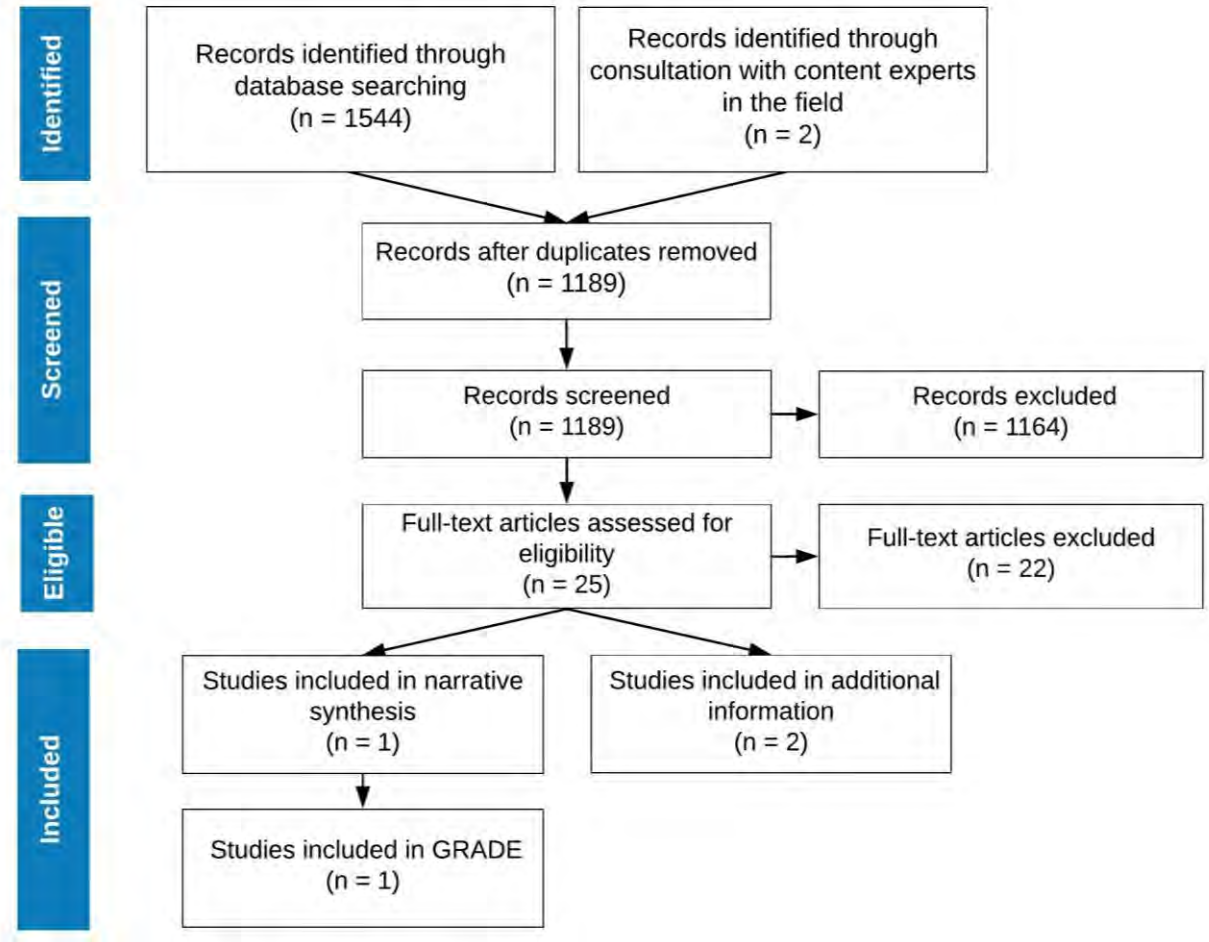
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

*__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

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

Annex: PRISMA[1] flow diagram for systematic review of reviews – treatment of depression



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Treatment of depression for reducing the risk of and cognitive decline and/or dementia

Evidence-to-Decision table

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds (1). Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. A review carried out as part of the World Alzheimer Report (2014) reported that the presence of depression nearly doubled the risk of dementia (pooled effect size = 1.97, 95% CI 1.67 to 2.32). (2)	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	*Desirable effects* **Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** No data on MCI or incident dementia. For cognitive function, the volume of evidence is high (12 RCTs, with 3 studies in vortioxetine, 4 studies in duloxetine, and single studies for sertraline, citalopram, escitalopram, phenelzine, nortriptyline) and overall quality of evidence is very low. A network meta-analyses (3) was conducted which found standardised mean difference in Digit Symbol Substitution Test (raw scores not provided). The review reported cognitive function was improved with vortioxetine (vs placebo) SMD 0.34 (0.18:0.49) and no effect for duloxetine SMD= -.13 (-0.03:0.28), sertraline SMD= -017 (-0.57:0.22), citalopram	A narrative review ((4)l) reported that the evidence supports a beneficial effect of Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Norepinephrine Reuptake Inhibitors (NRIs) or bupropion (a norepinephrine dopamine reuptake inhibitor) on cognition and suggest that Selective Serotonin Reuptake Inhibitors (SSRIs) would be especially useful in treating young patients. Mixed results were found with regards to psychological treatment for depression. One review (5) reported results in favour of huperzine A as a treatment for depression with positive cognitive outcomes, however the studies were considered to have a high risk of bias.

	SMD = -0.04 (-0.33:0.26), escitalopram SMD= -0.25 (-0.57:0.06), phenelzine SMD = -0.02 (-0.52:0.48), nortryptyline SMD = 0.01 (-0.56:0.58). Specifically, for the three studies of vortioxetine, which found significant improvement in cognitive function as measured on the DSST, the volume of evidence was low and the quality was moderate. There was no robust information on clinical significance. **Psychological interventions to treat depression compared to placebo or no intervention** No data available, inestimable.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	*Undesirable effects* **Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** No data on undesirable outcomes were reported by the systematic reviews described above. **Psychological interventions to treat depression compared to placebo or no intervention** No data available, inestimable.	Undesirable effects of antidepressants in general include (6) 1. Selective Serotonin Reuptake Inhibitors (SSRIs; e.g. fluoxetine) Serious side-effects (these are rare): marked / prolonged akathisia (inner restlessness or inability to sit still); bleeding abnormalities in those who regularly use aspirin and other non-steroidal anti-inflammatory drugs. Common side-effects (most side-effects diminish after a few days; none are permanent): restlessness, nervousness, insomnia, anorexia and other gastrointestinal disturbances, headache, sexual dysfunction. Cautions: risk of inducing mania in people with bipolar disorder 2. Tricyclic antidepressants (TCAs; e.g. amitriptyline) Serious side-effects (these are rare): cardiac arrhythmia. Common side-effects (most side-effects diminish after a few days; none are permanent): orthostatic hypotension (fall risk), dry mouth, constipation, difficulty urinating, dizziness, blurred vision and sedation.

		Cautions: risk of switch to mania, especially in people with bipolar disorder; impaired ability to perform certain skilled tasks (e.g. driving) – take precautions until accustomed to medication; risk of self-harm (lethal in overdose); less effective and more severe sedation if given to regular alcohol users.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** **Findings:** For cognitive function the certainty of the evidence is very low. No data on MCI, incident dementia, quality of life, adverse events, functional level or dropout rates. **Psychological interventions to treat depression compared to placebo or no intervention** **Findings:** No data available, inestimable.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability	A review conducted by Anderson et al 2009(7) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about	Additional sources like the Saga Survey (10) and Alzheimer's Research UK (11) have reported high percentage of people in the

○ Probably no important uncertainty or variability ● No important uncertainty or variability	declines in cognition or memory. Further studies in Australia (8) and the United Kingdom (9) (UK) and have shown a general trend of individuals being fearful of developing dementia. There is no evidence showing that individuals would oppose dementia risk reduction, of view cognitive decline favourably. Data from low and middle income countries is unavailable. There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● Don't know	**Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** No data on adverse effects was available e.g. drug-related side effects or interactions, so difficult to ascertain true balance of effects. May favour the use of vortioxetine to treat depression for reducing the risk of cognitive decline or dementia. Evidence does not favour other pharmacological interventions. **Psychological interventions to treat depression compared to placebo or no intervention** No data available, inestimable.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Various medications can be used to treat moderate to severe depression and costs are dependent the drug administered (see additional considerations). No data on resources required were reported by the systematic reviews described above.	The WHO (12) recommendations for antidepressive medications are listed below. The prices are taken from the International Drug Price Indicator Guide (13) and are listed as price per unit. · Amitriptyline è Tablet: 25 mg; Median Price US$ (Supplier/Buyer) = 0.0072/0.0288; 75mg. (hydrochloride) (price not listed). · Fluoxetine è Solid oral dosage form: 20 mg (as hydrochloride); Median Price US$ (Supplier/Buyer) = not listed/0.0168 Depression treatment can be provided by non-specialists in primary care in LMIC (mhGAP)

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Antidepressive medication is commonly prescribed as a treatment option for moderate to severe depression. They are included in the WHO model list of essential medicines (12) and their costs are listed in the International Drug Price Indicator Guide (13).	The WHO Factsheet on Depression (http://www.who.int/en/news-room/fact-sheets/detail/depression) states that: "There are effective treatments for moderate and severe depression. Health-care providers may offer psychological treatments (such as behavioural activation, cognitive behavioural therapy [CBT], and interpersonal psychotherapy [IPT]) or antidepressant medication (such as selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]). Health-care providers should keep in mind the possible adverse effects associated with antidepressant medication, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences. Different psychological treatment formats for consideration include individual and/or group face-to-face psychological treatments delivered by professionals and supervised lay therapists.

		Psychosocial treatments are also effective for mild depression. Antidepressants can be an effective form of treatment for moderate-severe depression but are not the first line of treatment for cases of mild depression. They should not be used for treating depression in children and are not the first line of treatment in adolescents, among whom they should be used with extra caution.”

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Various medications can be used to treat moderate to severe depression and costs are dependent the drug administered, however there is evidence to show that antidepressives can be cost-effective in the treatment of depression (14) (see additional considerations). No data on cost effectiveness were reported by the systematic reviews described above.	The regional cost effectiveness of antidepressants in adults (retrieved from the Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition (14): · Intervention = episodic treatment in primary care with older antidepressant drug (TCAs) à Cost per disability-adjusted life year averted or healthy life year gained, 2012 (US$) Sub-Saharan Africa = 1,410 Latin America and the Caribbean = 3,491 Middle East and North Africa = 3,171 Europe and Central Asia = 2,668 South Asia = 786

		East Asia and Pacific = 899 · Intervention = episodic treatment in primary care with newer antidepressant drug (SSRIs) à Cost per disability-adjusted life year averted or healthy life year gained, 2012 (US$) Sub-Saharan Africa = 1,395 Latin America and the Caribbean = 3,361 Middle East and North Africa = 3,057 Europe and Central Asia = 2,456 South Asia = 788 East Asia and Pacific = 894 Cost of combined medication and psychosocial interventions For depression, treatment in primary health care on an episodic basis costs between US$800 and US$3,500 per healthy life year gained; for a little more cost, as well as more overall health gain in the population, treatment on a proactive, maintenance basis is also a cost-effective alternative, because so many persons experience recurrent episodes (US$1,300–US$4,900 per healthy life year gained).
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons (15) studies health equities in England, they found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less	

○ Don't know	supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Varies; Drug-related side effects are a key consideration in acceptability of the intervention. There are no other apparent reasons for which pharmacological interventions for depression to reduce the risk of cognitive decline and/or dementia would not be acceptable to key stakeholders.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Yes, antidepressive medication already available and used in individuals with depression.	Diagnosis of depression may be challenging in some settings Continuous supply of antidepressants in primary care settings may be challenging in LMIC

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Guidelines for risk reduction of cognitive decline and dementia

Evidence profile:
treatment of hearing loss and cognitive decline and/or dementia

Scoping question:
For adults with normal cognition or mild cognitive impairment and hearing loss, is treatment of hearing loss more effective than usual care, or no intervention in reducing the risk of cognitive decline and/or dementia?

Background

Hearing loss is a prevalent age-related disorder. As the fourth leading cause of years lived with disability in the global population[1], it is estimated to affect one in three adults aged 65 and older, with this statistic growing annually[2]. The implications of hearing loss however, are often underestimated both at the individual and population level[3].

Hearing impairment has debilitating consequences on functional ability and social and emotional welfare. Deteriorations in hearing impact on individuals' ability to communicate with others, which in turn can result in feelings of frustration, isolation, loneliness[4]. Older adult populations who already experience the isolating effects of age-related factors such as diminished mobility, driving cessation, death of partners or living alone are particularly vulnerable to these psychosocial impacts.

Another significant effect of hearing loss is that of increased risk of cognitive decline or dementia[5]. A recent meta-analysis of prospective cohort studies showed that the relative risk of hearing impairment on incident Alzheimer's and MCI was 2.82 (95% CI 1.47 to 5.42)[6]. Additionally, a meta-analysis published by the Lancet Commission showed that hearing loss can almost double the risk of incident dementia (RR 1.94, 95% CI 1.38 to 2.73)[7]. Although the results should be interpreted with caution as this analysis was not preceded by a systematic review. Hearing loss and cognitive impairment or dementia, individually, and in combination, predict functional ability and burden of care; hearing loss interventions therefore have the potential to substantially improve outcomes for the elderly on multiple domains.

As the population ages, solutions to tacking dementia and increasing healthy life expectancy are key to sustaining global health and wellbeing. While there is a growing literature which suggests correcting hearing loss may reduce risk of cognitive decline and dementia in later life, the effects of hearing loss interventions on cognition remain unclear. Studies investigating the cognitive effects of hearing loss interventions in older persons are scarce, methodologically heterogeneous and reported findings have been inconsistent.

To synthesize the available evidence in this field, a systematic review of reviews was conducted. This review was undertaken with a view to provide evidence-based recommendations for the efficacy of hearing loss interventions in reducing cognitive decline and dementia.

Evidence profile: hearing loss interventions and cognitive decline and/or dementia

Part 1: Evidence review

Scoping questions in PICO format (population intervention, comparisons, outcome)

For adults with normal cognition or mild cognitive impairment and hearing loss, is treatment of hearing loss more effective than usual care, or no intervention in reducing the risk of cognitive decline and/or dementia?

Populations

- Adults with normal cognition or mild cognitive impairment with hearing loss

Interventions

- Interventions to treat hearing loss (e.g. hearing aids)

Comparison

- Care as usual or no intervention

Outcomes

- Critical:
  - Cognitive function (or cognitive test results using validated instruments)
  - Incident MCI
  - Incident Dementia
- Important:
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

Search Strategy

Searches using the following strategies (or similar) were conducted as follows

- (hearing aids OR Cochlear implants Or hearing implants) AND (hearing loss OR deafness OR hearing impairment OR hypoacusis OR intervention OR treatment) AND (dementia OR cognit* OR mild cognitive impairment OR Alzheimer's disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsycholog*)[1]

Searches were conducted in:

- Medline
- Cochrane
- PsycInfo
- Embase
- NICE
- Global index medicus/Global Health Library
    - WHO regional data base
    - WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth

List of systematic reviews identified by the search process

Included in GRADE[2] tables

- Cherko, M., Hickson, L., & Bhutta, M. (2016). Auditory deprivation and health in the elderly. *Maturitas, 88*, 52-57. doi:10.1016/j.maturitas.2016.03.00

[1] Dates searched were inception - 1 May 2018. Additionally, the 2016 AHRQ review[(8)] was consulted for relevant records which searched between Jan 2009 – Sept 2016. In combination, the search period spanned >9 years. All abstracts were screened by two independent reviewers and with any discrepancies resolved by discussion. Full text articles were read by the same two independent reviewers and any discrepancy resolved by discussion.

[2] GRADE: Grading of Recommendations Assessment, Development and Evaluation. More information: http://gradeworkiggroup.org

PICO table

	Intervention/Comparison	Outcomes	Systematic reviews used for GRADE	Explanation
1	Interventions to treat hearing loss (e.g. hearing aids) versus care as usual or no intervention • Hearing aids versus none (not specified)	Cognitive function (or cognitive test results using validated instruments) • Cognition (not defined)	Cherko, M., Hickson, L., & Bhutta, M. (2016). Auditory deprivation and health in the elderly. *Maturitas, 88*, 52-57. doi:10.1016/j.maturitas.2016.03.008	Systematic review is relevant. Includes samples of adults with normal cognition and hearing loss which are treated with hearing aids. Cognitive outcomes were included. AMSTAR 2[3] rating is Critically Low*. *Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria.
		Incident MCI	No reviews identified.	No reviews identified.
		Incident Dementia	No reviews identified.	No reviews identified.
		Quality of life • Measure not defined	Cherko, M., Hickson, L., & Bhutta, M. (2016). Auditory deprivation and health in the elderly. *Maturitas, 88*, 52-57. doi:10.1016/j.maturitas.2016.03.008	Systematic review is relevant. Includes samples of adults with normal cognition and hearing loss which are treated with hearing aids. Reported on quality of life measures. AMSTAR 2[3] rating is Critically Low*. *Despite the critically low AMSTAR rating, this review was included because it provides the best quality evidence available based on the relevant criteria.

[3] AMSTAR: A Measurement Tool to Assess Systematic Reviews. More information: https://amstar.ca/index.php

		Functional level (ADL, IADL)	No reviews identified.	No reviews identified.
		Adverse events	No reviews identified.	No reviews identified.
		Drop-out rates	No reviews identified.	No reviews identified.

Narrative descriptions of the studies that went into the analysis

GRADE table 1: hearing loss intervention versus usual care or no intervention

Cherko et al[9] conducted a systematic review to appraise the evidence on the impact of age-related hearing loss and hearing loss interventions on cognition and quality of life in the elderly. Searches were only conducted in one database, pubmed. The population of interest was adults aged over 65 years old. Screening was carried out by two independent reviewers. Of the 51 articles, only two included cognitive outcomes[10, 11] and another two reported quality of life measures[12, 13] in hearing aid users. The specific outcome measures employed were not reported. No meta-analyses were performed and results were reported narratively with no numerical data to support conclusions. Based on two studies including measures of cognitive function, the authors concluded that while hearing aids use was found to be associated with improvements in cognitive function[11], these benefits may be limited in that cognitive improvements have been shown to revert to baseline at one year follow up[12]. They also concluded that use of hearing aids in the elderly was associated with improvements in quality of life outcomes based on two studies[13, 14]. In addition to drawing on a limited number of primary studies, evidence from this review was of critically low quality as rated on the AMSTAR 2[14], due to flaws on several critical domains. These included the absence of a registered protocol prior to commencement of the review, inadequate search strategy, no justification of excluded studies, and the lack of a risk of bias assessment.

GRADE table 1: Treatment of hearing loss versus usual care or no intervention for reducing the risk of cognitive decline and/or dementia

Author(s): Nicole Ee, Ruth Peters
Date: May 2018
Question: Treatment of hearing loss compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hearing loss
Setting: Community
Bibliography: Cherko, M., Hickson, L., & Bhutta, M. (2016). Auditory deprivation and health in the elderly. Maturitas, 88, 52-57. doi:10.1016/j.maturitas.2016.03.008

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Cognitive function (or cognitive test results using validated instruments) (assessed with: Unclear)									
2	observational studies	serious [a]	not serious [b]	not serious [c]	serious [d]	publication bias strongly suspected [e]	This review searched pubmed only and provided a narrative review of two studies with cognitive outcomes. No numerical results are provided. The authors conclude that there is no conclusive evidence.	⊕◯◯◯ VERY LOW	CRITICAL
Incident MCI - not measured									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Incident Dementia - not measured									
-	-	-	-	-	-	-	No data available.	-	CRITICAL
Quality of life (assessed with: Unclear)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
2	observational studies	serious [a]	not serious [b]	not serious [c]	serious [d]	publication bias strongly suspected [e]	This review searched pubmed only and provided a narrative review of two studies with quality of life outcomes. No numerical results are provided. The authors conclude that there is no conclusive evidence.	⨁◯◯◯ VERY LOW	IMPORTANT
Functional level (ADL, IADL) - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Adverse events - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT
Drop-out rates - not measured									
-	-	-	-	-	-	-	No data available.	-	IMPORTANT

CI: Confidence interval

Explanations

a. Risk of bias: Downgraded once as primary study limitations were unclear and review lacks formal assessment of risk of bias.

b. Inconsistency: No meta-analysis conducted. No data on CIs or I^2 or effect sizes across primary studies but general conclusions were similar.

c. Indirectness: Population, intervention, outcomes and comparisons are relevant.

d. Imprecision: Downgraded once as sample sizes were small (n=34; 192); no numerical results on CIs or event rate.

e. Publication bias: Downgraded once as only published records in English were included; no formal assessment of publication bias was carried out.

Additional evidence not mentioned in GRADE tables

Cochlear implantation versus hearing aids

Miller et al[15] conducted a systematic review to investigate the impact of cochlear implantation on cognition in older adults. A literature search was conducted across eight databases in line with the methods detailed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[16]. The population included were adults aged 65 or older and individuals with hearing aids. Three studies were identified as meeting the review criteria, but the study methodology and quality of life measures employed were unclear. Cognition was primarily measured with varied versions of Wechsler Adult Intelligence Scale. Three studies included quality of life measures and demonstrated significant improvements post-cochlear implantation[17-19] . Only two studies measured cognitive function pre- and post-intervention[17, 18]**Error! Bookmark not defined.** and review authors concluded cognitive benefits of cochlear implantation were inconclusive. This evidence was of critically low quality according to the AMSTAR 2[14] checklist.

Computer-based auditory based training

Henshaw et al[20] conducted a systematic review to appraise the evidence for the efficacy of computer-based auditory based training to improve cognition in adults with hearing loss, with or without hearing aids. Searches were conducted in eight databases. Data extraction and screening was conducted by two independent reviewers. Of the 13 eligible articles only one RCT included cognition as an outcome[21], which was assessed with Listening span and the Stroop Task. While the primary study reported finding improvements in cognition, information on effect sizes for cognitive outcome measures or statistical test was not reported. The review authors highlighted that it was not possible to determine which elements of the auditory training resulted in improvements in cognition due to its hybrid nature. Due to the limited studies and lack of numerical data reported in primary studies, it is difficult to draw general conclusions about the effects of computer-based auditory training on cognition in adults with hearing loss. This evidence was of moderate quality according to the AMSTAR 2[14] checklist.

Other relevant guidelines

Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset: https://www.nice.org.uk/guidance/ng16

Part 2: From evidence to recommendations

Summary of evidence

Treatment of hearing loss compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hearing loss

Patient or population: Adults with normal cognition or mild cognitive impairment and hearing loss

Setting: Community

Intervention: Treatment of hearing loss

Comparison: Usual care or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Cognitive function (or cognitive test results using validated instruments) assessed with: Unclear	This review searched pubmed only and provided a narrative review of two studies with cognitive outcomes. No numerical results are provided. The authors conclude that there is no conclusive evidence.	0 cases 0 controls / exposed / unexposed (2 observational studies)	⨁◯◯◯ VERY LOW [a,b,c,d,e]
Incident MCI - not measured	No data available.	-	-
Incident Dementia - not measured	No data available.	-	-
Quality of life assessed with: Unclear	This review searched pubmed only and provided a narrative review of two studies with quality of life outcomes. No numerical results are provided. The authors conclude that there is no conclusive evidence.	(2 observational studies)	⨁◯◯◯ VERY LOW [a,b,c,d,e]
Functional level (ADL, IADL) - not measured	No data available.	-	-
Adverse events - not measured	No data available.	-	-

Treatment of hearing loss compared to usual care or no intervention for reducing the risk of cognitive decline and/or dementia in adults with normal cognition or mild cognitive impairment and hearing loss

Patient or population: Adults with normal cognition or mild cognitive impairment and hearing loss

Setting: Community

Intervention: Treatment of hearing loss

Comparison: Usual care or no intervention

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Drop-out rates - not measured	No data available.	-	-

***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

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

Explanations

a. Risk of bias: Downgraded once as primary study limitations were unclear and review lacks formal assessment of risk of bias.

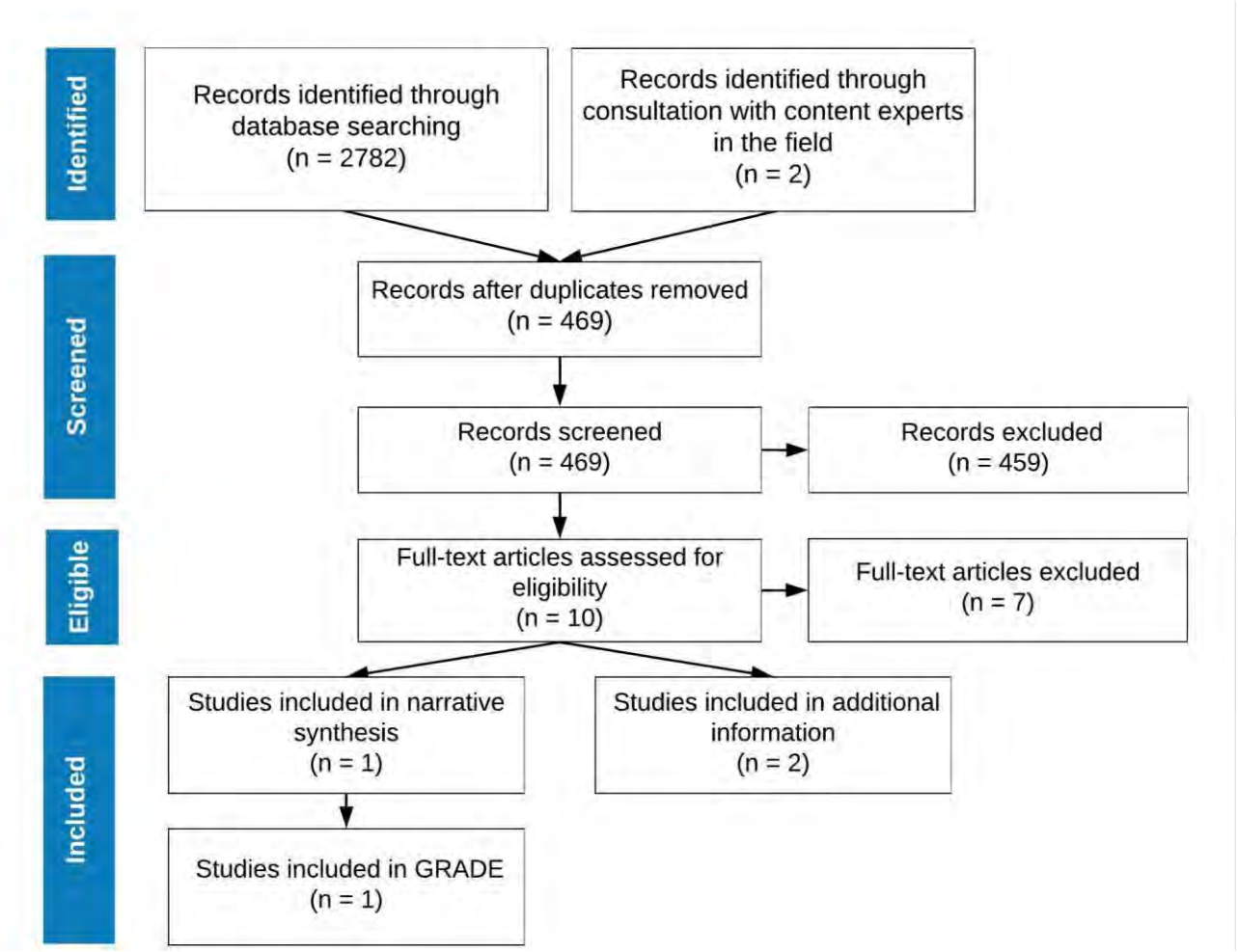
b. Inconsistency: No meta-analysis conducted. No data on CIs or I^2 or effect sizes across primary studies but general conclusions were similar.

c. Indirectness: Population, intervention, outcomes and comparisons are relevant.

d. Imprecision: Downgraded once as sample sizes were small (n=34; 192); no numerical results on CIs or event rate.

e. Publication bias: Downgraded once as only published records in English were included; no formal assessment of publication bias was carried out.

Annex: PRISMA[1] flow diagram for systematic review of reviews – treatment for hearing loss to reduce risk of dementia or cognitive decline



[1] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*, *6*(7), e1000097.

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Treatment of hearing loss and cognitive decline and/or dementia

Evidence-to-recommendation table

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds(1) Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. Hearing loss is a prevalent age-related disorder. It is the fourth leading cause of years lived with disability in the global population(2) It also increases the risk of cognitive decline/dementia(3). Hearing loss and cognitive impairment or dementia, individually, and in combination, predict functional ability and burden of care. Correcting hearing loss may reduce risk of cognitive decline and dementia in later life and also improve outcomes for the elderly on multiple domains.	A recent meta-analysis of prospective cohort studies showed that the relative risk of hearing impairment on incident Alzheimer's and MCI was 2.82 (95% CI 1.47 to 5.42) (4)
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	*Desirable effects:* For cognitive function and quality of life outcomes the volume and quality of evidence was very low. No data on MCI or incident dementia. No meta-analyses were conducted, and there was not robust information on clinical significance of results.	Primary review ((5).) reported that hearing aids use was found to be associated with improvements in cognitive function, however these benefits were limited. Cognitive improvements were shown to revert to baseline at one year follow up. The review also reported that the use of hearing aids in the elderly may be associated with improvements in quality of life, however there is no conclusive evidence. One review ((6)) reported that the use of cochlear implantation improved quality of life but the cognitive benefits were inconclusive. One review (Henshaw et al.) examined computer-

		based auditory based training and found poor quality evidence which was not possible to draw conclusions from.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	*Undesirable effects:* No evidence on functional level, dropout rates or adverse events.	Possible problems associated with of hearing aid may include background interference, or other issues with sound, volume and comfort.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	For cognitive function and quality of life, the certainty of evidence is very low. No evidence for MCI, dementia, functional level (ADL, IADL), adverse events, drop outs.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	A review conducted by Anderson et al 2009(7) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia(8)and the United Kingdom(9)(UK) and have shown a general trend of individuals being fearful of developing dementia. Data from low and middle income countries is unavailable. There is no evidence showing that individuals would oppose dementia risk reduction, or view cognitive decline favourably. Hence, there is no reason to believe there is important	Additional sources like the Saga Survey(10) and Alzheimer's Research UK(11) have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%).

	uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Does not favour either the intervention or the comparison (hearing aids may improve quality of life but the amount of evidence available is limited). No data on adverse effects was available.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	N/A (no conclusive evidence favouring the hearing aids as an intervention for reducing the risk of cognitive decline or dementia). For hearing aid interventions, there no data with respect to cost in the included studies. The resource requirements of hearing aid interventions are likely to involve associated costs for hearing assessments, audiology appointments and hearing aid devices; this will vary between healthcare policies and between different countries.	The NICE guidelines(12)tate that adults with suspected or diagnosed dementia or cognitive impairment should be referred for a hearing assessment, and list hearing aids as one of the treatment pathways for adults with hearing loss that affects their ability to communicate or hear, followed by audiology follow up appointments six to twelve week following fitting.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	N/A (No conclusive evidence favouring the hearing aids as an intervention for reducing the risk of cognitive decline or dementia). For hearing aid interventions, there is great uncertainty due to lack of data in the included studies. No formal evidence reporting on mean cost of hearing aid interventions to the individual or to government; this would depend on individual countries welfare rebates and policies. Also the resource costs are variable depending upon type of intervention.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Inconclusive, no high quality review evidence available on cost effectiveness of hearing aids. A cost effectiveness analysis conducted in 2008 (13) reported hearing aids in elderly populations was a cost effective strategy. It reported "incremental cost for gaining an additional hearing-related quality-adjusted life-years in women and men were US $13615 and 9702 respectively". However, the model was based on a small number of primary studies with data from higher income countries and modelled solely on hearing improvement. Another important cost-effectiveness factor which was not consider in this analysis is that many fitted with hearing aids do not wear them.(14) Data from low and middle income countries is unavailable.	The only review(15) was conducted on the cost-effectiveness compared digital hearing aids to analogue hearing aids. It showed no additional benefit of digital over analogue hearing aids.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons(16)studies health equities in England, They found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment, and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES	

○ Varies ○ Don't know	groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	A scoping review(14) and the Epidemiology of Hearing Loss Study has been shown that a large proportion hearing impaired elderly adults do not utilise their hearing aids.(17) The scoping review by McCormack et al 2013 suggested hearing aid value, fit and comfort and maintenance of the hearing aid, attitude, device factors, financial reasons, psycho-social/situational factors, healthcare professionals attitudes, ear problems, and appearance were some of the nominated reasons for this. Data from low and middle income countries is unavailable. Lack of public awareness about modifiable dementia risk factors can interfere with help seeking and public acceptability of these interventions.	A recent review by Cations et al, 2018(18) on the general public's perception and prevention of dementia suggests that knowledge about the potential for dementia risk reduction remains poor but may be improving over time. However, hearing correction was not a dementia prevention strategy covered by primary studies and individuals may lack awareness of the link between dementia and hearing impairment.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Both hearing aids and usual care/no intervention are already being used in hearing impaired populations currently. However, issues with compliance may cause barriers to proper implementation. A scoping review(14) and the Epidemiology of Hearing Loss Study has been shown that a large proportion hearing impaired elderly adults do not utilise their hearing aids(17) The scoping review by McCormack et al 2013 suggested hearing aid value, fit and comfort and maintenance of the hearing aid, attitude, device factors, financial reasons, psycho-social/situational factors, healthcare professionals attitudes, ear problems, and appearance were some of the nominated reasons for this. Based on the limited high quality evidence available on feasibility, it is not possible to make conclusions.	

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