Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Vascular Cognitive Impairment Evidence Tables

7th Edition, Update 2024

Management of Vascular Cognitive Impairment

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Vascular Cognitive Impairment Writing Group and in collaboration with the
Canadian Stroke Consortium CanStroke Recovery Clinical Trials Platform.

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Published Guidelines

Guideline	Recommendations
Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R Jr, Montero-Odasso M, Rockwood K, Rosa-Neto P, Seitz D, Sivananthan S, Smith EE, Soucy JP, Vedel I, Gauthier S; CCCDTD5 participants. **Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia.** ***Alzheimer's Dement*. 2020 Aug;16(8):1182-1195.** **(selected)**	*Risk Reduction* Nutrition 1a. We recommend adherence to a Mediterranean diet to decrease the risk of cognitive decline. 1B (91%) 1b. We recommend a high level of consumption of mono- and polyunsaturated fatty acids and a low consumption of saturated fatty acids, to reduce the risk of cognitive decline. 1B (92%) 1c. We recommend increasing fruit and vegetable intake. 1B (88%) *Physical Exercise* 2a. We recommend physical activity interventions of at least moderate intensity to improve cognitive outcomes among older adults. 1B (96%) 2b. We recommend aerobic exercise and/or resistance training of at least moderate intensity to improve cognition outcomes among older adults. 1B (94%) 2c. There is promising evidence that dance interventions and mind-body exercise (for example, Tai Chi, Qigong) of moderate dose improve cognitive outcomes among older adults but results from larger, high-quality trials are needed. 2B (84%) 3a. We recommend physical activity interventions involving aerobic exercise to improve cognitive outcomes among people with mild cognitive impairment (MCI). 2B (94%) 3b. We recommend aerobic exercise to improve cognitive outcomes among people with MCI. 2B (94%) 3c. There is promising evidence to support resistance training and mind-body exercise (eg, Tai Chi, Qigong) to improve cognitive outcomes among older adults with MCI but results from larger, high-quality trials are needed. 2C (83%) 4. We recommend physical activity interventions to reduce the risk of dementia, including Alzheimer's disease and vascular dementia. 2B (96%) *Psychosocial interventions* Individual Level 1. We recommend exercise (group or individual physical exercise) for people living with dementia.98-101 We cannot recommend any specific exercise duration or intensity at this time. 1B (93%) 2. Group cognitive stimulation therapy is an intervention for people with dementia which offers a range of enjoyable activities providing general stimulation for thinking, concentration, and memory usually in a social setting, such as a small group. We recommend considering group cognitive stimulation therapy for people living with mild to moderate dementia 2B (96%). 3. Psychoeducational interventions for caregivers aim at the development of problem-focused coping strategies while psychosocial interventions address the development of emotion-focused coping strategies. These can include education, counseling, information regarding services, enhancing carer skills to provide care, problem solving, and strategy development. We recommend considering psychosocial and psychoeducational interventions for caregivers of people living with dementia.2C (96%) Community Level 4. Dementia friendly organizations/communities are defined as the practice and organization of care/communities that is aware of the impact dementia has on a person's ability to engage with services and manage their health. It promotes the

Guideline	Recommendations
	inclusion of people living with dementia and their caregiver in decisions and discussions with the aim of improving outcomes for the persons living with dementia and their caregivers. We recommend considering the development of dementia friendly organizations/communities for people living with dementia. 2C (91%) 5. Case management is defined as the introduction, modification, or removal of strategies to improve the coordination and continuity of delivery of services which includes the social aspects of care. We recommend considering the use of case management for people living with dementia. 2B 93%
Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A. **Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.** ***Neurol.* 2018 Jan 16;90(3):126-135.** **(selected)**	For patients diagnosed with MCI, clinicians should perform a medical evaluation for MCI risk factors that are potentially modifiable (Level B). For patients diagnosed with MCI, clinicians should discuss diagnosis and uncertainties regarding prognosis. Clinicians should counsel patients and families to discuss long-term planning topics such as advance directives, driving safety, finances, and estate planning (Level B). Clinicians should assess for behavioral and neuropsychiatric symptoms in MCI and treat with both pharmacologic and nonpharmacologic approaches when indicated (Level B).
Gorelick PB, Scuteri A, Black SE, et al. **Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart association/America Stroke Association.** ***Stroke* 2011;42:2672-2713.**	8. Impact of Cardiovascular Risk Factors at Different Ages on the Risk of Cognitive Decline Recommendations 1. In people at risk for VCI, treatment of hypertension is recommended (Class I; Level of Evidence A). 2. In people at risk for VCI, treatment of hyperglycemia may be reasonable (Class IIb; Level of Evidence C). 3. In people at risk for VCI, treatment of hypercholesterolemia may be reasonable (Class IIb; Level of Evidence B). 4. In people at risk for VCI, it is uncertain whether treatment of inflammation will reduce such risk (Class IIb; Level of Evidence C). 9. Concomitant Clinical Vascular Disease *"Prevention of chronic vascular diseases may help reduce the population burden of vascular dementia. Initial and recurrent stroke significantly increase the risk of clinical dementia. Although this is caused in part by loss of brain tissue, it may also reflect a direct effect of vascular risk factors on both risk of stroke and cognitive function. That is, stroke could be serving as a marker of cumulative exposure to vascular risk factors. In an analogous manner, disease of the coronary or peripheral arterial circulations, atrial fibrillation, and clinically detectable renal and cardiac failure have each been associated with cognitive impairment."* 11. Prospects for Prevention of VCI and Alzheimer Disease by Risk Factor Control Hypertension Recommendations 1. In patients with stroke, lowering blood pressure is effective for reducing the risk of PSD (Class I; Level of Evidence B). 2. There is reasonable evidence that in the middle-aged and young-elderly, lowering blood pressure can be useful for the prevention of late-life dementia (Class IIa; Level of Evidence B). 3. The usefulness of lowering blood pressure in people >80 years of age for the prevention of dementia is not well established (Class IIb; Level of Evidence B).

Guideline	Recommendations
	Diabetes 1. The effectiveness of treating diabetes/hyperglycemia for the prevention of dementia is not well established (Class IIb; Level of Evidence C). Lipids Recommendations 1. The usefulness of treatment of hyperlipidemia for prevention of dementia is uncertain (Class IIb; Level of Evidence C). Other Recommendations 1. A Mediterranean-type dietary pattern has been associated with less cognitive decline in several studies and may be reasonable (Class IIb; Level of Evidence B). 2. Vitamin supplementation is not proven to improve cognitive function, even if homocysteine levels have been positively influenced, and its usefulness is not well established (Class IIb; Level of Evidence B). 3. Physical activity might be considered for the prevention of cognitive impairment (Class IIb; Level of Evidence B), but the usefulness of other lifestyle or vitamin interventions is uncertain (Class IIb; Level of Evidence B). 4. The effectiveness of antiaggregant therapy for VCI is not well established (Class IIb; Level of Evidence B).
Driving	
Canadian Medical Association. Determining fitness to operate motor vehicles: CMA Driver's Guide, 9th ed. Ottawa: Canadian Medical Association, 2017.	Section 8: Dementia and mild cognitive impairment • Diagnosis of dementia is not sufficient to withdraw driving privileges. • Moderate to severe dementia is a contraindication to driving. • Driving is contraindicated in people who, for cognitive reasons, have an inability to independently perform multiple instrumental activities of daily living or any of the basic activities of daily living. This degree of functional impairment describes a moderate or worse stage of dementia. • People with mild dementia should receive comprehensive off- and on-road testing at specialized driving centres. • No test, including the MMSE (Mini–Mental State Examination), has sufficient sensitivity or specificity to be used as a single determinant of driving ability. However, abnormalities on tests, including the MMSE, clock drawing, and Trails B, should trigger further in-depth testing of driving ability. • Patients with mild dementia who are deemed fit to continue driving should be re-evaluated every 6 to 12 months or sooner if indicated. • (Note recommendations are rated by CCCD3 at Grade B, Level 3: Fair evidence to support this manoeuvre. Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.)
Iverson DJ, Gronseth GS, Reger MA, Classen S, Dubinsky RM, Rizzo M et al. Subcomittee of the American Academy of Neurology. **Practice parameter update: evaluation and management of driving risk in dementia: report of the Quality Standards**	Q1. How strongly are global measures of dementia severity associated with decreased driving ability? The Clinical Dementia Rating Scale is established as useful for identifying patients at increased risk for unsafe driving (2 Class I and 2 Class II studies); however, a substantial number of patients with a CDR of 0.5–1 (41%–85%) will be found to be safe drivers by an on-road driving test (ORDT). An MMSE score of <24 is possibly useful in identifying patients at increased risk for unsafe driving (1 Class II study). Otherwise, the correlation between MMSE scores and driving performance is unclear, as data are conflicting. Q2. To what extent are patients and their caregivers able to assess driving ability and risk?

Guideline	Recommendations
Subcommittee of the American Academy of Neurology. ***Neurology*. 2010 Apr 20;74(16):1316-24.**	A caregiver's rating of marginal or unsafe is probably useful in identifying unsafe drivers (1 Class I study). A patient's self-rating of safe is established as not useful for determining that the patient is safe to drive (3 Class I studies) Q3. Which elements of the driving history are associated with decreased driving ability? A history of a crash in the previous 1 to 5 years or a traffic citation the previous 2 to 3 years is possibly useful in identifying patients with decreased driving ability (1 Class II and 5 Class III studies). A history of a crash is possibly more useful in identifying patients at risk for subsequent crashes than the presence of mild dementia alone (3 Class III studies). In mixed-population studies of aged drivers and drivers with mild dementia, reduced driving mileage is possibly associated with an increased risk of poor driving performance (1 Class II, 1 Class III study). In aged drivers, self-reported avoidance is possibly useful to identify drivers at increased risk (1 Class II study). The absence of self-reported avoidance is possibly not useful for identifying safe drivers (1 Class II and 1 Class III study). Aggressive or impulsive personality characteristics are possibly useful to identify patients with increased driving risk (1 Class II and 1 Class III study). Q4. Which neuropsychological tests provide additional prognostic information? Comprehensive neuropsychological assessment is another means of assessing global cognitive impairment that may be complementary to that of a bedside examination and an informant interview. While neuropsychological testing itself may better define dementia severity, there is insufficient evidence to support or refute the benefit of neuropsychological testing in evaluating driving risk in patients with dementia. Q5. Are there interventions that reduce driving risk? There is insufficient evidence to support or refute a benefit of interventional strategies for drivers with dementia. For patients with dementia, consider the following characteristics useful for identifying patients at increased risk for unsafe driving: • The CDR scale (Level A) • A caregiver's rating of a patient's driving ability as marginal or unsafe (Level B) • A history of traffic citations (Level C) • A history of crashes (Level C) • Reduced driving mileage (Level C) • Self-reported situational avoidance (Level C) • MMSE scores of <24 (Level C) • Aggressive or impulsive personality characteristics (Level C). For patients with dementia, consider the following characteristics not useful for identifying patients at increased risk for unsafe driving: • A patient's self-rating of safe driving ability (Level A) • Lack of situational avoidance (Level C)

Evidence Tables

Selected Modifiable Risk Factors for Dementia

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hypertension					
Ou et al. 2020 **China** **Systematic review &meta-analysis**	Mean NOS score was 7	209 prospective studies (of which 136 were eligible for meta-analysis, 2, 214,814 participants), including persons with normal cognition at study entry. Mean age ranged from 35.3 to 93.2 years, 46.6% were women.	The associations between hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood pressure variability and dementia were examined, with adjustment for age, gender, and educational level	**Primary outcomes:** Dementia	*Midlife hypertension* The risk of dementia was increased significantly in persons with hypertension (RR=1.20, 95% CI 95% CI, 1.06–1.35). A dose-response analyses including the results of 5 studies indicated the risk of cognitive impairment and dementia increased by >34% in persons with midlife systolic BP >130 mmHg. *Late life hypertension* The risk of dementia and MCI was not increased significantly in persons with hypertension (RR=1.02, 95% CI 0.94-1.10 and RR= 1.19, 95% CI, 0.98–1.43, respectively). The risk of vascular dementia was increased significantly in persons with hypertension (RR=2.12, 95% CI, 1.50–2.99). High SBP, low DBP, excessive BP variability, and orthostatic hypotension were all associated with an increased risk of dementia.
Walker et al. 2019 **USA** **Retrospective study**	NA	4,761 middle-aged participants (45-65 years) included in the ARIC cohort. Mean age at visit 5 was 75 years, 59% were women.	The association between midlife/late-life blood pressure and dementia was examined over the course of 24 years, represented by 5-6 in-person visits from (1987-1989 to 2016-2017). 5 groups were assembled. 1) midlife normotension and late-life hypertension (n=1,559), 2) midlife and late-life hypertension (n=1,030), 3) midlife normotension and	**Primary outcome:** Dementia onset For persons attending a 6th visit (n=3,265), dementia diagnosis was based on a comprehensive neuropsychological battery and an informant interview For persons who did not attend visit 6,	There were 516 (11%) incident dementia cases between visits 5 and 6. Rate of dementia incidences (per 100-pertson years) were: Group 1: 1.99 (95% CI, 1.69-2.32) Group 2: 2.83 (95% CI, 2.40-3.35) Group 3: 2.07 (95% CI, 1.68-2.54) Group 4: 4.26 (95% CI, 3.40-5.32) Group 5: 1.31 (95% CI, 1.00-1.72) Compared with persons who were normotensive in mid and late life, the risk of incident dementia was increased significantly in those with midlife

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			late-life hypotension (n= 927), 4) midlife hypertension and late-life hypotension (n=389) and 5) midlife normotensive and late-life normotensive (n=833). Hypertension was defined as SBP>140 mm Hg or DBP> 90 mm Hg. Hypotension was defined at visit 5 as SBP < 90 mm Hg or DBP <60 mm Hg At visits 5 and 6, participants underwent a comprehensive cognitive and functional assessment	dementia was identified using the 6-Item Screener, Ascertain Dementia 8-Item Informant Questionnaire, hospital discharge codes, and death certificates	and late-life hypertension (adj HR=1.49, 95% CI 1.06 to 2.08) and those with midlife hypertension and late-life hypotension (adj HR=1.62, 95% CI 1.11 to 2.37).
McGrath et al. 2017 **USA** **Prospective cohort study**	NA	1,440 participants (53% women, mean age 69 years) from the Framingham Offspring participants who were free of dementia at study entry.	Participants attended 5 consecutive examinations at 4-year intervals starting at midlife (1983–1987, mean age 55 years) until late life (1998–2001, mean 69 years) and who were followed up for incident dementia. The effect of midlife hypertension (≥140/90 mm Hg), late life hypertension, lower late life blood pressure (<100/70 mm Hg), and the persistence of hypertension during mid- to late life on the development of dementia was examined.	**Primary outcome:** Incident dementia (using DSM-IV criteria) adjusted for age, sex, education, cardiovascular disease, and *APOE4* carrier status.	Mean duration of follow-up was 8 years. 107 people developed dementia. Both midlife systolic hypertension and persistence of systolic hypertension into late life were associated with an elevated risk of incident dementia (HR=1.57, 95% CI 1.05-2.35 and HR=1.96, 95% CI 1.25-3.09, respectively). Each 10-mmHg increment in SBP during midlife was associated with a significantly increased risk of dementia (HR=1.17, 95% CI 1.05–1.31). A steep decline in systolic blood pressure in late life in persons who were normotensive in midlife was also associated with a significantly increased risk of dementia (HR= 2.40, 95% CI 1.39–4.15).
Diabetes					
Chatterjee et al. 2016 **Australia**	NOS scores ranged from 6 to 9.	14 studies, including 2,310,330 individuals recruited from the general population, without dementia. Mean age ranged	The risk of dementia in persons with diabetes (versus no diabetes) was examined by pooled analysis, stratified by sex. Most studies adjusted	**Primary outcomes:** Incident all-cause dementia, vascular dementia, and nonvascular dementia	During a mean duration of follow-up, ranging from 3-15 years, there were 102,174 incident cases of dementia, including 9,253 cases of vascular dementia and 90,233 cases of nonvascular dementia.

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Systematic review & meta-analysis		from 43 to 83 years. 48% were women. There were 683,962 persons with diabetes.	for age, systolic blood pressure and BMI, at minimum). (Neither the duration of diabetes, nor glycemic control achieved through medication uses were adjusted for).		The risk of dementia in persons with diabetes was increased significantly (RR=1.68, 95% CI 1.64–1.71 in women and RR=1.61, 95% CI 1.42– 1.83 in men). The risk of vascular dementia was significantly higher in persons with diabetes (RR=2.34, 95% CI 1.86–2.94 in women and RR=1.73, 95% CI 1.61–1.85 in men). The risk of nonvascular dementia was significantly higher in persons with diabetes (RR=1.53, 95% CI 1.35–1.73 in women and RR=1.49, 95% CI 1.31–1.69 in men). Women with diabetes had a significantly higher risk for the development of vascular dementia than men (multiple-adjusted RRR=1.19, 95% CI 1.08–1.30, $p < 0.001$).
Smoking					
Gottesman et al. 2017 **USA** **Prospective study** ***ARIC***	NA	15,744 participants aged 44 to 66 years at baseline, recruited from 1987-1989 from 4 communities. 55.2% of the sample were women.	Demographic and vascular risk factors were measured at baseline (obesity, smoking, diabetes, prehypertension, hypertension, and hypercholesterolemia) and the presence of the APOE ε4 genotype. After the baseline visit, participants had 4 additional in-person visits, for a total of 5 in-person visits. Data from 2015-2016 was used to assess the association between risk factors and the development of incident dementia.	**Primary outcome:** Incident dementia	There were 1,516 incident cases of dementia. Mean age at baseline was 57 years, 57% were women. Midlife smoking was associated with an increased risk of dementia (HR=1.41, 95% CI, 1.23-1.61).
Overweight/obesity					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ma et al. 2020 **UK** **Prospective study**	NA	6,582 participants included in the English Longitudinal Study of Ageing (ELSA) aged ≥50 years without dementia at baseline.	BMI was measured at baseline and categorized into normal weight (18.5– 24.9), overweight (25–29.9) and obese (>30). Waist circumference (WC) was also measured, whereby abdominal obesity was defined as WC > 88 cm for women and >102 cm for men. The association between baseline BMI levels or abdominal obesity and dementia, was assessed.	**Primary outcome:** Incident dementia	Mean duration of follow-up was 11.4 years. 453 people (6.9%) developed dementia during follow-up. In the fully adjusted model (age, sex, *APOE E4*, education, marital status, smoking, physical activity, hypertension and diabetes at baseline), the risk of dementia was increased significantly in persons who were overweight (RR=1.27, 95% CI 1.03-1.51) and obese (RR=1.31, 95% CI 1.03-1.59), compared with persons who were normal weight. The risk of incident dementia was increased significantly in women with abdominal obesity at baseline (HR=1.39; 95% CI, 1.12–1.66), but not men (HR= 0.84; 95% CI, 0.55–1.19). The risk of dementia was significantly higher in persons who were both obese and had a high WC (HR=1.28, 95% CI 1.03- 1.53).
Albanese et al. 2017 **Switzerland** **Systematic review & meta-analysis**	Across 7 domains of bias assessed, the methodological quality was low in at least one domain in 17 studies	19 prospective studies including 589,649 participants.	BMI was measured at baseline (mean age ranged from 43 to 59 years) and was categorized into underweight (≤18.5) normal weight (>18.5 to <25), overweight (≥25 to <30) and obese (≥30). The risk of midlife weight and incident dementia in later life (≥65 years) was assessed.	**Primary outcome:** Incident dementia	There were 2,040 incident dementia cases over an average of 42 years of follow-up. Compared with persons who were normal weight, the risk of dementia was increased in those who were underweight (RR=1.39; 95% CI 1.13–1.70) and obese (RR=1.33; 95% CI, 1.08–1.63), but not overweight (RR=1.07; 95% CI, 0.96–1.20). Data from 12 studies were included.
Alcohol use					
Sabia et al. 2018 **UK** **Prospective study**	NA	9,087 participants in the Whitehall II study, aged 35-55 years at study entry (1985-88). Mean age was 50.3, 32% were women.	Alcohol consumption was classified based on the mean of 3 assessments between 1985/88 and 1991/93 (midlife), as abstinence, 1-14 units/week, and >14 units/week.	**Primary outcome:** Incident dementia Models were adjusted for age, sex, ethnicity, education, occupational position, marital status,	During a mean duration of 23 years of follow-up, there were 397 cases of dementia. Mean age at dementia diagnosis was 75.6 years. Compared with persons who consumed 1-14 units/week, in midlife, the risk of dementia was increased significantly in abstainers (HR=1.45, 95% CI 1.12 to 1.86), but not in those consuming

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				physical activity, smoking status, fruit and vegetable consumption, SBP, cholesterol, diabetes, BMI, general health questionnaire score, cardiovascular disease, and cardiovascular disease drugs	>14 units/week (HR=1.02, 95% CI 0.77 to 1.35); however, in those consuming >14 units/week, the risk increased per 7 units of alcohol (HR=1.18, 95% CI 1.04 to 1.34). The excess risk of dementia associated with abstinence in midlife was partly explained by cardiometabolic disease.
Physical Activity					
Kivimäki et al. 2019 **UK** **Participant-level meta-analysis**	NA	404, 840 people included in 19 prospective studies, without dementia. Mean age was 45.5 years, 57.7% women.	The association between physical inactivity and dementia was examined using data from studies that included self-reported leisure-time physical activity at baseline and dementia status at follow-up, that was obtained through national hospital admissions, death registries and medical billing codes for dementia.	**Primary outcomes:** Incident all-cause dementia and Alzheimer's disease **Secondary outcome:** Incident cardiometabolic disease (diabetes, coronary heart disease, and stroke)	Mean duration of follow-up was 14.9 years. During 6.0 million person-years at risk, there were 2,044 incident cases of all-cause dementia. The number of incident cases of Alzheimer's disease was 1,602 in 5.2 million person-years. The prevalence of physical inactivity was 40.5%. Adjusting for age, sex, ethnicity, and socioeconomic status/ education, the risk of all-cause dementia was significantly higher in inactive persons compared with active persons (HR=1.40, 95% CI 1.24 to 1.59), when duration of follow-up was <10 years, but not when follow-up was ≥10 years (HR=1.01, 95% CI 0.89 to 1.13). The pattern of results was similar for Alzheimer's disease. The risk of stroke was significantly higher in inactive people with follow-up of < 10 years and ≥10 years (adj HR=1.49, 95% CI 1.33 to 1.67 and adj HR=1.16, 95% CI 1.05 to 1.27, respectively).
Sofi et al. 2011 **Italy**	NA	15 prospective cohort studies (n=33,816) including participants without dementia at baseline. 14	The association between physical activity (assessed at baseline using self-reported questionnaires) and cognitive	**Primary outcome:** Cognitive decline or cognitive impairment.	Duration of follow-up ranged from 1-12 years, during which time, 3210 cases of incident cognitive decline were reported.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic Review & Meta-analysis		studies included participants >65 years. Studies included men only (n=5), women only (n=5) and both sexes (n=5)	function assessed at baseline and end of study follow-up using MMSE, Mental Status Questionnaire and Clifton Assessment Procedure for the elderly (CAPE)	Analyses were adjusted for age, gender, education and other potential confounders	Compared to those who reported being sedentary, participants who reported a high level of physical activity at baseline were at significantly reduced risk of cognitive decline (HR=0.62, 95% CI 0.54 to 0.70, p<0.001), as were those who reported low-to-moderate levels of physical activity (HR 0.65, 95% CI 0.57 to 0.75, p<0.001).
Middleton et al. 2008 **Canadian Study of Health & Ageing** **Prospective study**	NA	6,434 participants, without dementia, ≥65 years, recruited from the community from 1991-92 from 10 provinces	4,683 participants (including those from Newfoundland) completed a 5-year follow-up (1996-97). Those who developed dementia were identified using a 3-stage process. The association between physical activity (PA) and incident dementia was examined. PA was classified as low, moderate or high, based on frequency and intensity of exercise. (High and moderate PA levels were subsequently collapsed to moderately high).	**Primary outcome:** Cognitive impairment-no dementia (CNID), Vascular cognitive impairment-no dementia (VCI ND), Mild Cognitive Impairment (MVI) and other	At the end of 5 years 3,935 participants remained cognitively intact, 464 had developed CIND, 163 developed VCI-ND, 100 had MCI, 284 had developed dementia, and 1,276 had died. Moderately-high levels of PA were associated with a lower risk of CIND and VCI-ND compared with low PA, after adjusting for age, sex, education level, use of NSAIDS and vascular risk factor index (OR=0.73, 95% CI 0.59-0.91 and OR=0.59, 95% CI 0.40-0.88, respectively). The risk of MCI was not significantly reduced (OR=0.96, 95% CI 0.62-1.47). When stratified by sex, moderate-high levels of PA vs. low PA were not protective for CIND, VCI-ND or MCI among men. The risk of CIND and VCI-ND among women with moderate-high PA was significantly reduced compared with low PA (OR=0.62, 95% CI 0.46-0.84 and OR=0.34, 95% CI 0.18-0.63, respectively).
Laurin et al. 2001 **Canadian Study of Health & Ageing** **Prospective study**	NA	6,434 participants, ≥65 years, recruited from the community from 1991-92 from 10 provinces, without dementia	4,615 participants completed a 5-year follow-up (1996-97), excluding those from Newfoundland. Those who developed dementia were identified using a 3-stage process. The association between physical activity (PA) and incident dementia was examined. PA was classified as low, moderate or	**Primary outcome:** Cognitive impairment-no dementia (CNID), Alzheimer's disease (AD), Vascular dementia (VaD), any dementia	At the end of 5 years 3,894 participants remained cognitively intact, 436 had developed CIND, 285 had developed dementia, 1,172 had died and there were 647 non-responders. PA was protective for the development of dementia. Using no PA as the reference standard, the odds of CIND were: Low PA OR=0.66, 95% CI 0.46-0.96 Moderate PA OR=0.67, 95% CI 0.52-0.87

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			high, based on frequency and intensity of exercise. Models were adjusted for age, sex and education level		High PA OR=0.58, 95% CI 0.41-0.93 P for trend <0.001 Using no PA as the reference standard, the odds of AD were: Low PA OR=0.67, 95% CI 0.39-1.14 Moderate PA OR=0.67, 95% CI 0.46-0.98 High PA OR=0.50, 95% CI 0.28-0.90 P for trend 0.02 Using no PA as the reference standard, the odds of any dementia were: Low PA OR=0.64, 95% CI 0.41-1.02 Moderate PA OR=0.69, 95% CI 0.50-0.95 High PA OR=0.63, 95% CI 0.40-0.98 P for trend 0.04 There was no association between PA and VaD. When stratified by sex, there was a significantly reduced risk of the development of dementia (CIND, AD and any type) and increasing levels of PA for women, but not for men.

Non-Pharmacological Interventions to Reduce the Risk of Dementia or Cognitive Decline

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Diet					
Barnes et al. 2023 **USA** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	604 persons ≥65 years who were overweight (BMI ≥25) with a MoCA score of ≥ 22, a reported a family history of Alzheimer's dementia and who had suboptimal diets (defined as a MIND-diet score of ≤8, based on a 14-item diet questionnaire).	Participants were randomized 1:1 to groups, which were instructed to consume the MIND diet with mild caloric restriction or a control diet with mild caloric restriction.	**Primary outcome:** Change in overall cognition (z score) at 3 years from baseline. **Secondary outcome:** Changes in MRI- derived measures of total brain volume, hippocampal	From baseline to year 3, there were improvements in global cognition (z) scores in both groups (0.205 in the MIND-diet group vs. 0.170 in the control-diet group). The difference in mean change between groups was not significant (MD=0.035 standardized units; 95% CI −0.022 to 0.092).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		Mean age was 70 years, 35% were men.		volume, and volume of white-matter hyperintense lesions	Changes in white-matter hyperintensities, hippocampal volumes, and total gray- and white-matter volumes on MRI were similar in the two groups. 93.4% of the participants completed the trial.
Adjibade et al. 2019 **France** **Prospective study**	NA	6,011 participants ≥60 years, without subjective memory complaints (SMC) recruited from the general population by a vast multimedia campaign. Mean age was 64.4 years.	The association between adherence to the MIND diet (a combination of the Mediterranean Diet and DASH diet) and SMC, measured by the Cognitive Difficulties Scale (CDS) was examined. Adherence to the MIND diet was assessed by a series of 24-hour recalls (baseline and twice annually). Adherence was scored 1-15, with higher scores indicating greater adherence. The CDS is a 37-item questionnaire with scores ranging from 0 and 148 points, with a higher score indicating more frequent and severe cognitive difficulties. CDS scores were converted to binary variables (low level of complaints vs a high level) using a cut-off value of 43.	**Primary outcome:** Risk of SMC Models were adjusted for age, sex, marital status, educational level, occupational categories, household income, energy intake without alcohol, number of recording days, and inclusion month	Mean duration of follow-up was 6.1 years. There were 1,053 (17.5%) cases of SMC. Of these, 15.7% were among persons aged 60-69 years and 30.6% were among persons aged ≥70 years. Overall, the risk of SMCs was not significantly lower among persons in the highest vs. lowest tertile, nor was it reduced in Q2 vs. Q1 (ref). Among persons aged 60-69 years (n=5,270), the risk of SMC was not reduced significantly in comparisons of Q3 vs. Q1 and Q2 vs. Q1 Among persons aged ≥70 years (n=741), the risk of SMC was significantly reduced (Q3 vs. Q1; HR= 0.69, 95% CI 0.47- 0.99). Each one-point increase in the MIND diet score was associated with a 14% reduction in the risk of SMC. (HR=0.86, 95% CI 0.77-0.96). There was no significant reduction in SMC comparing Q2 vs. Q1: HR= 0.76, 95% CI 0.56-1.04.
McEvoy et al. 2017 **USA**	NA	5,907 community-dwelling older adults selected from the Health & Retirement Study. Mean age was 67.8 years, 60% were women.	The association between the Mediterranean diet (MedDiet) and the Mediterranean-	**Primary outcome:** Global Cognition scores (Impaired cognitive performance, defined as	Impaired cognition was found in 831 (14%) participants. In the fully adjusted model (sex, age, race, education, current smoking, total wealth, obesity

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cross-sectional study			DASH diet Intervention for Neurodegeneration Delay (MIND diet) and cognition was examined. Adherence to dietary patterns was determined from food frequency questionnaires using criteria determined a priori to generate diet scores for the Med-Diet (range 0–55) and MIND diet (range 0–15). Cognitive performance was measured using a composite test score of global cognitive function (range 0–27). Linear regression was used to compare cognitive performance according to tertiles of dietary pattern.	more than1 SD [4.3 points] below the mean global cognitive score)	[BMI ≥30], hypertension, diabetes mellitus, physical inactivity, depression score, and total energy intake), persons with mid MedDiet scores (Q2) had lower odds of poor cognitive performance than those with low scores (Q1: OR = 0.85, 95% CI 0.71–1.02, P = .08). Persons with high MedDiet scores (Q3) had significantly lower odds of having poor cognitive performance than those with the lowest scores (OR = 0.65, 95% CI 0.52–0.81, P < .001). Results were similar for individuals with mid (OR = 0.85, 95% CI 0.70–1.03, P = .10) and high (OR = 0.70, 95% CI 0.56–0.86, P = .001) MIND diet scores. In fully adjusted linear models, each 1 SD increase (5.4 units) in MedDiet was associated with 15% lower odds of poor cognitive performance (OR = 0.85, 95% CI 0.78–0.93, P < .001) Each 1 SD increase (1.8 units) in MIND diet was associated with 14% lower odds of poor cognitive performance (OR = 0.86, 95% CI 0.79–0.94, P < .001).
Valls-Pedret et al. 2015 **Spain** **RCT**	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	447 cognitively healthy volunteers from the PREDIMED trial (Barcelona, Spain) at high cardiovascular risk. Mean age was 66.9 years, 52.1% were women.	Participants were randomized to a Mediterranean diet (MD) supplemented with extra-virgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat)	**Primary outcome:** Rates of cognitive change over time based on a neuropsychological test battery (standardized to z scores)	Median duration of follow-up was 4.1 years. 113 participants were lost to follow-up. At the end of follow-up, there were 37 cases of incident MCI, with no significant differences among diet groups. Memory: in the 2 MD groups there was no significant change in scores in fully adjusted models (MD+olive oil, mean change=0.04, 95% CI −0.10 to 0.17 and MD+nuts, mean change=0.10, 95% CI −0.04 to 0.24) but there was a significant decline in the control group (mean change=−0.16, 95% CI −0.32 to −0.01).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The same pattern of results was reported for measures of frontal cognition and global cognition, whereby there were slight, but non-significant changes in the 2 MD groups, and a slight but significant decline in the control group.
Morris et al. 2015 **USA** **Prospective study**	NA	960 participants from the Memory and Aging Project (MAP), which included residents of >40 retirement communities and senior public housing units in the Chicago area. Persons were free of dementia at baseline but those with mild cognitive impairment were included. Mean age was 81.4 years, 75% were women.	The association between adherence to the MIND diet (by tertile) and DASH diets and overall cognitive performance, assessed across 5 cognitive domains was examined.	**Primary outcome:** Decline in cognitive performance	Mean duration of follow-up was 4.7 years. In a model adjusted for age, sex, MIND diet score, sex, education, participation in cognitive activities, APOE ε4 (any ε4 allele), smoking history (current, past, and never), physical activity hours per week, total energy intake, time and interaction terms between time and each model covariate, higher adherence to the MIND diet was associated with a significantly slower rate of cognitive decline (global cognition, episodic memory, semantic memory, perceptual organization, perceptual speed and working memory). Compared to the decline rate of participants in the lowest tertile of scores, the rate for participants in the highest tertile was substantially slower. The difference in rates was the equivalent of being 7.5 years younger.
Tangney et al. 2011 **USA** **Prospective study** ***Chicago Health and Aging Project (CHAP)***	N/A	3,790 community-residing individuals >56 years of age, included in the CHAP cohort who had at least 2 cognitive assessments. Mean age was 75 years.	Data obtained from the Harvard Food-Frequency Questionnaire (FFQ) was used to assess adherence to the Mediterranean-type diet (total possible score=55 with higher values indicating greater adherence) and a Healthy Eating Index-2005 score (HEI). Total	**Primary outcome:** Changes in global cognition Timing of assessment: Baseline and every 3 years.	Mean duration of follow-up was 7.6 years. The mean MedDIet score was 28.1. The overall rate of decline in global cognition was 0.06 units per year. Greater adherence to a Mediterranean diet was significantly associated with a reduced decline in cognitive functioning ($p<0.001$), as based on MedDiet score, adjusting for age, sex, race, education, total energy intake, and participation in cognitive activities.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			possible score =100, with higher scores indicating better diet quality Cognitive functioning was assessed using East Boston tests of immediate and delayed recall, MMSE and the Symbol Digit Modalities Test and the results combined.		Scores on the HEI-2005 were not significantly associated with the rate of cognitive decline.
Feart et al. 2009 **France** **Prospective study**	N/A	1,410 participants recruited from waves 1, 2 and 3 of the 3 City study without dementia who had at least one follow-up exam over 5 years. Mean age was 76 years, 60% were female.	Baseline diet assessments were completed by a dietitian using a FFQ and 24-hour recall were used to estimate a Mediterranean Diet score (0-9). 3 diet groups were formed (low: scores 0-3; middle:4-5 and high: 6-9) A battery of neuropsychological tests was administered at baseline and at each of 3 follow-ups, conducted over 7 years.	**Primary outcome:** Cognitive performance based on 4 tests: MMSE, Isaacs Set Test (IST), Benton Visual Retention Test (BVRT), and Free and Cued Selective Reminding Test (FCSRT), adjusting for sociodemographics, and other pertinent covariates **Secondary outcome:** Incident dementia	Median duration of follow-up was 4.1 years. 44% of participants had a Med diet score of 4-5. 99 participants developed incident dementia and 66, Alzheimer's dementia. A 1-point increase on the Med diet score was associated with fewer MMSE errors (=−0.006; 95% CI, −0.01 to −0.0003, p=0.04). Performance on the IST, BVRT, or FCSRT over time was not significantly associated with Mediterranean diet adherence. When Med Diet scores were analyzed categorically, greater adherence was not associated with better cognitive performance. The risk of developing dementia was not significantly reduced among participants with high Med Diet adherence scores 6-9 (HR=1.12; 95% CI, 0.60 to 2.10, p=0.72).
Physical Activity					
Young et al. 2015	N/A	12 RCTs (754 participants) including cognitively healthy participants > 55 years.	RCTs comparing the effect of aerobic physical activity programmes of	**Primary outcome:** Cognitive function (cognitive speed, verbal	Aerobic exercise programmes were not associated with significant benefits on any of the cognitive outcomes assessed.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
UK **Cochrane review**			any intensity, duration or frequency which was aimed at improving cardiorespiratory fitness with any other active intervention, or no intervention. Trials ranged 8 to 26 weeks in duration.	memory functions, visual memory functions, working memory, executive functions, perception, cognitive inhibition, visual attention, auditory attention)	
Multifactorial					
Andrieu et al. 2017 **France** **RCT** ***Multidomain Alzheimer Preventive Trial (MAPT)***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,680 frail elderly participants, with in good cognitive and functional status aged ≥70 years, living independently in the community, with MMSE scores ≥24, with at least one of the following frailty criteria: a subjective memory complaint, an inability to perform one of instrumental activities of daily living, a slow walking (i.e 5 seconds to walk 4 meters). Mean age was 75.3 years, 64% were women.	Participants were randomized to one of 4 groups: Dietary omega-3 fatty acid supplement (800 mg DHA per day), multi-domain intervention including nutrition, physical exercise, cognitive training and social activities, and preventive consultations), omega-3 + multidomain intervention or placebo group for 3 years.	**Primary outcome:** The change from baseline to 36 months on a composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test, ten Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test)	There were no significant differences in 3-year cognitive decline between any of the three intervention groups and the placebo group. The composite Z score of participants in the multidomain plus polyunsaturated fatty acids group improved by a mean of 0·024 points, whereas the Z score of those in the placebo group fell by a mean of 0·069 points (between-group difference 0·093, 95% CI 0·001–0·184, adjusted p=0·142).
Moll van Charante et al. 2017, van Dalen et al. 2017 **Netherlands** ***Prevention of Dementia by Intensive Vascular care (preDIVA)***	CA: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	3,526 older adults aged 70–78 years, recruited through participating general practices. Mean age was 74.5 years, 45% women.	Participants were randomized to either a 6-year nurse-led, multidomain cardiovascular intervention with visits every 4 months or usual care	**Primary outcome:** Cumulative incidence of dementia and disability score (Academic Medical Center Linear Disability Score [ALDS]) at 6 years of follow-up **Secondary outcomes:** Cardiovascular disease (MI, stroke, and peripheral arterial disease) and cardiovascular and all-cause mortality	Median follow-up was 6.7 years. Dementia developed in 7% of participants in the intervention group and in 7% in the control group (HR=0·92, 95% CI 0·71–1·19; p=0·54). Mean ALDS scores did not differ during follow-up between groups (85·7 vs. 85·7, adjusted mean difference –0·02, 95% CI –0·38 to 0·42; p=0·93). There was no difference in the risk of cardiovascular events between groups (19% vs. 17%, HR=1·06, 95% CI 0·86–1·31, p=0·57.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Van Dalen et al. 2017 (MRI Imaging) 195 patients without dementia with a SPB ≥140 mm Hg were consecutively recruited to undergo MRI at 2-3 and 5-6 years after baseline. 126 participants were available for longitudinal analysis (64 intervention and 62 control). Mean annual white matter hyperintensity volume increase was similar for intervention and control groups (0.73 vs. 0.70 mL, adj mean difference=−0.08 mL; 95% CI −0.30 to 0.15; P=0.50).

Cholinesterase Inhibitors

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Battle et al. 2021 **UK** **Cochrane review**	6 trials were judged to be at unclear risk of bias across ≥1 domains, 2 trials were at low risk of bias across all domains	8 RCTs including adults with vascular dementia and other VCI.	Participants were randomized to receive a cholinesterase inhibitor or placebo. In 3 trials, participants received 5 mg or 10 mg donepezil daily (n= 2,193); in 3 trials, they received rivastigmine at a maximum daily dose of 3 to 12 mg (n= 800); and in 2 trials, they received galantamine at a maximum daily dose of 16 to 24 mg (n= 1,380).	**Primary outcomes:** Clinician's Interview-Based Impression of Change (CIBIC), dichotomized to improved or worse/stable, The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)	*Donepezil 5 mg* Using the results from 3 trials (1,601 participants), there was a significantly greater improvement in mean ADAS-Cog change scores from baseline to end of study in the donepezil group (MD=−0.92, 95% CI −1.44 to −0.40). The odds of improvement in clinical global impression were significantly higher in donepezil group, using data from 2 trials, 712 participants (OR=1.58, 95% CI 1.10 to 2.27). *Donepezil 10 mg* Using the results from 2 trials (608 participants), there was a significantly greater improvement in mean ADAS-Cog change scores from baseline to end of study in the donepezil group (MD=−2.21, 95% CI −3.07 to −1.35).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					The odds of improvement in clinical global impression were not significantly higher in donepezil group, using data from 2 trials, 699 participants (OR=1.15, 95% CI 0.78 to 1.70). *Rivastigmine 3 to 12 mg* Using the results from 2 trials (748 participants), there was no difference between groups in mean change from baseline in ADAS-Cog scores (MD= 0.03, 95% CI −3.04 to 3.10). *Galantamine 16 to 24 mg* Using the results from 2 trials (1,188 participants), there was a significantly greater improvement in mean ADAS-Cog change scores from baseline to end of study in the galantamine group (MD=−2.01, 95% CI −3.18 to −0.85). The odds of improvement in clinical global impression were significantly higher in donepezil group, using data from 2 trials, 1,326 participants (OR=1.32, 95% CI 1.03 to 1.70). In a network meta-analysis, using the results from 7 trials, donepezil 10 mg ranked first in terms of benefit (cognition), compared with the other drugs and placebo but was 3rd in harm. Galantamine ranked second in terms of both benefit and harm. Rivastigmine had the lowest ranking in both benefit and harm estimates.
Donepezil					
Chang et al. 2011 **Korea** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☒	14 patients, aged 18-75 years, recovering from first-ever stroke, (right hemisphere lesion), with stroke onset of >3 months and signs of cognitive impairment, based on MMSE scores 10-26, and a Clinical Dementia Rating	Patients were randomized to receive 5 mg donepezil daily, or matching placebo for 4 weeks. Assessment of cognitive function was performed before, immediately after	**Primary Outcome:** Improvement in measures of cognitive function	Mean baseline MMSE scores were 24.2 and 24.8 for patients in the donepezil and placebo groups, respectively. Patients in the donepezil group demonstrated significantly greater improvements in mean MMSE scores over the study period, compared with patients in the placebo group (p<0.01).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		(CDR) of 0.5 to 2.0. Mean age was 55 years, 64% were male. Time from stroke onset ranged from 4-40 months.	and one month after treatment using the MMSE, Rey-Osterreith Complex Figure Test (ROCFT), and the Verbal Learning Test (VLT). Functional MRI was performed before and after treatment.		There were no significant differences between groups over time in mean ROCFT or VLT change scores. Patients in the donepezil group showed significantly greater increased activation in both prefrontal areas, both inferior frontal lobes, and in the left inferior parietal lobe on fMRI, following treatment, compared with patients in the placebo group.
Roman et al. 2010 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	974 patients, 35-94 years with possible or probable vascular dementia with previous stroke, but who had been stroke-free for ≥3 months, had not taken acetylcholinesterase inhibitors or memantine for at least 6 weeks. Mean age was 73 years, 57% were male. 74% of those screened for eligibility were included in the study.	Participants were randomized to receive donepezil (5mg/day; n=648) or placebo (n=326), for 24 weeks.	**Primary outcomes**: Changes in the Vascular Alzheimer's Disease Assessment Scale cognitive subscale (V-ADAS-cog) and the Clinician's Interview-Based Impression of Severity Plus version (CIBIS-Plus). **Secondary outcomes**: MMSE, clock drawing task, Executive Interview (EXIT25), Disability Assessment for Dementia (DAD), and the Clinical Dementia Rating – Sum of Boxes (CDR-SB).	At the end of treatment, participants in the donepezil group demonstrated significantly greater improvement on the V-ADAS-cog ($p<0.01$). The two groups did not differ significantly in terms of improvement in global function rated on the CIBIS-Plus ($p>0.05$). At the end of treatment, participants in the donepezil group demonstrated significantly greater improvement on MMSE ($p=0.03$). There were no significant differences between groups for any of the secondary outcomes. The number of adverse events were similar for those receiving donepezil (80.7%) and placebo (77.6%) and were generally mild-moderate in severity. Whereas no deaths occurred in the placebo group, 11 participants in the donepezil group died during the study period, with 3 deaths determined to be possibly related to the use of donepezil. Lost to follow-up: donepezil =17.4%; placebo=13.2%.
Black et al. 2003 **Canada**	CA: ☒ Blinding:	603 stroke patients aged ≥40 years with possible (29.5%) or probable (70.5%)	Participants were randomized to receive 5 mg donepezil (n=198),	**Primary outcomes**: Alzheimer's Disease Assessment Scale	Over the 24- week study period, participants in both the 5 and 10 mg donepezil groups demonstrated significantly greater improvement

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	Patient ☑ Assessor☑ ITT: ☑	vascular dementia of >3 months duration. mean age, 73.9 years; 55.2% men. Patients with neurodegenerative disorders other than vascular dementia, MMSE>26 or <10, and diagnosis with a major depression or other psychiatric disorder, were excluded. 63% of those screened for eligibility were included in the study.	10 mg (n=206) donepezil daily or placebo (n=199) for 24 weeks.	cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Severity Plus version (CIBIS-Plus). **Secondary outcomes**: Mental State Examination (MMSE), Sum of the Boxes of the Clinical Dementia Rating (CDR-SB), Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).	on the ADAS-cog, compared with the placebo group (p<0.01 and p<0.001, respectively). Those in the 5-mg group, but not the 10 mg group, were also rated as having made significantly greater improvement in global function (CIBIS-Plus) than those in the placebo group (p=0.01). Significantly greater improvements in mean MMSE scores were demonstrated in patients in both 5 and 10 mg groups, compared with control (p<0.05 and p<0.001, respectively) The proportion of patients with treatment-emergent events was significantly higher in the 10/mg treatment group than in the placebo group (94.7% vs. 88.4%, p=0.03). The 5mg and placebo groups did not differ significantly in the rate of treatment-emergent events (88.9% vs. 88.4%, p>0.05). In General, adverse events were mild-moderate and affected the digestive system, musculoskeletal system or nervous system. Lost to follow-up: donepezil 5m/day=18.7%, donepezil 10m/day=28.2%, placebo=15.1%.
Donepezil 308 Study Group Wilkinson et al. 2003 **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	616 stroke patients with probable (76%) or possible (24%) vascular dementia of >3 months duration. Mean age 75.0 years, 40% women. Patients with neurodegenerative disorders other than vascular dementia age<40, MMSE>26 or <10, uncontrolled hypertension, diabetes or cardiac disease,	Participants were randomized to receive 5 mg donepezil (n=198), 10 mg (n=206) donepezil daily or placebo (n=199) for 24 weeks.	**Primary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Severity Plus version (CIBIS-Plus). **Secondary outcomes**: Mental State Examination (MMSE), Sum of the Boxes of the Clinical Dementia Rating (CDR-SB),	At the end of the study period, participants in both the 5ml and 10ml donepezil groups demonstrated significantly greater improvement on the ADAS-cog than did those in the placebo group (least squares mean change= -0.75 [±0.33] and -2.65 [±0.48] vs. -0.10 [±0.39], respectively, both at p<0.01). Compared to placebo, donepezil was also associated with a significantly better rating on the CIBIC-Plus at the end of the treatment period (p=0.004 for 5ml/day and p=0.047 for 10ml/day). The rate of treatment-emergent adverse events

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		recurrent stroke within the past 3 months, or diagnosis with a psychiatric disorder, were excluded. 69% of those screened for eligibility were included in the study.		Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).	was 86.5% in the placebo group, 90.4% in the 5ml/day donepezil group, and 91.6% in the 10ml/day donepezil group. Diarrhea, Nausea, abnormal dreams, leg cramps, and rhinitis were each significantly more frequent in the active treatment groups. Lost to follow-up: donepezil 5m/day=19.2%, donepezil 10m/day=24.7%, placebo=16.6%.
Rivastigmine					
Birks et al. 2013 **UK** **Cochrane Review**	N/A	3 RCTs (n=800) examining the use of rivastigmine for the treatment of vascular cognitive impairment, vascular dementia, or mixed dementia. The percentage of participants recovering from stroke within these trials was 100% (Narasimhalu et al. 2010), 70% (Mok et al 2007) and 66% (Ballard et al. 2008)	In the 3 trials, participants were randomized to receive 1) 3-12 mg rivastigmine or placebo for 24 weeks; 2) maximum dose of 6 mg or placebo for 26 weeks and 3) 6-9 mg or placebo for 24 weeks	**Primary outcomes:** Measures of global impression, functional performance, behavioural disturbance, and cognitive function	No pooling of results was possible for any outcomes. A single study (n=710) demonstrated a significant treatment effect in favour of rivastigmine in cognitive response (change in Mini Mental State Exam score: MD= 0.06, 95% CI 0.11 to 1.09, p=0.02, and change in Vascular Dementia Assessment Scale from baseline MD= -1.3, 95% CI-2.62 to 0.02, p=0.05. No significant effects of treatment were reported for either of the other two trials (n=40 and 50) with respect to cognition, neuropsychiatric symptoms, function, or global performance.
Narasimhalu et al. 2010 **Singapore** **RCT**	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	50 patients aged 55– 85 years, with cognitive impairment, without dementia, recruited 3 months following ischemic stroke. Mean age was 69 years, 66% were women. Mean MMSE baseline score was 23.8. 32.5% of those screened for eligibility were included in the study.	Participants were randomized 1:1 to receive rivastigmine (6-9 mg daily, as tolerated) or placebo for 24 weeks.	**Primary outcomes**: Changes in The Ten-Point Clock Test and the Color Trails Test 1 and 2. **Secondary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), the AD Cooperative Study Assessment of Daily Living (ADCS-ADL), and the Geriatric Depression Scale (GDS).	At 24 weeks, there were no significant between group differences for either primary outcome. Mean change from baseline (rivastigmine vs. placebo): Clock drawing test 0.1 vs. 0.5, p=0.39; Color Trails 1 -12.7 vs. -21.4, p=0.53; Color Trails Test 2 -16.1 vs.-0.6, p=0.09. There were no significant differences between groups for any of the secondary outcomes, with the exception of the verbal fluency subscale of the ADAS-cog, for which participants in the treatment group demonstrated significantly more improvement (mean change from baseline was 1.7 vs. 0.03, p=0.02).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Losses to follow-up were 28% in both groups.
Ballard et al. 2008 **USA** **RCT** ***Vascular Dementia trial studying Exelon (VantagE)***	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	710 persons aged 50–85 years with vascular dementia. Mean age was 72.8 years, 62% were women. Mean baseline MMSE score was 19.2.	Participants were randomized 1:1 to receive rivastigmine capsules (3–12 mg/day) or placebo for 24 weeks	**Primary outcomes:** Vascular Dementia Assessment Scale (VaDAS) and the Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change (ADCS-CGIC) **Secondary outcomes:** MMSE, ADAS-cog	Mean dose of rivastigmine reached at the end of the titration phase was 9.4 mg/day. At 24 weeks, the mean change in VaDAS score was -0.7 in the rivastigmine group and 0.6 in the placebo group (between group difference =-1.3, p=0.028). At 24 weeks, the mean change in ADCS-CGIC was 4.0 in the rivastigmine group and 4.1 in the placebo group (between group difference =0.1, p=n/s). At 24 weeks, the mean change in MMSE score was 0.4 in the rivastigmine group and -0.2 in the placebo group (between group difference =0.6, p=0.007). At 24 weeks, the mean change in ADAS-cog score was -0.7 in the rivastigmine group and 0.4 in the placebo group (between group difference =1.1, p=0.029). Older patients aged ≥75 years presumed to have concomitant AD, derived more benefit, compared with younger persons, presumed not to have an AD component, and had more adverse events.
Moretti et al. 2003 **Italy** **RCT**	CA: ☒ Blinding: Patient ☒ Assessor☒ ITT: ☒	208 patients aged 65-80 years, with probable vascular dementia (assessed using DSM-IV criteria) and evidence of moderate-to-severe ischemic white matter changes and at least 1 lacunar infarct, with MMSE scores ≥14. Mean age was 75.7 years.	Participants were randomized 1:1 to receive 3-6mg rivastigmine or 100 mg aspirin daily for one year.	**Primary outcomes:** The Clinical Dementia Rating (CDR), MMSE, the Ten-Point Clock (TPC) Test, word fluency phonological tests, the Behavioral Pathology in AD Rating Scale (BEHAVE-AD), the Geriatric Depression Scale (GDS), and the Cumulative Illness	At the end of the study, significant deterioration was observed for participants in both groups in terms of scores on the MMSE, phonological fluency, and the Ten-point Clock Test. Participants randomized to receive rivastigmine demonstrated significantly less deterioration on both the MMSE and the Ten-point Clock Test (p<0.05). Participants in the rivastigmine group also

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Rating Scale (CIRS).	demonstrated significantly more improvement on the GDS and on the BEHAVE-AD total score and each of the subscales except delusions (all at p<0.001). Transitory nausea was reported by 21% and 27% of patients in the rivastigmine and aspirin groups, respectively. Muscle contraction were reported by 14% of those in the rivastigmine group whereas 25% of those in the aspirin group reported heartburn.
Galantamine					
Auchus et al. 2007 (GAL-INT-26 Study Group) **USA** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	788 patients, 40-90 years with probable vascular dementia, confirmed by MRI. MMSE score 10-26, and a score of ≥ 12 on the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog/11). Mean age was 72.3 years, 64% were men. Mean MMSE score was 20.3. 45.3% of those screened for eligibility were included in the study.	Patients were randomized to receive 8 or 12 mg galantamine (n=396) b.i.d. or placebo (n=390) for 26 weeks.	**Primary outcomes:** Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog/11) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL) total score.	91% of participants had cardiovascular risk factors, including stroke. The mean Hachinski score was 11.7. At the end of 26 weeks, patients treated with galantamine had experienced significantly greater improvement in ADAS-cog/11(mean change =-1.8 vs. -0.3, p<0.001). At 26 weeks, there was no difference between groups in ADCS-ADL score (mean change =0.7 vs. 1.3, p=0.783). 77% of patients in the galantamine group completed the trial vs. 85% in the placebo group. More adverse events were reported in the galantamine group (14% vs. 7%). More adverse events in the galantamine group led to treatment discontinuations (13% vs. 6%). receiving
Erkinjuntti, et al. 2002 **Finland** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	592 patients with probable vascular dementia or possible Alzheimer's disease and evidence of stroke within the previous 12 months, MMSE score 10–25, and ≥ 12 on the Alzheimer's disease	Participants were randomized to receive 24 mg galantamine (n=396) or placebo (n=196) for 6 months.	**Primary outcomes**: Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus).	Participants in the galantamine group demonstrated significantly more improvement on the ADAS-cog (mean change = -1.7±0.4 vs. 1.0±0.5, p<0.001). Significantly more patients in the galantamine group improved or reported no change on the CIBIC-plus (213±74% vs. 95%±59%, p=0.001) at

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		assessment scale cognitive subscale (ADAS-cog). Mean age was 75 years, 47% were male. 79% of those screened for eligibility were included in the study.		**Secondary outcomes**: An extended version of the ADAS-cog and the Neuropsychiatric Inventory.	the end of the study period. The galantamine group also demonstrated significantly more improvement on the extended version of the ADAS-cog ($p<0.0001$) and the Neuropsychiatric Inventory ($p=0.016$). The rate of adverse events was 20% in the galantamine group and 8% in the placebo group. Most of the adverse events were reported to be mild to moderate in severity and of short duration. The most frequently reported adverse events were nausea and vomiting. Lost to follow-up: galantamine=25.8%; control=16.8%
Methylphenidate or galantamine vs. placebo					
Leijenaar et al. 2020 **The Netherlands** **RCT** ***Symptomatic Treatment of Vascular Cognitive Impairment" (STREAM-VCI)***	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	30 VCI patients with MCI of vascular origin, with MMSE scores ≥ 16 and Clinical Dementia Rating score 0.5–1.0. Mean age was 67 years, 30% were women.	After a baseline assessment, in random order, participants received a single dose of galantamine (16 mg), methylphenidate (10 mg), and placebo on three separate study visits with a washout period of a week between each study visit.	**Primary outcome:** Change in performance from baseline on the adaptive tracker for executive functioning and performance on the Visual Verbal Learning Test-15 (VVLT-15) for memory **Secondary outcomes:** Stop Signal Task, and N-back task	The improvement in performance on the adaptive tracker, was significantly higher after methylphenidate compared with placebo (mean change was 1.40%, 95% CI 0.56–2.25, $p = 0.002$), while there was no significant improvement following administration of galantamine compared with placebo. There was no significant improvement in performance on the VVLT-15 immediate word recall in trials 1 and 2, among persons in the methylphenidate group compared with placebo group; however, there was significantly greater difference in the remembered words among persons in the methylphenidate group on the third trial of immediate word recall of the VVLT15 (0.59, 95% CI 0.03, 1.15). There was no significant difference from baseline in either the VVLT-15-Delayed word recall correct or VVLT-15- Delayed word recognition correct from baseline among persons in the methylphenidate group, compared with placebo.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Patients remembered significantly fewer words after galantamine on delayed word recall compared with after placebo (-0.84, 95% CI -.65 to -0.03, p=0.04). There were no significant differences in mean change from baseline on any of the secondary outcomes (methylphenidate vs. placebo or galantamine vs, placebo).

MNDA Receptor Antagonists (Memantine)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
McShane et al. 2019 **UK** **Cochrane review**	Wilcock et al. (2002) was assessed as being at high risk of bias in ≥2 domains	44 RCTs including persons with dementia, most of whom had Alzheimer's dementia. 2 trials included persons with vascular dementia (Orgogozo et al. 2002, Wilcock et al, 2002)	Participants in both trials were randomized to receive 20 mg memantine or placebo for 28 weeks.	**Primary outcomes:** Clinician's Interview-Based Impression of Change (CIBIC), a 7-point Likert scale, The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)	There was no significant difference in mean change in CIBIC scores from baseline to end of study (SMD= -0.02, 95% CI -0.23 to 0.19). GRADE: moderate The mean difference (MD) from baseline in ADAS-Cog scores was significant between groups, favouring memantine (MD=-2.15, 95% CI -3.25 to -1.05). GRADE: moderate
Wilcock et al. 2002 **UK** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	579 individuals with probable vascular dementia, with onset at least one-year prior, with baseline MMSE scores of 10-22 Mild to moderate disease). Mean age was 75 years, 52% male. Mean MMSE score was 17.6. 69% of those screened for eligibility were included in the study.	Participants were randomized to receive 20 mg memantine (n=295) or placebo (n=284) daily for 28 weeks.	**Primary outcome**: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinical Global Impression of Change (CGI-C) **Secondary outcomes**: (MMSE, the Gottfries-Brane-Steen Scale (GBS), and the Nurse's Observation Scale for Geriatric Patients (NOSGER).	Memantine was associated with significantly greater improvement on the ADAS-cog at the end of the 28-week study period (mean change =-1.75, 95% CI -3.02 to -0.49; p<0.01). There were no significant between group differences reported with respect to the CGI-C. Treatment-emergent adverse events occurred in 77% of those in the treatment group and 75% of those in the control group. The most common adverse events for patients in the memantine group were dizziness and constipation. Lost to follow-up: memantine=19%;

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					placebo=20%
Orgogozo et al. 2002 **France** **RCT**	CA: ☒ Blinding: Patient ☑ Assessor☑ ITT: ☑	321 patients ≥60 years, with mild-moderate symptomatic vascular cognitive impairment of 6 months duration, a Modified Ischemic Score ≥5 and MMSE score 12-20. Mean age was 76.5 years, 49% were women. Mean MMSE score was 16.9. 79.7% of those screened for eligibility were included in the study.	Participants were randomized to receive a maximum dose of 20 mg memantine daily (n=165) or placebo (n=156) for 28 weeks.	**Primary outcome**: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus) **Secondary outcomes**: MMSE, Gottfries-Brane-Steen Scale (GBS), and Nurse's Observation Scale for Geriatric Patients (NOSGER).	At the end of the study period, participants who received memantine gained an average of 0.4 points on the ADAS-cog, whereas the placebo group mean score had declined by 1.6 points, (a difference of 2.0 points, 95% CI 0.49 to 3.60). Although a greater number of participants in the memantine group were rated as improved or stable on the CIBIC-Plus (60% vs. 52%), this difference was not significant (p=0.227). The Mean change in MMSE scores over the study period was significantly greater for participants in the memantine group (1.75 vs. 0.52, p=0.003) Adverse events were reported by 76% of those in the memantine group and 74% of those in the placebo group. Serious adverse events were reported by 23% and 26% for the memantine and placebo groups, respectively. The most common adverse events were agitation, confusion, and dizziness. Lost to follow-up: memantine=43.6%; placebo=39.1%

Pharmacological Interventions to Reduce Cognitive Decline in Persons with Vascular Risk Factors

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hypertension					
Peters et al. 2022 **Australia**	All trials were placebo controlled, double-blind. All analyses	28,008 individuals recruited from 20 countries who were participants from 5 RCTs (ADVANCE, HYVET, PROGRESS, SHEP and	Regression models were developed to examine the association between antihypertensive treatment and incident dementia (MMSE	**Primary outcome:** Incident dementia	During a median follow-up of 4.3 years incident dementia occurred in 403 (2.9%) and 458 (3.3%) of those in active and placebo groups, respectively.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Individual patient-level meta-analysis	were intention-to-treat.	SYST-EUR). Mean age was 69.1 years, 53.2% were men. Mean baseline SBP was 155.8 mmHg and mean DBP was 82.9 mmHg. Mean MMSE score was 27.9.	score ≤24 for at least two consecutive annual or biannual visits).		The mean differences in BP between the placebo and antihypertensive treatment groups at 12 months were 9.6 mmHg (SBP) and 3.7 mmHg (DBP). The odds of dementia were decreased significantly in persons receiving antihypertension therapy (adjusted OR=0.87, 95% CI 0.75-0.99).
White et al. 2019 **USA** **RCT** ***Intensive Versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline In the Elderly (INFINITY)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	199 persons ≥75 years, with systolic HTN based on clinic and ambulatory blood pressure measurements, (or SBP 150 to 170 mm Hg if taking ≥1 antihypertensive drugs, or >170 mm Hg if taking 0 to 1 antihypertensive drug at screening) and with visible white matter hyperintensity lesions on MRI (typically ≥0.5% lesion volume). Persons with a history of stroke were excluded. Mean age was 85 years, 54% were women.	Patients were randomized to receive intensive treatment (24- hour SBP target ≤130 mmHg), or to standard treatment (≤145 mmHg),	**Secondary outcomes:** Change in cognitive function (executive function, processing time) **Safety outcomes:** Mortality, major nonfatal cardiovascular events Outcomes were assessed at 18 and 36 months	The mean 24-hour SBP was 127.7 mmHg in the intensive treatment group and 144.0 mmHg in the standard treatment group (mean difference of 16.3 mmHg). There were no differences between groups in mean changes from baseline and 18 or 36 months in any of the mobility measures. There were no differences between groups in changes from baseline and 36 months in any of the assessments of cognitive function except for the California Computerized Assessment Package Sequential Reaction Time (-23.2 vs. 32.6 msec), favouring the intensive group. The percentage increase in white matter hyperintensity was significantly less in the intensive group (0.29% vs. 0.5%, p=0.03).
Williamson et al. 2019, Nasrallah et al. 2019, Dolui et al. 2022 **USA** ***Systolic Blood Pressure Intervention Trial- Memory***	CA: ☑ Blinding: Patient ☑ Assessor☑ ITT: ☑	9,250 participants aged ≥ 50 years with SBP ≥130-180 mm Hg and at least one additional CVD risk factor were recruited from 102 clinical sites. Patients with diabetes or previous stroke were excluded. Mean age for patients in both study groups was	Patients were randomized to an intensive BP arm with a goal of SBP <120 mm Hg using 2-drug therapy, if required (n=4,678) vs. a standard arm with a goal of SBP <140 mm Hg (n=4,683) for up to 6 years. Participants were seen monthly for the first 3 months and every	**Primary Cognitive outcome:** Probable dementia **Secondary Cognitive outcomes:** MCI and a composite outcome of MCI or probable dementia	Median intervention period was 3.34 years, with a median follow-up of 5.11 years. Over the study period, the mean SBP of patients in the intensive group was lower (121.6 vs. 134.8 mm Hg). There were no cognitive outcomes available for 798 patients (outcomes imputed).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
and cognition IN Decreased hypertension (SPRINT-MIND)		67.9 years, 36% were female. Mean Framingham 10-year risk score was 20.1%. <10% of patients in both groups were not taking any antihypertensive agents	3 months thereafter, with adjustments to medications, as required. Lifestyle modification was encouraged as part of the management strategy		Probable dementia occurred in 149 participants in the intensive treatment group vs 176 in the standard treatment group (7.2 vs 8.6 cases per 1,000 person-years; HR= 0.83; 95% CI, 0.67-1.04, p=0.10). There were no interactions based on subgroup analyses (age, sex, race, history of CVD, kidney disease, SBP at baseline, orthostatic hypotension) The risk of MCI was significantly lower in the intensive group (287 vs. 353 cases per 1,000 persons years; HR=0.81; 95% CI, 0.69-0.95, p=0.007). The risk of the composite outcome was significantly lower in the intensive group (20.2 vs. 24.1 cases per 1,000 person-years; HR=0.85, 95% CI 0.74-0.97, p=0.01). *Nasrallah et al. 2019 (MRI sub study)* 449 patients had a baseline and follow-up MRI (a median of 3.97 years after randomization). After a median intervention period of 3.40 years, patients in the intervention group had significantly smaller mean increase in cerebral white matter lesion volume (between-group difference in change, −0.54 cm^3 95% CI, −0.87 to −0.20) and a greater decrease in total brain volume (between-group difference in change, −3.7 cm^3 95% CI, −6.3 to −1.1). *Dolui et al. 2022 (Cerebral blood flow)* Among 547 participants with CBF measured at baseline, 315 completed follow-up MRI a median of 4.0 years after randomization. Mean CBF increased from 38.90 to 40.36 mL/100 g/min in the intensive treatment group, with no mean increase in the standard treatment group (37.96 to 37.12 mL/100

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					g/min). The mean between-group difference was 2.30 (95% CI, 0.30-4.30). *de Havenon et al. 2022 (subgroup with MCI)* Among a subgroup of 5,091 patients with a MoCA score of between 19 and 25, the risk of incident stroke was significantly reduced in those in the intensive therapy group during a mean follow-up of 3.8 years (1.5% vs. 2.3%, adj HR=0.65, 95% CI, 0.43–0.98).
van Middelaar et al. 2018 **The Netherlands** **Systematic review & meta-analysis**	Using the Cochrane RoB tool, 2 trials were at high risk of performance bias (unable to blind participants). One trial was at high risk of bias due to other reasons.	9 RCTs including persons with/without hypertension and with/without prior cerebrovascular disease. In all trials, mean age at baseline was ≥ 60 years. The percentage of men ranged from 34 to 70. In 4 trials, participants had a mean baseline SBP >160 mmHg.	Trials compared ≥1 antihypertensive agent vs. placebo (n=7), intensive vascular care vs. standard care (n=1) and an intensive lifestyle vs. diabetes support & education vs. diabetes support & education (n=1). Duration of follow-up ranged from 2.2 to 11.4 years.	**Primary outcome:** Dementia	Overall, 3.6% of persons were diagnosed with incident dementia in the intervention group compared with 3.8% in the control group (RR=0.93, 95% CI 0.84–1.0). Blood-pressure lowering interventions did not significantly reduce the risk of vascular dementia cases (RR=0.83, 95% CI 0.57–1.21, n=3 trials).
McGuinness et al. 2009 **UK** **Cochrane Review**	N/A	4 RCTs (n=15,936) investigating an intervention to lower blood pressure in participants with hypertension and no history of cerebrovascular disease. Study duration was at least 6 months.	Trials meeting inclusion criteria included HYVET (2008), SCOPE (2003), SHEP (1991), and Syst EUR (1997).	**Primary outcomes**: Incident dementia, cognitive change.	Mean baseline blood pressure across the included trials was 171/86 mm Hg. Treatment with antihypertensive agents was not associated with prevention of incident dementia (OR=0.89, 95% CI 0.74 to 1.07; p=0.21). Results of 4 trials included. The change in MMSE score from baseline favoured those in the placebo group (MD=0.42, 95% CI 0.30 to 0.53). Results of 3 trials included.
Forette et al. 2002 **European**	CA: ☑ Blinding: Patient ☒ Assessor☑	2,092 patients ≥60 years without dementia with SBP and DPBs of 160-219 and <95 mm Hg. Median age was 68 years	Patients were randomized to receive nitrendipine (10-40 mg/day) with/without enalapril (5-20m g/day) or hydrochorothiazide (12.5-25	**Secondary outcome:** Incident dementia	Median duration of follow-up was 3.9 years. Both SBP and DBPs were significantly lower among patients in the active treatment group at all visits. At 8 years, the differences were

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Open-label follow-up of Syst-Eur RCT	ITT: ☑		mg/day) or both second line drugs with the aim of lowering SBP to ≤150 mm Hg vs. placebo. At the end of the main phase of the trial, patients in the control group were offered the active treatment. The MMSE was used to screen patients annually. A score <24 indicated possible dementia, while dementia was confirmed using DSM-III-R criteria + brain imaging.		4.2 mm Hg systolic and 2.9 mm Hg diastolic (p<0.01). At the end of follow-up there were a total of 64 incident cases of dementia (41 AD, 10 mixed or VaD and 4 of unknown origin). The incidence of dementia was significantly higher among patients in the control group (43 vs. 21; 7.4 cases/1000 vs. 3.3/1000, p<0.0001). Nitrendipine was associated with a significantly reduced risk of incidence dementia (HR=0.38, 95% CO 0.23-0.64, p<0.001). An estimated 1000 patients would need to be treated for 5 years to prevent 20 new cases of dementia.

Prevalence of Mood and Behavioral Disorders

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lammers et al. 2021 **The Netherlands** **Prospective study**	NA	117 patients from the Preventive Antibiotics in Stroke Study (PASS), recruited from 30 sites from 2011 to 2015, with an mRS score ≤3 at 3 months post stroke. Mean age was approximately 72 years, 56% were men. Baseline MMSE score was approximately 28.	Using the Apathy Scale (AS) and cognitive tests of memory, processing speed and executive functioning, the associations between AS scores and change in cognitive scores at 6 and 15 months, were examined.	**Primary outcomes:** MMSE, Rey's Auditory Verbal Learning test (AVLT), the Trial-Making Test (TMT) part A, and B and the Letter Digit Substitution Test (LDST)	At 6 months, 42% of patients had apathy, while 39% had apathy at 15 months post-stroke. 29% of patients had persistent apathy. Apathy resolved in 13% of patients over time, while 10% developed between 6 and 15-months follow-up. 48% of patients had no apathy at either assessment. In cross-sectional analysis, at 6 and 15 months, higher apathy scores were associated with significantly worse performance on MMSE, LDST and AVLT and with longer time needed to complete TMT.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					In longitudinal analysis, higher AS scores at baseline were associated with significant declines in AVLT direct recall between 6- and 15-months post-stroke, but was not significantly associated with a change in scores on any other cognitive tests. A change on AS scores between 6- and 15-months post-stroke, was not associated with any of the cognitive outcomes.
Vlachos et al. 2021 **Sweden** **Prospective study**	NA	117 persons aged 18-70 years, who had sustained a mild stroke (NIHSS score ≤ 3) >12 months previously and who were cognitively intact prior to stroke. Mean age was 55.7 years, 77% were men.	Patients were assessed for cognitive impairment, mood, fatigue, and pathological laughter and crying, using previously validated instruments.	**Primary outcomes:** Cognitive impairment and emotional disturbances	Depending on the outcome, between 1% and 40% of the sample fell below the cut-off scores established for cognitive impairment. 13% of the sample scored >14 points on the HADS, 33% scored ≥4 on the Fatigue Severity Scale, 25% scored ≥34 on the Apathy Evaluation Scale-Self Report, and 3% scored ≥13 points on the Pathological Laughter and Crying Scale. At 12-month follow-up, 39% of the sample had only cognitive deficits, 15% had only emotional deficits, while 28% had both cognitive and emotional deficits; 18% of the sample had no cognitive or emotional deficits.
Douven et al. 2018 **The Netherlands** **Prospective study** ***Cognition and Affect after Stroke: A Prospective Evaluation of Risks (CASPER)***	NA	250 patients >40 years, admitted to hospital for acute stroke who were available for participation 3 months post stroke. Mean age was 67.6 years, 64.2% were men. Mean MMSE score at baseline was 28.2.	At baseline, 6 months and 12 months, neuropsychological assessment and neuropsychiatric questionnaires were administered by a trained research (neuro)psychologist. The association between VCI (any and multidomain) at baseline and depression and/or apathy at follow-up was examined.	**Primary outcomes:** The Montgomery-Åsberg Depression Rating Scale (MADRS), The Apathy Evaluation Scale (AES-C)	At baseline, 24.2% of patients had single-domain VCI, 20.4% had multidomain VCI, 19.4% had impaired memory, 31.8% had impaired information processing speed and 22.9% had impaired executive function. *Depression* There was no significant difference in depression scores between patients with and without any VCI at baseline or at follow-up. Nor was there a significant difference between persons with single and multidomain VCI at baseline or follow-up

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					Apathy There was no significant difference in apathy scores between patients with and without any VCI. At 6 and 12 months, apathy scores were significantly higher in persons with any VCI vs. no VCI. There was also a significant increase in apathy scores from T0 to T2 in persons with any VCI. At baseline, there were no significant differences in apathy scores between persons with multidomain VCI vs. single-domain VCI. Patients with multidomain VCI had higher apathy scores at the 6- and 12-month follow-up compared with patients with single-domain VCI. Persons with impaired information processing speed had significantly higher apathy scores at baseline, which remained significant at 6 months, but not from baseline to 12 months. There was no significant difference in apathy score between persons with and without impaired performance on executive function at baseline, but those with impaired executive function had higher apathy scores at 6 and 12 months.
Gupta et al. 2014 **India** **Prospective study**	NA	60 persons with VCI association with a stroke occurring >3 months previously. Mean age was 59 years, 67% were men.	Based on the results of MRI findings, participants were classified as having multi-infarct dementia (MID n=25), strategic (single) infarct (n=21) or subcortical ischemic vascular disease (SIVD, n=14) subgroups. The occurrence and severity of behavioural and psychological symptoms of dementia (BPSD) was compared between the	**Primary outcomes:** PBSD	Overall, the mean number of symptoms, assessed using NPI was 3.98. Depression, appetite disturbances, irritability and anxiety were the most common symptoms. Mean prevalences were 73%, 65%, 52% and 42%. Frequencies did not differ significantly across groups. The frequency of apathy was significantly higher in the SIVD group (62%) vs. MID (28%) or strategic (7%).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			subgroups, using the neuropsychiatric inventory (NPI), based on interview with caregiver present		The frequencies of agitation/aggression were 52% (MID), 48% (SIVD) and 7% (strategic) Based on the NPI subscale scores, depression was the most severe symptom, followed by irritability, appetite disturbances, apathy, and agitation/aggression (mean subscale scores 5.63, 3.7, 3.35, 3.083, and 3.08, respectively.)

Non-Pharmacological Interventions to Treat Behavioural Disturbances in Persons with Dementia

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Möhler et al. 2023 **Germany** **Cochrane review**	Using the Cochrane RoB tool, there were some concerns with bias in all trials.	11 RCTs including 1,071 participants with dementia living in long-term care facilities. Mean age ranged from 78 to 88 years and most had moderate or severe dementia. In most trials there were more women vs. men.	Trials examined personally tailored activities delivered by staff or family members. The interventions varied in terms of the theoretical basis (e.g. Treatment Routes for Exploring Agitation [TREA], Montessori-based activities etc). Examples of activities offered were music, family videotapes and pictures, illustrated magazines and large print books, board games and puzzles. Control conditions included usual care (n=5) and active control (n=5). One study included both types of control group. The duration of follow-up ranged from 10 days to nine months.	**Primary outcomes:** Agitation or challenging behaviour, EQ-5D **Secondary outcomes:** Affect, mood, level of engagement	Personally tailored activities were not associated with significant improvement in agitation (SMD=-0.26, 95% CI -0.53 to 0.01, 7 trials, n=485; GRADE: low) or improved EQ-5D scores as assessed by participant (SMD=0.26, 95% CI -3.04 to 3.56, 1 trial, n=42; GRADE: low) or proxy (SMD=-0.83, 95% CI -3.97 to 2.30, 2 trials, n=177; GRADE: low). Personally tailored activities were not associated with significant improvement in positive or negative affect or mood after follow-up of 10 days to 9 months.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Abraha et al. 2020 **Italy** **Cochrane review**	Trials were at high or uncertain risk of bias	3 RCTs including 144 persons with severe dementia living in nursing homes. Mean ages were 83, 87, and 79 years. 63%, 81% and 77% of participants were women.	Trials compared simulated presence therapy (SPT) vs. usual care, music or sham interventions. SPT was performed using an audio or video recording prepared by family members or surrogates and included positive experiences from the participant's past life. The frequency of the intervention was provided twice a day, for 17 days in trial 1; daily for 30 consecutive minutes for 14 days in trial 2; and daily for 15 minutes for 3 weeks in trial 3.	**Primary outcomes:** Any behavioural and psychological symptoms, Quality of Life (QoL) **Secondary outcomes:** ADL, caregiver burden	Pooling of data was not possible for any of the outcomes. *Agitation* Agitation was significantly reduced in the SPT group in one study. In the other 2 trials, multiple assessment methods were used to assess agitation (direct observation, staff observation logs and nurses' assessments), yielding conflicting results. GRADE: Very low *Depression* Depression, defined as "withdrawn behaviours" which included a lack of interest was assessed in one trial. Weekly staff surveys did not show any effect of SPT on mood, although the intervention was associated with increased interest. Staff reported that SPT compared to usual care statistically significantly improved withdrawn behaviour. GRADE: Ver low Anxiety and QoL were not assessed in any of the trials.
Möhler et al. 2020 **Germany** **Cochrane review**	All studies were assessed to be at high risk of bias in at least one domain	5 RCTs including 262 persons with dementia living in the community. Mean age ranged from 71 to 83 years, 60%-80% were women in 4 trials (0% in the 5th trial). Mean MMSE scores ranged from 11 to 24.	Trials compared an activity plan tailored to the individual's present or past preferences, which could also be adapted to their cognitive and functional status vs. a control condition or usual care, delivered in a group or individual setting. In 4 trials family caregivers were trained to deliver the intervention. In the 5th trial, activities were offered directly to the participants. The duration of follow-up ranged	**Primary outcomes:** Challenging behaviors, Quality of Life (QoL) **Secondary outcomes:** Mood, affect	Pooling the results of 4 trials, there was a significant reduction in challenging behaviors in the active intervention group at follow-up, (SMD= - 0.44, 95% CI -0.77 to -0.1). GRADE: Low QoL: Results from the 2 trials that assessed this outcome could not be pooled. The results from the 2 trials were conflicting (one trial, positive, the other, no significant difference between groups) GRADE: Low Affect: In the one RCT that assessed this outcome, there was no significant improvement in the intervention group compared with control at 4 months (SMD=

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			from two weeks to four months. Examples of acceptable types of activities included instrumental activities of daily living (e.g. housework, preparing a meal), arts and crafts (e.g. painting, singing), work-related tasks (e.g. gardening), and recreational activities (e.g. games).		-0.47, 95% CI -1.37 to 0.43). GRADE: Low
Leng et al. 2020 **China** **Systematic review & network meta-analysis**	Included trials were generally at low risk of bias	65 RCTs including persons with agitation due to dementia	The effectiveness of non-pharmacological interventions for the treatment of agitation was compared with usual care. Interventions included: personally tailored interventions (n=14); massage therapy (n=8); aromatherapy (n=6); reminiscence therapy (n=4); light therapy (n=4); animal-assisted interventions (n=4); physical exercise (n=5), intervention; pet robot interventions (n=3); dementia-care mapping (n=3); and horticultural therapy (n=2). The number of participants ranged from 13 to 435. The intervention periods ranged from 10 days to 15 months, the frequencies from 1 time/week to 21 times/week, and the duration of each time from 5 min to 120 min.	**Primary outcome:** Scales measuring agitation	In traditional pairwise meta-analysis, 3 interventions were associated with a significant reduction in agitation. Personally tailored intervention (SMD, −0.39, 95% CI −0.64, −0.14), massage therapy (SMD, −0.77, 95% CI −1.27, −0.27) and pet robot intervention (SMD, −0.38, 95% CI −0.65, −0.11). In network meta-analysis, the rank probability showed that massage therapy was most likely to be rank 1 (43%), animal-assisted intervention rank 2 (16%), personally tailored intervention rank 3 (18%), and pet robot intervention rank 4 (11%).
Abraha et al. 2017	AMSTAR scores (11	38 systematic reviews including 142 primary studies	Trials examined non-pharmacological interventions	**Primary outcome:**	Among sensory stimulation interventions, only music therapy was associated with a reduction

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Italy **Systematic review of systematic reviews**	items) ranged from 1 to 11	(RCTs and non RCTs), published prior to 2009	designed to treat behavioural disturbances in patients with dementia. Where possible, results were pooled. Interventions included: (1) sensory stimulation interventions (12 SRs, 27 primary studies of acupressure, aromatherapy, massage/ touch therapy, light therapy and sensory garden; (2) cognitive/emotion-oriented interventions (33 SRs; 70 primary studies) of cognitive stimulation, music/dance therapy, dance therapy, snoezelen, transcutaneous electrical nerve stimulation, reminiscence therapy, validation therapy, simulated presence therapy; (3) behaviour management techniques (6 SRs; 32 primary studies) and (4) other therapies (5 SRs, 12 primary studies) of exercise therapy, animal-assisted therapy, special care unit and dining room environment-based interventions	Behavioural and psychological symptoms in dementia (BPSD) outcomes, including multidomain scales and scales specific to agitation	in behavioral symptoms (SMD, −0.49; 95% CI −0.82 to −0.17; p=0.003), and anxiety (SMD, −0.64; 95% CI −1.05 to −0.24; p=0.002). There was no convincing evidence that cognitive-emotion oriented interventions were effective at reducing BPSD. There was some evidence that multicomponent interventions that use a comprehensive, integrated multidisciplinary approach combining medical, psychiatric and nursing interventions can reduce severe behavioural problems in nursing home patients. Other types of interventions were not effective in decreasing BPSD.
van der Ploeg et al. 2013 **Australia** **Crossover RCT**	CA: ☒ Blinding: Patient ☑ Assessor☒ ITT: ☒	44 residents of a long-term care home for > 3 months who exhibited agitation several times per day. Mean age was 78.1 years, 68% were women. Mean MMSE score was 6.	Participants were randomized to Montessori or control blocks for two weeks then switched to the other condition, with no washout period. Both conditions were delivered for 30 minutes 2x/week (total of 4 sessions of each condition) Observations of behavior,	**Primary outcome:** Agitation, during each 1-minute interval over the three 30-minute periods before, during, and after each condition (scores ranged from 0 to 30) **Secondary outcomes:**	Baseline mean agitation scores were 16.7 and 17.1 for the Montessori and control conditions, respectively. During the intervention the mean scores dropped to 8.4 and 10 (Montessori and control). After the intervention, mean agitation scores increased again to 17.6 (Montessori) and 17.0 (control).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			engagement, and affect were conducted in the 30 minutes before, during, and after each session. The intervention was provided by activity facilitators, who selected up to 10 activities per participant based on discussion with the family about participants' former interests and hobbies. Typical selections included listening and singing along to favorite music, looking at and sorting pictures. The control condition was a non-personalized activity featuring one-to-one interaction.	Philadelphia Geriatric Center Affect Rating Scale (PGCARS), Menorah Park Engagement Scale (MPES)	During both the Montessori and control sessions, there was significantly more positive and more interested affect, less neutral affect, more constructive and passive engagement, and less negative engagement.
Cohen-Mansfield et al. 2012 **Israel** **Cluster RCT**	CA: ☒ Blinding: Patient ☒ Assessor☒ ITT: ☒	125 residents of 11 nursing homes with advanced dementia age ≥ 60 years, who lived in the facility for > 3 weeks and who exhibited agitation several times per day. Mean age was 86 years, 74% were women. Mean MMSE score was 8.12.	Participants were randomized into an intervention group (n = 89 from 6 care homes) and a placebo control group (n = 36 from 5 care homes). Persons in the intervention group participated in an activity programme targeted at an unmet need based on the Treatment Routes for Exploring Agitation (TREA) framework. The most common interventions included a simulated social interaction with robotic animals, stuffed animals, etc; one on one interaction; magazine/book reading and listening to music. A placebo intervention was provided for staff on the control units. The treatment phase lasted 2 weeks, with observations	**Primary outcome:** Agitation Behavior Mapping Instrument (ABMI) **Secondary outcome:** Lawton's Modified Behavior Stream (LMBS)	There was a significant decrease in the primary outcome from baseline to end of the intervention among those in the intervention group. The effect was significant for total score, verbal and nonaggressive agitation. There was no significant reduction in any of the AGBI scores for persons in the control group. The difference between groups was significant for both total and subscores. The intervention group showed significant increases in pleasure and interest from baseline to the treatment condition, whereas the control group remained constant. The difference between groups was significant for pleasure and interest, but not for negative affect.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			recorded during the first and last 3 days of this period.		

Non-Pharmacological Interventions to Treat Mood Disorders in Dementia or MCI

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Orgeta et al. 2022 **UK** **Cochrane review**	Using the Cochrane RoB tool, only one domain (detection bias) was high in 1 trial, due to a lack of blinding of outcome assessor. For all other domains, the risk of bias was low or unclear.	29 RCTs including 2,599 participants with dementia (n=24) or MCI (n=5) recruited from any setting. Mean age was >70 years in most trials.	Trials compared psychological interventions with usual care or a placebo intervention (social contact control). Types of intervention included cognitive behavioural therapy (CBT), behavioural activation (BA), problem-solving therapy (PST), all considered forms of CBT (n=15 trials) supportive and counselling therapies (n=11), mindfulness-based cognitive therapy (MBCT, n=3) and interpersonal therapy (IPT, n=1)	**Primary outcomes:** Depression, depression remission **Secondary outcomes:** Patient quality of life (QoL), Activities of daily living (ADL) and cognition, caregivers' QoL, burden, and depressive symptoms	*CBT vs. usual care* At 8-24 months, CBT was associated with a significant reduction in depressive symptoms (SMD=-0.23, 95% CI -0.37 to -0.10, 13 trials, n=893. GRADE: moderate) At 10-12 weeks, the odds of depression remission were significantly higher in the CBT group (OR=1.84, 95% CI 1.18 to 2.88, 2 trials, n=146. GRADE: low) At 3 months to 15 weeks, CBT was not associated with an improvement in symptoms of anxiety (SMD=-0.03, 95% CI -0.36 to 0.30, 3 trials, n=143. GRADE: very low). At 8-15 weeks, CBT was associated with a significant improvement in QoL (SMD=0.31, 95% CI 0.13 to 0.50, 7 trials, n=459. GRADE: moderate) At 12 weeks to 2 years, CBT was associated with significant improvement in ADL performance (SMD=- 0.25, 95% CI -0.40 to -0.09, 7 trials, n=680. GRADE: moderate). At 10 weeks to 2 years, CBT was not associated with significant improvement in cognition (SMD=0.13, 95% CI -0.04 to 0.30, 5 trials, n=401. GRADE: very low).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Supportive and counselling interventions vs. usual care At 9 weeks to 3 years, CBT was not associated with a significant reduction in depressive symptoms (SMD=-0.05, 95% CI -0.18 to 0.07, 9 trials, n=994. GRADE: low) At 9 weeks to 3 years, CBT was associated with a significant improvement in QoL (SMD=0.15, 95% CI 0.02 to 0.28, 8 trials, n=935. GRADE: moderate) At 6 months to 3 years, CBT was not associated with significant improvement in ADL performance (SMD=0.17, 95% CI -0.01 to 0.34, 3 trials, n=511. GRADE: very low). At 10 weeks to 3 years, CBT was not associated with significant improvement in cognition (SMD=0.11, 95% CI -0.03 to 0.26, 6 trials, n=730. GRADE: low)
Tonga et al. 2021 **Norway** **RCT CORDIAL program**	CA: ☒ Blinding: Patient ☒ Assessor☑ ITT: ☒	198 people with MCI or early-stage dementia and their caregivers (n=80). Mean age was 70 years, 53% were men. 65% of participants were not depressed at baseline.	Participants were randomized to receive 11 individual weekly sessions of the CORDIAL program, which included elements from CBT, cognitive rehabilitation, and reminiscence therapy (n=100) or usual care (n=98). Assessments were completed before and after the intervention and at 6-month follow-up.	**Primary outcome:** Montgomery–Åsberg Depression Rating Scale (MADRS) **Secondary outcomes:** Neuropsychiatric Inventory Questionnaire (NPI-Q), and Quality of Life in Alzheimer's disease (QoL-AD)	At 6 months, depressive symptoms were significantly more reduced in the intervention groups (p<0.001). At 6 months, there were no significant differences between the groups in NPI-Q scores or QoL-AD. There were no significant differences in overall trend between the control and intervention group in quality of life or depressive symptoms or anxiety symptoms for caregivers
Cai et al. 2020 **China**	Using the AMSTAR 2 tool, the average level of overall confidence	9 systematic reviews, published from 2005-2019 that included persons with dementia and apathy. The number of original studies (RCTS and non-RCTs)	Reviews included studies that examined non-pharmacological interventions for apathy vs. a control condition (usual care or other interventions) including: 1)	**Primary outcome:** Apathy, assessed using validated scales	2/7 reviews included a pooled analysis; therefore, the results are presented as narrative. Multisensory stimulation: 5/6 reviews were positive.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Review of reviews	was high in one review and low or critically low in the remainder.	contained within each review ranged from 1-30.	sensory stimulation (e.g., sensory stimulation, music therapy, and art therapy), 2) cognitive stimulation, reminiscence therapy, and validation therapy; 3) behavioral management techniques (therapeutic conversation, occupational therapy, progressive muscle relaxation, psychomotor therapy, and nursing staff education); and 4) other interventions (e.g., pet therapy, exercise therapy, dementia special care units, and comprehensive interventions of ≥2 interventions).		Music therapy: 6/6 reviews were positive. Art therapy: 3/4 reviews were positive. Cognitive therapy: 4/7 reviews were positive. Reminiscence therapy: 1/2 reviews were positive. Validation therapy: 1/1 review demonstrated insufficient evidence. Therapeutic conversation: 2/2 positive reviews Occupational therapy: 2/3 positive reviews Progressive muscle relaxation: 1/1 positive review Psychomotor therapy: 1/1 review demonstrated insufficient evidence. Nursing staff education: 1/4 positive reviews Pet therapy: 2/3 reviews were positive. Exercise therapy: 1/1 review was positive. Dementia special care units: 1/1 review was positive. Comprehensive interventions: 1/4 reviews were positive
van der Steen et al. 2018 **The Netherlands** **Cochrane review**	The methodological quality of the studies varied. No trials blinded participants. Bias was unclear or high in most of the other domains	22 RCTs including 1,097 persons with varying degrees of dementia. All participants lived in institutions.	Trials compared a music intervention (≥5 sessions, individual or group) vs. usual care. The interventions were active, whereby persons sang or played instruments (n=10), receptive (listening interventions while there was communication with the therapist, n=2); or a mixture of the two forms (e.g., clapping hands and dancing). Median number of sessions was 14.	**Primary outcomes:** Emotional well-being, mood disturbance, behavioral problems, **Secondary outcomes:** Social behavior, cognition	*End of treatment outcomes* Music therapy was associated with significantly improved emotional well-being (i.e., quality of Life, SMD=0.32, 95% CI 0.2-0.62). Results from 9 trials included. GRADE: Low Music therapy was associated with significantly improved mood/depression (SMD=-0.27, 95% CI -0.45 to -0.09). Results from 11 trials included. GRADE: Moderate Music therapy was associated with significantly improved mood/anxiety (SMD=-0.43, 95% CI -0.72 to -0.14). Results from 13 trials included. GRADE: LOW and decreased behavioral problems (SMD=-0.23, 95% CI -0.46 to -0.01; 10 RCTs, GRADE: moderate).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Music therapy was not associated with decreased aggression, improved social behavior or improved cognition. *Follow-up outcomes (>4 weeks post treatment)* There was no significant improvement at follow-up assessments for any outcomes among persons in the music therapy group.
Leng et al. 2018 **China** **Systematic review**	The risk of performance bias was high. Other biases (detection, selection, attrition and reporting bias) were judged to be low.	21 RCTs including 1,160 patients with MCI and 1,429 patients with dementia. Mean age of participants ranged from 68.5 to 83.1 years. 38% were men. Unclear if some/all participants had depressive symptoms at baseline.	Trials compared physical activity vs. usual care or a non-physical therapy control group. Interventions included a range of activities including Tai Chi, multicomponent training, cycling, treadmill training, walking, and aerobic exercise. Intensity varies from 15-60 minutes, 3-7 days/week. Duration of treatment ranged from 6 weeks to 15 months.	**Primary outcome:** Depressive symptoms **Secondary outcomes:** Neuropsychiatric symptoms, Quality of Life (QoL), Activities of Daily Living (ADL), anxiety and apathy	Physical activity was associated with a significant reduction in depressive symptoms (SMD = −0.23 95% CI, −0.39 to −0.07; p = 0.00). The reduction was significant in trials with short and long-term follow-up. Physical activity was associated with a significant reduction in neuropsychiatric symptoms (MD = −4.62; 95% CI, −9.07 to −0.16; p = 0.04), improvement in QoL (SMD = 0.23; 95% CI, 0.01–0.46; p = 0.04), and ADL (SMD = 0.27; 95% CI, 0.12–0.43; p = 0.0005). There were no significant improvements in anxiety or apathy.
Theleritis et al. 2018 **Greece** **Systematic review**	Using the PEDro scale, 13 studies were high quality, 16 were of moderate quality and 7 were of poor quality	43 studies (38 RCTs, 4 case-control studies, and one retrospective study) including persons with dementia and apathy. Most participants were living in nursing homes and other institutional settings.	Trials examined a variety of interventions including multisensory behavior therapy, music, reminiscence therapy, activity programs, physical activity programs, therapeutic conversation, cognitive stimulation, art therapy, and muscle relaxation, among others. Treatment duration ranged from a one-time session (e.g., music) to 104 weeks.	**Primary outcome:** Narrative synthesis of apathy outcomes	14 studies assessed apathy using an instrument specifically designed for this purpose (e.g, Apathy Inventory). Of these, 9 were positive. 6 studies assessed apathy, when it was a subcomponent of broader scale (e.g, NPI-apathy, Dementia Care Mapping). Of these 5 were positive. In the remaining studies, apathy was not assessed directly.
Tang et al. 2018 **China**	CA: ☒ Blinding: Patient ☒	77 residents of a residential nursing facility aged ≥60 years with mild to moderate dementia (MMSE 10-27) and	Participants were randomized 1:1 to a 12-week sensory stimulation with music program or a control group	**Primary outcome:** AES-C score (18 items; score of 0-75, with higher	The mean AES-C scores at baseline were: Intervention group: 55.1 Control group: 54.5

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
RCT	Assessor☑ ITT: ☒	with an Apathy Evaluation Scale-Clinician (AES-C) score of ≥40. Mean age was 76 years, 49% were women. Mean baseline MMSE score was 16. Mean AES-C score was 54.8.	that received usual care. The intervention group received a 50- minute music intervention, 3x/week, which involved listening to traditional music, and sounds from nature, singing songs and playing a musical instrument (xylophone).	scores indicating greater apathy) **Secondary outcomes:** MMSE, Holden communication scale	The mean AES-C scores after the study were: Intervention group: 52.1 Control group: 55.3 There was no significant difference between groups. There was significant improvement within the intervention group. There were no significant differences between groups for the secondary outcomes.
Woods et al. 2018 **UK** **Cochrane review**	Risk of bias was generally low	22 RCTs including 1,972 people with dementia. Mean age was >75 in the majority of trials. In most trials participants had mild to moderate dementia. 14 trials recruited participants from residential/hospital care settings, 8 recruited participants that were community-dwelling.	Trials compared reminiscence therapy (RT) provided for ≥6 sessions vs. usual care or a control condition. The least intensive intervention was provided as weekly 30-minute sessions for 6 weeks (3 hours total). The most intensive intervention was provided for 30 minutes a day, 5 days a week, for 4 weeks (10 hours total).	**Primary outcome:** Quality of Life (QoL) **Secondary outcomes:** Agitation, communication, ADLs and mood (apathy, anxiety and depression)	Overall, self-reported QoL was not significantly higher in the RT group at the end of the intervention (SMD= 0.11, 95% CI -0.12 to 0.33). Results from 8 trials included. GRADE: Moderate Communication and Interaction scores at end of treatment were significantly improved in the RT group (SMD= -0.51, 95% CI -0.97 to -0.05). Results from 6 trials included. GRADE: Low Agitation measures were not significantly improved in the RT group at the end of follow-up (SMD=0.03, 95% CI -0.17 to 0.24). Results from 3 trials included. GRADE: Moderate Depression measures were not significantly improved in the RT group at the end of follow-up (SMD=-0.03, 95% CI -0.15 to 0.10). Results from 10 trials included. GRADE: High
Virtual Delivery of Cognitive Behavior Therapy					
Mehta et al. 2019 **Canada** **Systematic review & meta-analysis**	1 trial was rated as good, quality, 19 as fair quality and 5 were poor quality	25 RCTs including adults with chronic health conditions including tinnitus (n=6), fibromyalgia (n=3), pain (n=7), rheumatoid arthritis (n=3), cardiovascular disease (n=2), diabetes (n=1), cancer (n=1), heterogeneous chronic	Trials compared the effectiveness of internet-delivered cognitive behavioural therapy (ICBT), self-guided or therapist guided vs. a control condition (information only, group CBT, online discussion, standard	**Primary outcome:** Anxiety and depression	ICBT was associated with significantly greater improvement in anxiety and depression, post treatment (SDM=0.45 and 0.31, respectively). The greatest effects for the outcome of anxiety were reported when the control group received online discussion (SMD=0.59), standard care (SMD=0.63) and waitlist control

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		disease population (n=1), and spinal cord injury (n=1) Unclear if any participants had MCI, VCI or dementia.	care, waitlist control) Duration of treatment ranged from 3 to 65 weeks.		(SMD=0.55). The greatest effects for the outcome of depression were reported when the control group received standard care (SMD=0.57) and waitlist control (SMD=0.60).

Pharmacological Interventions to Treat Neuropsychiatric Symptoms in Persons with Dementia

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mühlbauer et al. 2021 **Germany** **Cochrane review**	Most studies were at high risk of bias in at least one domain	24 RCTs that included 6,090 persons with Alzheimer's Disease or vascular dementia, with demonstrated agitation and/or psychosis. Participants lived in the community and in nursing homes or other institutional settings.	Trials compared typical (n=6) and atypical antipsychotic (n=20) medications vs. placebo. Typical medications included Haloperidol and Thiothixene. The most common atypical agents were Risperidone, Brexpiprazole and Aripiprazole	**Primary outcomes:** Agitation, psychosis, adverse events **Secondary outcomes:** Cognitive functioning	After 3 to 16 weeks, typical antipsychotic medication significantly reduced agitation (SMD= -0.36, 95% CI -0.57 to -0.15, 4 studies) GRADE: very low certainty evidence. Typical antipsychotic mediations were associated with a favourable response to treatment (RR=1.18, 95% CI 1.01 to 1.38, 4 studies). GRADE: moderate certainty of evidence. After 6 to 10 weeks, typical antipsychotic medication significantly reduced psychosis (SMD= -0.29, 95% CI -0.55 to -0.03, 2 studies) GRADE: low certainty evidence. Typical antipsychotic mediations were not associated with a favourable response to treatment (RR=1.31, 95% CI 0.90 to 1.92, 2 studies). GRADE: low certainty of evidence. After 3 to 12 weeks, atypical antipsychotic medication significantly reduced agitation (SMD= -0.21, 95% CI -0.30 to -0.12, 9 studies) GRADE: moderate certainty evidence. Atypical antipsychotic mediations were associated with a favourable response to treatment (RR=1.31, 95% CI 1.16 to 1.48, 4 studies). GRADE: moderate certainty of evidence.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					After 3 to 12 weeks, atypical antipsychotic medication significantly reduced psychosis (SMD= -0.11, 95% CI -0.18 to -0.03, 12 studies) GRADE: moderate certainty evidence. Atypical antipsychotic mediations were associated with a favourable response to treatment (RR=1.13, 95% CI 1.03 to 1.23, 7 studies). GRADE: low certainty of evidence. The risks of extrapyramidal symptoms and somnolence were significantly higher in the typical and atypical antipsychotic groups. GRADE: moderate and high certainty of evidence Quetiapine did not significantly improve cognition (SMD=-0.10, 95% CI -0.28 to 0.07, 4 studies)
Hsu et al. 2021 **Taiwan** **Systematic review & meta-analysis**	Jadad scores ranged from 1-5 (mean 3.5)	14 RCTs including persons with dementia (n = 1,374) with and without a major depressive disorder. Mean age was 76.8 years, 61.9% were women.	Trials compared serotonergic antidepressant treatment with placebo. Drug classes included SSRIs (citalopram/ escitalopram, sertraline, fluoxetine) and non SSRIs (trazodone). Length of treatment or timing of assessment was not stated	**Primary outcomes:** Mean change in scores for overall neuropsychiatric symptoms (NPS) and agitation **Secondary outcomes:** Mean change in depressive symptoms, cognition, and care burden scores	In patients with dementia, serotonergic antidepressants significantly improved overall NPS (Hedges' g = − 0.49, 95 % CI − 0.74 to − 0.24, p < 0.001) and agitation (Hedges' g = − 0.28, 95 % CI-0.43 to -0.14, p < 0.001). In subgroup analysis, SSRIs as a class were found to significantly reduce overall NPS, but non-SSRIs did not, while both drug classes reduced agitation. In patients with dementia, serotonergic antidepressants significantly improved depressive symptoms (Hedges' g = − 0.32, 95% CI − 0.49 to − 0.15, p < 0.001), cognition, (Hedges' g = 0.15, 95 % CI 0.002) and care burden (Hedges' g = − 0.24, 95 % CI − 0.41 to − 0.07, p = 0.01).
Dudas et al. 2018 **UK**	One study had a low risk of bias, one study had a high	10 RCTs including 1,592 patients with dementia and depression. Mean age ranged from 72 to 80 years (mean 75	Trials compared antidepressant medication provided for >4 weeks with placebo. Drug classes included SSRIs (n=5), SSNRIs	**Primary outcomes:** Depression **Secondary outcomes:**	At 6 to 13 weeks, the mean depression scores among persons in the treatment group were not significantly lower (SMD, -0.10, 95% CI -0.26 to 0.06; 614 participants; 8 studies).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Cochrane review	risk and the risk of bias in the remaining trials was unclear	years). Mean baseline MMSE score ranged from 10-24.	(n=1), and TCAs (n=3) and MAO inhibitor (n=1). Duration of treatment ranged from 6 to 24 weeks.	Cognition, quality of life (QoL), activities of daily living (ADL)	At 6 to 12 weeks, treatment with antidepressants did not significantly increase the odds of response to treatment (OR=1.71, 95% CI 0.80 to 3.67; 116 participants; 3 studies), but did increase the odds of remission (OR=2.57, 95% CI 1.44 to 4.59; 240 participants; 4 studies) Treatment with antidepressants did not significantly improve cognition or performance of ADL. Data on QoL could not be pooled. The odds of an adverse event were significantly higher in the treatment group (OR=1.55, 95% CI 1.21 to 1.98)

Safety, Risk Management and Instrumental ADLs

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Falls Reduction Interventions					
Li et al. 2021 **China** **Systematic review & meta-analysis**	All trials were assessed to be at uncertain risk of bias	9 RCTs including 1,411 persons with cognitive impairment including dementia (n=6 trials), dementia defined by severity (mild, mild-moderate (n=2), and MCI (n=1) living at home or in the community. Mean age was 78 years, 56% were women.	Trials compared the effects of physical training vs.a control condition (usual care, waitlist, education, placebo control). Physical activity interventions included home-based exercises, group exercise programs, strength and balance exercises, and Tai Chi. Duration of intervention ranged from 6 weeks to 12 months, and frequency ranged from 1-5 sessions/week.	**Primary outcomes:** Number of falls, incidence rate of falls or number of fallers	The incidence of falls was significantly lower in the intervention group (incident rate ratio [IRR]=0.70, 95% CI 0.52 to 0.95. Results of 9 trials included. GRADE: Low There was no significant reduction in the risk of falls in the intervention group (RR=1.01, 95% CI 0.90 to 1.14). Results of 9 trials included. GRADE: Low
Brims & Oliver 2019 **UK**	Risk of bias was assessed as low or	3 RCTs including 245 people aged ≥65 years, living in a domestic setting with dementia (Alzheimer's	Trials compared the safety of assistive technologies (AT) vs. usual care. ATs were defined as a product, equipment or	**Primary outcomes:** Care home admissions, improved safety (e.g,	There was no significant reduction in the likelihood of admission to a care home (RR= 0.85, 95% CI 0.37- 1.97). Results from 2 trials included.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review & meta-analysis	unclear using Effective Practice and Organisation of Care (EPOC)	Disease, n=2; mild unstated dementia, n=1).	device which is usually electronic or mechanical in nature, and designed to improve independence, safety and/or quality of life. Interventions were 1) a safety tool kit, which including AT items such as a grab rail and a sensor night light, and advice booklet, 2) same as previous + physiotherapist prescribed exercises and 3) night light, a teleassistance service involving a remote intercom, an electronic bracelet and a teleassistance support centre, and a falls prevention class	reduced number of falls, wandering) Outcomes were assessed 3-12 months from baseline	The number of people who fell was significantly lower in the AT group (RR=0.50, 95% CI 0.32- 0.78). Results from 2 trials included.
Booth et al. 2016 **UK** **Systematic review & meta-analysis**	Mean quality score was 7.5 using the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI)	8 RCTs including 1,041 persons ≥65 years, with cognitive impairment. No participants had severe cognitive impairment. The mean age ranged from 70 to 82.5 years, The residential status of the participants was community/home-dwelling (n=3 trials), institutionalized (n=3 trials) and a combination of both settings (n=2 trials).	Trials compared multifactorial or multiple interventions, combining physical and cognitive elements aimed at improving falls risk factors vs. standard care or a single element intervention. 4 studies had two intervention arms, 2 had 3 arms and one had 4 intervention arms.4 Duration of the intervention ranged from 1-12 months. Frequency was ≥2x/week in 8/9 trials. In most of the trials, interventions were completed within a group setting.	**Primary outcome:** Falls **Secondary outcomes:** Berg Balance Scale (BBS), Timed-up-an-go (TUG) and gait speed	Total number of falls was reported in 4 trials, but data could not be pooled. In 2 trials there was a significant reduction in the number of falls in the intervention group from baseline until the end of the intervention period (6 and 12 months. GRADE: Very low Persons in the intervention group had significantly greater gains in BBS scores from baseline (MD=2.3, 95% CI 1.78-2.83. Results from 4 trials included. GRADE: Very low Persons in the intervention group had significantly greater improvement in TUG times from baseline (MD=1.09 sec, 95% CI -1.57 to -0.62. Results 3 trials included. GRADE: Moderate Persons in the intervention group had significantly greater gains in gait speed from baseline (MD=0.8 m/sec, 95% CI 0.03-0.12. Results from 3 trials included. GRADE: Low

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Driving					
Toepper & Falkenstein 2019 **Germany** **Systematic review**	NA	53 studies including persons with Alzheimer Disease and non-Alzheimer Disease Dementias (vascular dementia, frontotemporal dementia, dementia with Lewy bodies and Parkinson disease dementia).	The effects of severity and type of dementia on driving fitness were reviewed and the results reported as a narrative synthesis.	**Primary outcome:** Not applicable	*Vascular dementia* Among the 6 studies that were included suggest that drivers with VaD exhibit severe driving difficulties. Patients with multi-infarct dementia show poorer on-road driving skills than older people with diabetes, healthy older people, or healthy young drivers. Driving scores were inversely associated with cognitive skills, number of collisions, and violations per 1,000 miles driven. One case report highlighted the difficulties of a family in the interaction with a driving family member with multi-infarct dementia. Two more recent studies indicated that about 70% of drivers with very mild and mild VaD fail an on-road driving test, compared to 11% of healthy controls. Following a single stroke, driving performances are poor. Results of a meta-analysis suggests that 46% of these patients do not pass an on-road test.
Financial Capacity					
Bangma et al. 2021 **The Netherlands** **Systematic review & meta-analysis**	NA	47 studies, including persons with a neurodegenerative disease (NDD), the majority of whom had Alzheimer's disease (AD) and MCI (n = 38). Severity of dementia was mild to moderate in most cases.	Studies compared financial decision-making (FDM) in persons with NDDs vs. healthy controls, using a standardized performance-based test (e.g., The Actual Reality test, The Advanced Finances Test, The Financial Assessment and Capacity Test).	**Primary outcome:** Effect size (Hedge's g)	Data from 31 studies were available for pooled analysis. *AD* In cross-sectional studies, FDM was significantly worse in persons with AD compared to healthy control (g=2.69, 95% CI 2.15-3.23], based on 17 studies. In 3 longitudinal studies with follow-up, there was significant deterioration of FDM over a one-year period in persons with AD. *MCI*

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Twenty-six studies investigated FDM in people living with MCI. In cross-sectional studies, FDM was significantly worse in persons with MCI compared to healthy control (g=0.59, 95% CI 0.78-1.11], based on 16 studies. In 7 longitudinal studies with follow-up, there was significant deterioration of FDM over time in persons with MCI, but not in healthy controls. 13 studies included persons living with AD and MCI. Generally, persons with AD fared worse on FDM measures than those with MCI. *Frontotemporal Dementia (FTD)* Three studies investigated FDM in people living with FTD. In 3 cross-sectional studies, FDM was significantly worse in persons with FTDI compared to healthy control (g=2.56, 95% CI 1.73-3.39)
Sudo et al. 2017 **Brazil** **Systematic review**	NA	10 studies including 1,050 participants with any form of dementia (352 with AD, 17 with Parkinson's disease dementia, 25 with dementia of different etiologies). Additionally, there were 189 with MCI, 424 normal controls, 20 family caregivers and 23 family informants. Mean ages of persons with dementia ranged from 69 to 77 years. Most persons had mild to moderate dementia.	In 9 cross sectional studies, performances in financial capacity tasks were compared between persons with dementia and a comparison group (including normal controls, MCI or dementia in a different stage). In the 10th study, the financial capacity of persons with dementia was tracked over time.	**Primary outcome:** Financial capacity, assessed using Financial Competency Questions (FCQ), Financial Capacity Instrument (FCI), Prior Financial Capacity Form (PFCF), Current Financial Capacity Form (CFCF), Semi-Structured Clinical Interview for Financial Capacity (SCIFC) and/or Financial Competence Assessment Inventory (FCAI)	*Basic monetary skills* In the 3 studies that assessed this outcome, the majority of persons with mild AD had preserved function. In the 3rd study, the majority of persons with moderate AD were incapable. *Financial conceptual knowledge* Three studies assessed this outcome. The majority of persons with mild AD were deemed capable in one study. In the second study, 47%, 13% and 40% of subjects with mild AD were capable, marginally capable and incapable for this domain, respectively. In the 3rd study, only 5% of persons with moderate AD were capable. *Cash transactions* Three studies assessed this outcome. The majority of persons with mild AD were deemed capable in one study. In the second study,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					47% of persons with mild AD were capable and 10% were marginally capable. In the 3rd study, none of persons with moderate AD were deemed capable. *Checkbook management* In 2 studies, persons with both mild and moderate AD were deemed incapable in performing this task. *Bank statement management* In 2 studies, persons with both mild and moderate AD were deemed incapable in performing this task. *Financial judgment* In one study, financial judgment was at least marginally impaired in 53% of the subjects with mild AD. In a 2nd study, half of the persons mild AD were considered incapable, while 94% of persons with moderate AD demonstrated incapacity in financial judgment. In the single longitudinal study, there was a 10% decline over one year (from 80% to 70%) in overall financial capacity, assessed using the FCI in persons with mild AD.
Instrumental IADLs					
Zilbershlag et al. 2019 **Israel** **Prospective study**	NA	110 community-residing older adults aged 65 to 92 years with cognitive decline who had been referred by the geriatric clinic team to receive a cognitive-functional evaluation in their natural home environment. 65.5% of participants lived alone. Mean age was 80 years, 31% were men. Persons with an MMSE <10 were excluded.	The functional cognitive evaluation (FCE) was designed and developed to assess safety, capacity for decision making, executive function and IADL performance, administered in the person's home and involves the evaluation of the participants' actual task performance. Components of the FCE were derived from	**Primary outcome:** Predicters of Barthel Index and IADL	*Relationships between the geriatric assessment (clinic) and the FCE (home)* There were significant correlations between the participants' BI clinic scores and PASS scores (r = 0.50) and between IADL scores on the Lawton Instrumental Activities of Daily Living Scale (clinic) and the PASS (home) (r= 0.35). There were moderate significant correlations between FCE cognitive variables and the results of the cognitive clinic assessments.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			Performance Assessment of Self-Care Skills (PASS-Home, Version 3.1), (Barthel Index – dressing; IADL – cooking medical self-care, financial management, telephone use, mobility outside the home), The Executive Function Performance Test (EFPT), the Short Portable Assessment of Capacity for Everyday Decision Making (SPACED) Everyday decision-making capacity and The Home Occupational Environment Assessment (HOEA). In Phase I, the FCE was administered by 5 experienced geriatric OTs. In Phase II a phone survey was conducted with the participant/primary caregiver, two months after the first evaluation, to determine the degree to which the recommendations were being implemented. In phase III, four months after the first visit, another visit was conducted by a different assessor at the participants' homes in order to examine their functional status (BI, IADL) and the level of implementation (of the recommendations made during the first home visit).		*Cognitive predictors of BADL and IADL (first assessment)* In a series of regression models examining independent predictors of IADLs, components of FCE explained between 17% and 63% of the variance. *Predicting BI and IADL in the second assessment* Two multiple regression models were constructed to assess the explained variance in BI and IADL. BI score at first assessment was the biggest predictor of BI at second assessment. The other independent predicters were EFPT score and the extent of application of the recommendations. The model explained 54% of the variance. Independent predictors of IADL at second assessment were BI at first assessment, IADL at first pass, IADL subcomponents, self efficacy and the extent of application of the recommendations. The model explained 60% of the variance.
Jekel et al. 2015 **Germany**	NA	37 studies (29 cross-sectional and 8 longitudinal) including persons with MCI or dementia.	The performance of general IADL and/or specific subdomains was compared between persons with MCI and	**Primary outcome:** Effect sizes (Cohen's d)	In 35 studies, IADL deficits were found in persons with MCI compared with control subjects without cognitive impairment on at least one applied instrument.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic review			healthy controls and/or dementia patients. 10 performance-based assessment instruments, and 23 self-report and informant-report rating instruments were used to assess IADL performance.		*Using performance-based instruments* Total score: Persons with MCI scored lower compared with normal controls. Effect sizes ranged from 0.5-1.02. *Using informant-report rating instruments* Total score: Persons with MCI scored lower compared with normal controls. Effect sizes ranged from 0.29-1.62. *Using self-report rating instruments* Total score: Persons with MCI scored lower compared with normal controls. Effect sizes ranged from 0.17-1.29.
Medication Compliance					
El-Saifi et al. 2018 **Australia** **Systematic review**	NA	18 studies including persons with a primary diagnosis of dementia or cognitive impairment, ≥65 years, living in the community.	Medication adherence, reasons for nonadherence and discontinuation are described. Medications included in individual studies were cholinesterase inhibitors or acetyl cholinesterase inhibitor ChEIs (n=8); ChEIs + memantine (n=4); antihypertensives + dementia drugs (n=1); Donepezil (n=2), and other misc medications (n=1). The medications were not described in 2 studies.	**Primary outcomes:** Medication adherence, reasons for nonadherence and discontinuation	16 articles reported medication adherence and persistence or discontinuation. Medication adherence ranged from 17% to 42% in 7 studies. Medication persistence and discontinuation were reported in 9 studies with values ranging from 20% to 63% depending on the duration of the treatment. Factors associated with discontinuation were medication type, dose (high vs, low) and ease of administration (immediate vs. delayed release), treatment duration, the use of concomitant medications, lack of efficacy and side effects, patient factors (e.g. increasing age). Interventions to improve adherence were explored in 2 studies. Telehealth home monitoring and a switch to a transdermal patch were found to improve adherence.

Environmental Supports

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Woodbridge et al. 2018 **UK** **Systematic review**	NA	72 studies including persons with dementia, of whom 34.7% had moderate–severe cognitive impairment and 15.3% had mild–moderate cognitive impairment. 85% of the included studies were conducted in residential settings vs. 15% in private home environments. Sample sizes in most individual studies were small.	Narrative synthesis of the results of studies that assessed the 'physical environment', defined as everyday design aspects within the living space such as ambient features (e.g. music/ lighting), interior design features (e.g. furnishings and less permanent objects) and architectural features (permanent features, e.g. altering the spatial layout).	**Primary outcome:** Ability to perform ADLs	19 studies evaluated the impact of the physical environment on overall performance across all everyday activities. Factors assessed were size of the environment (n=5), quality of the environment (n=3), architectural layout (n=1), homelike atmosphere(n=4), and tailored individual adaptations (n=6). The results from these studies were largely positive. 4 studies evaluated specific environmental strategies for multiple everyday activities. Factors assessed were tailored individual adaptations (n=1), and assistive technologies (n=3). The one study reporting on adaptations reported a significant benefit associated with the intervention. Doesn't appear that inferential statistics were used in studies of assistive technologies. 15 studies evaluated strategies for assisting mealtimes. Factors assessed were tailored individual adaptations (n=1), assistive technologies (n=1), lighting and contrast (n=3), quality of the environment (n=4), environmental ambiance (n=2), choice of food service delivery (n=4). The outcomes assessed were varied. Results were mixed. 5 studies evaluating strategies for improving hygiene and self-care (handwashing, dental care, dressing and toileting). Factors assessed were tailored individual adaptations (n=1), assistive technology (n=2), familiar cues (n=1), simplifying the environment (n=1). The results of inferential statistical analyses were not reported in 4/5 studies. 5 studies evaluating strategies for improving oriental to time. Factors assessed were cueing

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(n=3) and assistive technologies (n=2). A significant increase in recognition scores was reported in 2 studies. 14 studies evaluating strategies for improving oriental to space. Factors assessed were architectural layout (n=3), familiar cues (n=5), and distracting cues (n=6). The outcomes assessed were varied. Results were mixed. 8 studies evaluating strategies for improving leisure activities. Factors assessed were gardens (n=5), environmental ambiance (n=2) and simplifying the environment (n=1). A significant improvement in quality of life was reported in with increasing garden usage in one study. 2 studies evaluating strategies for improving communications. Factors assessed were architectural layout (n=1) and homelike environment (n=1). Both studies reported significant benefits associated with the intervention.

Abbreviations

AMSTAR: A Measurement Tool to Assess Reviews	ARR: absolute risk reduction	CA: concealed allocation
ARIC: Atherosclerosis Risk in Communities Study	CBT: cognitive behavioral therapy	CI: confidence interval
DBP: diastolic blood pressure	DSM: Diagnostic and Statistical Manual of Mental Disorders	HR: hazard ratio
ITT: intention-to-treat	MMSE: Mini Mental State Examination	MoCA: Montreal Cognitive Assessment
NA: Not applicable, not assessed	NOS: Newcastle-Ottawa Scale	OR: odds ratio
RCT: randomized controlled trial	RR: relative risk	RRR: relative risk reduction
SBP: systolic blood pressure	SMD: standardized mean difference	SSRI: selective serotonin reuptake inhibitors

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