UK National Screening Committee

Population screening for dementia in adults

An evidence map to outline the volume and type of evidence related to screening for dementia in adults for the UK National Screening Committee

Version: 2 [FINAL]

Author: EnSygN Sheffield, SCHARR, University of Sheffield

Date: November 2025

The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care

Contents

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

UK National Screening Committee, Southside, 39 Victoria Street, London, SW1H 0EU

www.gov.UK/UKNSC

Blog: https://nationalscreening.blog.gov.uk

For queries relating to this document, please contact: https://view-health-screening-recommendations.service.gov.UK/helpdesk/

November 2025

Summary

This document discusses the findings of the evidence map on screening for dementia in adults.

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, no further work on screening for dementia should be commissioned at the present time. Although there is a substantial volume of new published research, it continues to lend no support for population screening for MCI and dementia, as the suitability of current screening tests remains in question. Furthermore, new pharmacological interventions are yet to demonstrate meaningful benefits for people with preclinical or early symptomatic dementia, especially when safety concerns and associated costs are taken into account. Non-pharmacological interventions, tend to be complex and/or experimental, with lacking links to population screening.

The UK National Screening Committee (UK NSC) will review the evidence related to screening for dementia in 3-years' time.

Introduction and approach

Background and objectives

The UK National Screening Committee (UK NSC) external reviews are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for dementia is a topic currently due for an updated external review.

Dementia is a progressive clinical syndrome characterised by an ongoing decline of brain functioning which interferes with activities of daily living. The United Kingdom is projected to experience an increase in the number of individuals living with dementia from 2019 to 2050, in line with global trends.[1] Population screening for dementia would involve offering people living in the community and not suspected of having dementia a rapid cognitive assessment test. Those who screen positive would undergo a full diagnostic assessment and would be able to access support from health and social care services while the disease was at a relatively early stage. The National Institute for Health and Care Excellence (NICE) has published guidance on dementia (NG97), covering assessment, management and support for people living with dementia and their carers[2].

Previous review on screening for dementia

The UK NSC does not currently recommend screening for dementia. The committee based this recommendation on the evidence provided by the 2019 evidence summary carried out by Solutions for Public Health. The 2019 review concluded that there remained key areas of concern regarding screening for dementia. These included uncertainties about the prognosis of Mild Cognitive Impairment (MCI) and its subtypes in relation to dementia, the potential from further research into biomarkers and imaging techniques, inconclusive evidence on the effectiveness of pharmacological and non-pharmacological interventions for people with MCI or dementia, and the mixed opinions expressed regarding the acceptability of population screening for dementia in the UK.

The UK NSC is undertaking an evidence map in accordance with its evidence review process of regular, scheduled reviews of existing recommendations.

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic. This evidence map has been developed to assess the volume and type of evidence on key issues related to screening for dementia.

The aim was to address the following questions:

1. What is the volume and type of evidence available on the accuracy of screening tests used to detect MCI and/or any type of dementia?
2. What is the volume and type of evidence available on the pharmacological and non-pharmacological interventions used to treat asymptomatic or pre-symptomatic adults with MCI and/or any type of dementia identified through screening?
3. What is the available evidence of active research or developments (including clinical trials, observational studies, evidence syntheses, patents, or opinions) investigating:
    - Innovative screening tests, diagnostic tools, care pathways or risk assessment approaches for MCI and dementia
    - Novel interventions (both pharmacological and non-pharmacological) to prevent, delay or treat MCI and dementia.

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on screening for dementia in 2025.

The aim of this document is to present the information necessary to inform the UK NSC's decision-making processes.

Search methods and results

Inclusion and exclusion criteria for the evidence map were developed in advance and set out in detail in the study protocols. We included studies from the UK and comparable countries (the United States, Canada, Scandinavia, Western Europe, Australia and New Zealand) published between January 2018 (reflecting the date of the previous review) and June to September 2024 (different search dates for different questions and evidence sources).

For question 1 (accuracy of screening tests), we included studies of the accuracy of any type of screening test in people living in the community and not already suspected of having dementia or MCI. Studies of people with a co-morbidity that could affect cognitive performance were excluded. The reference standard for diagnostic accuracy was a formal diagnosis of MCI or dementia using recognised criteria. Outcomes of interest were sensitivity, specificity, positive and negative predictive values, likelihood ratios and area under the receiver operating characteristic curve. We prioritised studies in randomly assigned or consecutively enrolled populations (diagnostic cohort studies) and systematic reviews of such studies. Case-control studies could be included if few studies of stronger designs were found.

For question 2 (pharmacological and non-pharmacological interventions), the population of most interest was pre-symptomatic/asymptomatic adults (early symptomatic adults if no evidence on asymptomatic populations was found). Participants would ideally be identified by screening but evidence on non-screened populations was also considered. Pharmacological and non-pharmacological approaches were both eligible. Outcomes of interest included but were not limited to reduced cognitive decline, improved physical function, reductions in depression and challenging behaviour, improved independence and quality of life, and reductions in mortality. We prioritised randomised controlled trials and systematic reviews. Further details are reported in the protocol, available at https://fundingawards.nihr.ac.uk/award/NIHR169164.

For question 3 (active research or developments), eligible evidence sources included study protocols, reports of ongoing clinical trials, conference abstracts, patent applications, company information and expert opinion/analysis. Evidence on emerging screening tests, diagnostic tools, and interventions for dementia or MCI were included.

Separate searches were conducted for each of the three review questions. Database searches were developed on Medline and then adapted for the other databases. The searches were limited to studies in English published between January 2018 and June 2024 and were conducted between June and September 2024.

The search for evidence on the accuracy of screening tests (Q1) combined terms for the population of interest (MCI or dementia) with those for the exposure (screening tests). For each facet database thesaurus and free-text terms were used. The Scottish Intercollegiate Guidelines Network diagnosis filter (https://www.sign.ac.uk/using-our-guidelines/methodology/search-filters/ (accessed 6 January 2025)) was applied to the search.

The search for evidence on pharmacological and non-pharmacological interventions (Q2) combined four facets: dementia, screening tests, interventions and a fourth facet that used subheadings with specific thesaurus terms for dementia.

The Medline searches are provided in Appendix 1.

The following databases were searched in July and August 2024: Ovid Medline, PsycINFO, Embase, the Cochrane Library and Social Sciences Citation Index (SSCI) and Conference Proceedings Citation Index – Science (CPCI-S).

For question 3, a database search was not used since the aim was to find emerging screening tests and interventions which are less likely to be in the database literature. However, the sifting process for the population screening evidence map did consider whether references would be more appropriate for the horizon scanning evidence map.

The following sources were searched in August 2024: ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), Prospective Register of Systematic Review Protocols (PROSPERO), AdisInsight, Biomedtracker, Europe PubMed Central (PMC), Patient-Centred Outcomes Research Institute (PCORI) Horizon Scanning Database. Recent proceedings of the Alzheimer Europe and Alzheimer's Disease International conferences were searched in September 2024.

Records retrieved by the literature search were stored in a shared Endnote 20 library and deduplicated before they were imported into EPPI Reviewer.

Results of literature search

The PRISMA flow diagrams (Figures 1 to 3) summarise the literature search and article screening (sifting) process. The flow diagrams were produced using software developed by Haddaway et al.[3]

For accuracy of screening tests (question 1), the database search retrieved 9374 references and deduplication removed 2906 references, leaving 6468 unique references for article sifting. For interventions (question 2), the database search retrieved 6735 references and deduplication removed 1754 references, leaving 4981 unique references for article sifting. In total there were 11189 unique references across both searches and 260 references appeared in both searches.

The search for available evidence on active research or developments (question 3) retrieved 1344 new references. The conferences search retrieved 45 potentially relevant abstracts.

Figure 1: PRISMA flow diagram for Q1

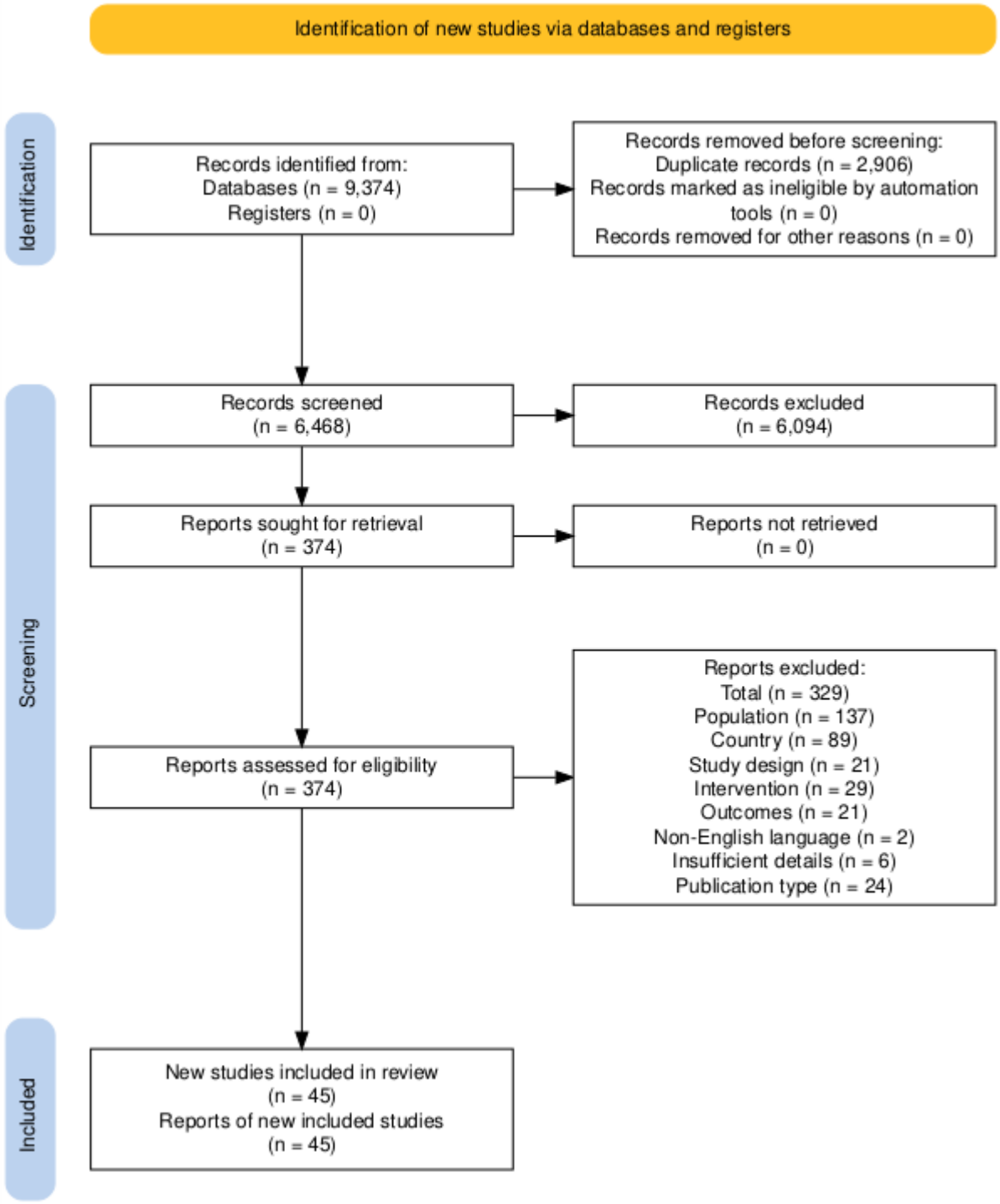


Figure 2: PRISMA flow diagram for Q2

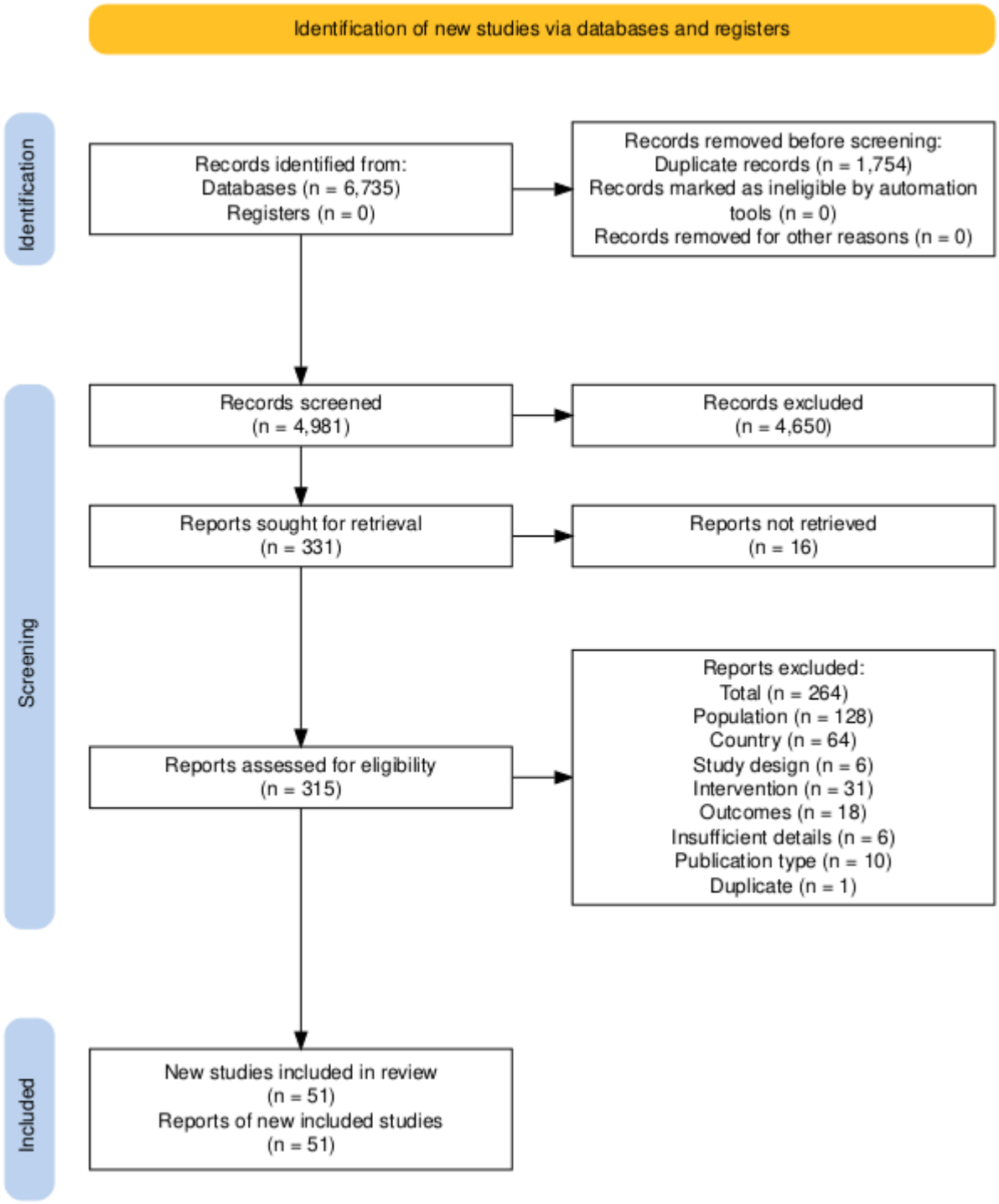
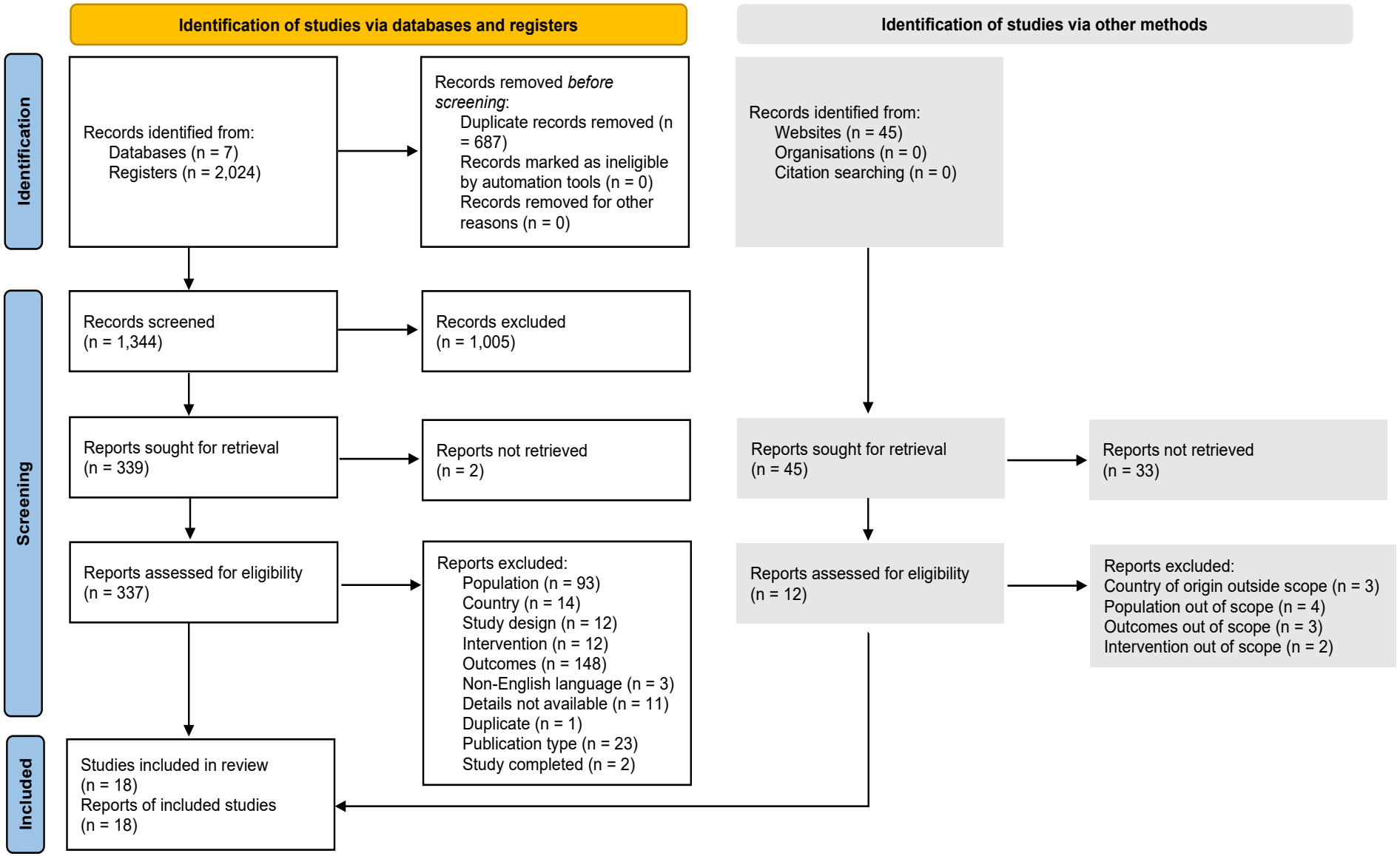


Figure 3: PRISMA flow diagram for Q3



Summary of findings

Question 1

What is the volume and type of evidence available on the accuracy of screening tests used to detect MCI and/or any type of dementia?

We identified 45 studies of screening tests for dementia or MCI, of which 19 were systematic reviews, 14 diagnostic cohort studies[4-17] and 12 diagnostic case-control studies[18-29]. This summary focuses on the best quality (systematic reviews and diagnostic cohorts) and most relevant (screening programmes (if any) and primary care/community settings) evidence.

Two systematic reviews, published in 2019 and 2022, respectively, reviewed screening tools for MCI and/or dementia in primary care settings. Abd Razik et al.[30] covered both dementia and MCI while Karimi et al.[31] focused on MCI. Abd Razak et al. included 30 studies in their review and concluded that the Montreal Cognitive Assessment (MoCA) was the most suitable test for screening for MCI (sensitivity 0.81-0.97, specificity 0.60-0.86). The Addenbrooke's Cognitive Examination (ACE; sensitivity 0.79-1.00, specificity 0.86) was recommended for dementia screening. Studies examined screening by healthcare providers, self-administered questionnaires and caregiver informant screening. A limitation of the review is that patient characteristics were not reported. Karimi et al. stated that all their included studies (n = 21) involved general population samples, mostly aged 60 and older. The authors concluded that a variety of tests, including the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Ascertain Dementia 8-item (AD8) and General practitioner assessment of cognition (GPCOG), as well as the Mini–mental state examination (MMSE), have good sensitivity and specificity in screening for MCI in primary care. The authors noted that none of the studies examined the feasibility of implementing general population screening in primary care.

Turning to studies of specific screening tests, two Cochrane reviews, evaluated the use of Mini-Cog to detect dementia in primary care[32] or community[33] settings. Two further systematic reviews evaluated the IQCODE[34] and AD8[35] screening tools across a range of healthcare settings.

The Cochrane review of Mini-Cog in primary care settings included four studies with a total of 1517 participants. Included studies were performed in Spain, Germany and the USA (two studies). Population characteristics varied across the studies, but three of the four studies (1375 participants) recruited randomly selected samples of primary care patients. The sensitivity of the test ranged from 0.76 to 1.00 and its specificity from 0.27 to 0.85. Only 1 study was judged to be at low risk of bias on all methodological domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. This study reported that the sensitivity and specificity of the Mini-Cog were 0.76 and 0.73, respectively. The authors concluded that in view of the small number of studies, wide range of estimates of accuracy and methodological limitations, there was insufficient evidence to recommend the Mini-Cog as a screening tool for dementia in a primary care setting[32].

The review of Mini-Cog in community settings included three studies with 1620 participants. All studies were conducted by the same research team in the USA. Sensitivity of the Mini-Cog in

included studies was 0.99, 0.76 and 0.99. Corresponding specificities were 0.93, 0.89 and 0.83. All the studies were judged to have methodological limitations; in particular, the prevalence of dementia in two of the studies was higher than would normally be expected in community samples and patients with 'questionable' dementia were excluded from two studies, which may have affected accuracy of the test and relevance of the studies to population screening. The authors' conclusions were similar to those of the review in primary care settings, namely that the small number of studies and their methodological limitations made it difficult to make recommendations for or against Mini-Cog as a dementia screening test[33].

Burton et al.'s Cochrane review of the IQCODE tool[34] included three studies (626 participants), all of which recruited from specialist centres, limiting their relevance to population screening. As with the other Cochrane reviews, the authors concluded that evidence was insufficient to make a recommendation on the use of the tool.

Chen et al. reviewed studies of AD8 for detecting early cognitive impairment in primary care, the community, clinics and hospitals[35]. Four of the seven included studies (3728 participants) were from community settings and one from primary care. All the studies were reported to be of good methodological quality. The sensitivity of the test was higher than its specificity, indicating that false positive results were likely. This was the only review that pooled results in a meta-analysis. Areas under the summary receiver operating characteristic (ROC) curve were 0.83 to differentiate normal cognition from MCI and dementia, and 0.92 to differentiate non-dementia from dementia. On average, the test took less than 3 minutes to administer. The authors concluded that the AD8 is a 'competitive' tool for screening for cognitive impairment in primary care settings. However, both IQCODE and AD8 are informant-based tools, which may make them less useful for general population screening because some people eligible for screening may not have a suitable and readily available informant.

Finally, among the key evidence sources, Patnode et al. (2020) published an updated systematic review on screening for cognitive impairment in older adults for the United States Preventive Services Task Force (USPSTF)[36]. This broad-ranging review covered accuracy of screening tools but also included studies of interventions to treat MCI and mild to moderate dementia, as well as interventions aimed at caregivers. In terms of screening tests, 59 studies (38531 participants) assessed the accuracy of 49 different screening tools. The most studied tool was the MMSE, with a pooled sensitivity of 0.89 (95% CI, 0.85 to 0.92) and specificity of 0.89 (95% CI, 0.85 to 0.93) to detect dementia. Overall, the review found moderate evidence of adequate sensitivity and specificity for detecting dementia. For MCI, very brief (5 minutes or less to administer) and brief (up to 10 minutes to administer) screening instruments were classified as inconsistent and imprecise, with wide variation in sensitivity and specificity.

Patnode et al. also identified one randomised trial (4005 participants) in the USA that compared screening with no screening in primary care patients aged 65 years or older[37]. Patients who screened positive were referred for further diagnostic assessment and if appropriate to a local memory clinic. This study found no differences in health-related quality of life between groups or over time (up to 12 months). There were also no significant differences in health care utilisation, advance care planning, and dementia recognition by physicians at 12 months. Patnode et al. concluded that this trial provides low strength evidence of no benefit from screening[36].

In addition to the above we identified a broad systematic review of MCI screening[38]; an additional systematic review of the accuracy of the Mini-Cog tool[39]; and reviews of the Quick Mild Cognitive Impairment (QMCI) tool[40] and 6-item cognitive impairment test (6-CIT)[41]. Elliott et al.[42] reviewed evidence on the accuracy of telephone-based cognitive screening tests and

concluded that there was limited diagnostic accuracy evidence for the many tools available (15 different tools were included).

Other approaches to screening covered by systematic reviews were drawing[43]; a variety of digital tools[44-46]; and changes in visual evoked potentials[47], spatial orientation[48] and gait[49].

We also identified 14 diagnostic cohort and 12 case-control studies but given the volume of systematic review evidence, these are not discussed further other than to highlight that the terminology around screening and diagnosis was inconsistent and populations were not always clearly defined. Summaries of selected studies are attached to this report.

In summary, new and updated systematic reviews continue to point to a lack of evidence to support population screening for MCI and dementia. Although there is a substantial volume of new evidence and that an evidence map does not include formal quality assessment; the type of evidence identified is unlikely to lead to a change in the UK NSC's current recommendation.

Question 2

What is the volume and type of evidence available on the pharmacological and non-pharmacological interventions used to treat asymptomatic or pre-symptomatic adults with MCI and/or any type of dementia identified through screening?

We included 51 studies related to treatment interventions. Evidence on asymptomatic or pre-symptomatic adults was limited (6 studies) so studies on other early symptomatic/non-screened populations (including people diagnosed with MCI or 'prodromal Alzheimer's disease (AD)') were considered for inclusion as specified in the protocol. No studies of people with screen-detected MCI associated with population screening programmes were identified. We have divided the included interventions into pharmacological and non-pharmacological groups; one systematic review is included in both groups[50].

Pharmacological interventions

Number of studies and designs

Overall, 15 studies were identified to evaluate the effectiveness of pharmacological interventions used to treat asymptomatic or pre-symptomatic adults with MCI. These included 1 systematic review with network meta-analysis[51], 1 systematic review with meta-analysis[52], 2 systematic reviews[50, 53], and 11 reports of randomised controlled trials (RCTs)[54-64].

Population samples, conditions of interest and settings of recruitment

Amongst those systematic reviews with or without meta-analyses, 3 reviews assessed individuals from mixed population samples[50-52], whereas the study population in Hort et al's systematic review[53] was primary care/community sample. These reviews targeted individuals with MCI and/or early dementia. All of them included studies published in multiple countries.

The majority of the RCTs targeted pre-symptomatic/asymptomatic [59, 64] or early symptomatic dementia/ AD[54-58, 60, 61, 63]. One RCT included patients with 'mild' dementia[62]. Most studies recruited participants primarily from secondary care settings[54, 55, 59, 60, 62, 64], while 2 recruited from primary care or community settings[58, 61]. Three RCTs did not report the study setting[56, 57, 63]. Of the 11 studies, 4 were conducted in the USA[58-61] and 7 were conducted across multiple countries[54-57, 62-64].

Interventions evaluated

Systematic reviews with or without meta-analyses evaluated the impact of various pharmacological interventions namely, anti-amyloid-ß monoclonal antibodies including donanemab, lecanemab, aducanumab[51, 52], acetylcholine esterase inhibitors including donepezil and galantamine[50], melatonin[51], Ginkgo biloba extract[50, 53], and memantine[50].

Donanemab was the most frequently evaluated pharmacological intervention in managing asymptomatic or pre-symptomatic adults with MCI and/or any type of dementia; assessed by

three RCTs[60, 61, 63]. Other interventions, each evaluated in a single trial, included gantenerumab[54], lecanemab[55], zagotenemab[56], tilavonemab[57], posiphen[58], atabecestat[59], neflamapimod[62], and solanezumab[64].

Outcomes/findings

A systematic review with network meta-analysis by Terao and Kodama 2024[51] included 10 randomised placebo-controlled trials with 4,599 patients. They evaluated the relative efficacy of melatonin compared to donanemab, lecanemab, and aducanumab in people with mild AD and MCI on cognitive function, tolerability and acceptability. Melatonin was significantly more effective than donanemab (standardised mean difference (SMD) –1.73 (–3.22 to –0.25)), lecanemab (–1.85 (–3.27 to –0.42)), aducanumab (–2.02 (–3.47 to –0.56)), and placebo (–2.27 (–3.42 to –1.12)) on cognitive function. However, donanemab, lecanemab, and aducanumab were not superior to placebo. They rated risk of bias as “not serious” and the level of certainty of evidence as high.

Dantas et al. (2023)[52] meta-analysed 19 studies with 15,275 patients that evaluated anti-amyloid-ß monoclonal antibody therapy in patients with early AD. Monoclonal antibody therapy reduced cognitive (SMD −0.80 (95% CI −1.25 to −0.35; p < 0.01)) and functional decline (mean difference (MD) −0.30 (95% CI −0.42 to −0.19; p < 0.01)) compared to placebo. Similar results were observed in different clinical stages such as MCI and mild dementia for both outcomes. However, anti-amyloid-ß monoclonal antibodies significantly increased the risk of amyloid-related imaging abnormalities (ARIA), including ARIA-oedema (relative risk (RR) 7.7), ARIA-haemorrhage (RR 1.8), and symptomatic or serious ARIA (RR 14.1).

Zhang et al. (2019)[50] reviewed 7 studies on pharmacological interventions to improve gait in people with cognitive impairment. Sample sizes ranged from 14 to 120 with a mean age from 67.8 to 85.4. The majority of participants in all studies were female. One study was rated as low risk of bias, 4 as moderate risk, and 2 as high risk. They included donepezil, galantamine, rivastigmine, memantine and gingko biloba extract in the intervention group. Findings suggested that memantine may improve gait variability, while Ginkgo biloba extract may enhance cadence in dual-tasking. Results for other medications were inconsistent.

Based on the randomised controlled trial results, donanemab and lecanemab showed significant clinical benefits[55, 60, 61, 63]. Other medicines such as gantenerumab, zagotenemab, tilavonemab, neflamapimod, and solanezumab did not show efficacy in slowing clinical or cognitive decline[54, 56, 57].

Pharmacological treatments for AD have shown mixed outcomes. Donanemab and lecanemab offer some promise, as they appear to slow cognitive and functional decline in early AD. However, these benefits come with significant safety concerns that need careful consideration. Other disease-modifying drugs such as gantenerumab, zagotenemab, tilavonemab, neflamapimod, and solanezumab did not show efficacy in slowing clinical or cognitive decline.

Non-pharmacological interventions

Number of studies and designs

Overall, 37 studies (18 systematic reviews and 19 empirical primary studies) were deemed eligible and included in this mapping review. Fourteen of these studies were systematic reviews with meta-analyses[65-78], while four were systematic reviews using various narrative synthesis approaches[50, 79-81]. From those systematic reviews with a meta-analysis, 10 reviews included RCTs[66, 68, 70-75, 77, 78] with one review including randomised sham-controlled trials[77]. The other four reviews with a meta-analysis included mostly cross-sectional studies[65], prospective cohort studies[67,] and experimental non-randomised studies[69]. The number of included studies in the meta-analyses ranged from five to 19 with most of the meta-analyses including more than 10 studies. The remaining 19 empirical primary studies were RCTs[82-100], with one[98] including a substratum of participants from a larger trial, and another[99] conducting subgroup analyses based on a larger trial. Among the RCTs, one was described as a sham-controlled cross-over trial[19], one as a cluster RCT[85,] one as a feasibility study[91] and one as a pilot study[93]. Additionally, one study[90] was described as having both feasibility and efficacy components. In three cases[84, 95, 96], double-blinding was implemented, while in 11 cases, single or partial blinding was performed. In five cases, the level of blinding was not reported, while in one case[90], no blinding was undertaken. Overall, six of the primary empirical studies were conducted in the USA, one in Canada, two in the UK[88, 94], one in Switzerland, and the rest were conducted in countries of the European Union.

Population samples, conditions of interest and settings of recruitment

Amongst those systematic reviews with meta-analyses, five reviews assessed individuals with diagnosed MCI)[65, 68, 70, 71, 73] and nine reviews assessed individuals diagnosed with MCI or mild-dementia[66, 75], cognitive healthy individuals and individuals with MCI or AD[67], individuals diagnosed with MCI or dementia or AD[69], cognitive healthy individuals and individuals with MCI[72], individuals diagnosed with early dementia[74], individuals with AD or MCI[76], individuals diagnosed with MCI, probable early dementia, or early dementia[77], and individuals diagnosed with MCI or subjective cognitive decline (SCD)[78]. Amongst those systematic reviews without a meta-analysis, one review assessed cognitive healthy individuals, individuals with MCI, and individuals with dementia[79], two reviews exclusively assessed individuals with amnestic mild cognitive impairment (aMCI)[80] and individuals with MCI[81], and one review assessed a combination of individuals with MCI, dementia, or AD[50].

Amongst the empirical primary studies (n=19), 10 studies targeted individuals with diagnosed MCI (e.g., aMCI, MCI, MCI due to AD)[82-87, 92, 93, 97, 98], one study targeted individuals with probable MCI[89], one study targeted individuals with early dementia or MCI[88], one study targeted individuals within early stages of dementia[90], one study targeted individuals with MCI or mild dementia[91], one study targeted individuals with mild dementia[94], one study targeted individuals with aMCI or mild AD[95], one study targeted individuals at-risk of cognitive decline or dementia[96], one study targeted individuals with early AD[99], and one study targeted individuals at early stages of dementia[100]. Amongst the primary empirical studies, nine studies recruited individuals from medical settings (e.g., medical centres, memory clinics, hospitals), three studies recruited participants from both community and medical settings[82, 88, 97], six studies recruited participants from community centres[91, 93, 94, 98-100], and one study recruited participants from the general public[96].

Interventions evaluated

Amongst reviews with a meta-analysis (n=14), six reviews assessed the impact of a variety of cognitive interventions[66, 70, 71, 75, 77, 78]. One review assessed the impact of a combination of cognitive and physical interventions[68], two reviews assessed the impact of stimulation methods, such as transcranial direct stimulation[72] and non-invasive brain stimulation[76], one review assessed the impact of online memory interventions[74], one review assessed the impact of virtual reality interventions[69], one review assessed the impact of Mediterranean diet[67], one review assessed the impact of walking interventions[73], and one review assessed the impact of walking, verbal fluency and counting tasks[65]. Amongst those reviews without a meta-analysis, one review assessed the impact of physical activity interventions[79], one review assessed the impact of cognitive intervention programmes (e.g., computer-based, cognitive rehabilitation, cognitive training programmes)[80], one review assessed the impact of dietary and nutritional interventions[81], and one review assessed the impact of a wide range of interventions (e.g., medication-based, medical devices, exercise-based, combination of cognitive and exercise) on gait improvement[50].

Amongst the primary empirical studies (n=19), two studies assessed the impact of exercise-based or physical activity interventions[97, 99], four studies assessed the impact of combined cognitive-based and physical activity/exercise interventions[82, 86, 88, 96], 11 studies assessed the impact of a wide range of cognitive-based psychological, psychotherapeutic, psycho-educational, self-management and health promotion interventions or combinations of those[80, 83, 85, 87, 90-94, 98, 100] and two studies assessed the impact of transcranial stimulation[84, 95].

Outcomes/findings

Findings drawn from systematic reviews with meta-analyses

Amongst those interventions with at least a clearly-demarcated cognitive-based component, two reviews assessed the effectiveness of mindfulness-based interventions on key outcomes. In the first review[70], mindfulness-based interventions were not found effective in reducing depression and anxiety and improving attention, while in the second review[78] mindfulness-based interventions were found effective in reducing depression (g = -0.58, 95% confidence interval (CI): -0.91, -0.24, p=0.37, I^2 = 5%) and anxiety (g = -0.30, 95%CI: -0.49, -0.11, p<0.01, I^2 = 73%) at immediate post-intervention. To note, the meta-analyses on depression and anxiety of the second review included four and eight studies, respectively[78]. Also, these statistically significant effects were not replicated at follow-up (3-9 months post-intervention), while no statistically significant effects of mindfulness-based interventions on stress, quality of life (QoL), and mindfulness were found. To note, in the first review[70] older adults with MCI were recruited, while in the second review[78] both adults with MCI and SCD were recruited. The rest of the reviews with meta-analyses that assessed the effects of cognitive-based interventions on key outcomes showed that cognitive interventions were found effective to improve QoL at post-intervention in adults with MCI (SMD=0.53, 95%CI: 0.23, 0.84, p<0.01, I^2 =80%), however these effects were not replicated at follow-up (3-24 months)[71]. Also, information and communication technology (ICT)-based cognitive training was found effective in improving overall cognitive functioning (SMD=0.37, 95%CI: 0.22, 0.51, p<0.00001, I^2 = 15%), verbal and semantic fluency (SMD=0.38, 95%CI: 0.09, 0.66, p=0.009, I^2 =40%), the forward digit span test results (SMD=0.98, 95%CI: 0.28, 1.68, p=0.006, I^2 = 71%), the backward digit span test results (SMD=1.20, 95%CI: 0.85, 1.56, p<0.00001, I^2 = 27%), in delayed recall results (SMD=0.85, 95%CI: 0.57, 1.13, p<0.00001, I^2 = 0%), in depression scores (SMD=−0.90, 95%CI: −1.33, −0.46, p<0.0001, I^2= 40%), in QoL (SMD=0.36, 95%CI: 0.05, 0.67, p = 0.02, I^2 = 0%) in community-dwelling older adults with cognitive

dysfunction[66]. Cognitive training was also found effective in improving overall attention (g=0.41, 95%CI: 0.13, 0.7, p=0.005, I^2 = 72.79%), selective attention (g=0.37, 95%CI: 0.19, 0.55, p=0, I^2 = 32.13%), divided attention (g=0.38, 95%CI: 0.03, 0.72, p=0.32, I^2 = 10.97%), global cognitive function (g=0.3, 95%CI: 0.02, 0.58, p<0.05, I^2 = 0%)[75]. Cognitive remediation interventions were found effective in improving the instrumental activity of daily living at post-intervention (SMD=0.17, 95%CI: 0.03, 0.31, p<0.02, I^2 = 22.17%)[77]. Multi-component cognitive-based interventions (i.e., simultaneous cognitive intervention based on cognitive stimulation, cognitive training and/or cognitive rehabilitation or combined cognitive and physical interventions) were found effective in improving overall cognition (SMD=-0.249, 95%CI: -0.431, -0.067, p<0.05, I^2 =0%) in older adults with MCI[68].

Two reviews assessed the effects of brain stimulation techniques on cognitive outcomes. The transcranial direct current stimulation was found effective in improving cognitive function in older adults with/without MCI at immediate post-intervention (SMD = 0.16, 95%CI: 0.03, 0.28, p = 0.05, I^2 = 54%), however these effects were not replicated for learning and memory, and executive function outcomes, and 1-month post-intervention cognitive function[72]. Non-invasive brain stimulation was found effective in improving global cognition (SMD=1.14; 95%CI: 0.49,1.78; p = 0.001; I^2 = 90.2%) and neuropsychiatric symptoms (SMD=0.82; 95% CI: 0.13, 1.50; p = 0.019; I^2 = 86.1%) in adults with AD and MCI[76].

Two reviews assessed the effects of walking interventions and motor dual-task on cognitive functioning and walking costs in individuals with MCI, respectively[65, 73]. Walking interventions were found to be effective in improving walking endurance in individuals with MCI (MD=23.70, 95%CI: 6.12, 41.28, p=0.008, I^2 =50%), while no significant effects of walking interventions on processing speed, global cognitive function, and verbal learning were found[73]. Compared to age-matched controls, individuals with MCI were found to have higher motor dual-task costs on serial subtraction (MD=9.54; 95%CI: 3.93, 15.15, p<0.05,) and verbal fluency tasks (MD=10.06; 95%CI: 6.26, 15.65, p<0.05)[65].

Two reviews assessed the effects of online memory training interventions and virtual reality interventions in individuals at the early stages of dementia[74] and individuals with MCI/dementia[69], respectively. Online training memory interventions were found to improve memory (d=0.57, 95%CI: 0.28, 0.85, p=0.0001, I^2 = 55%), overall cognition (d=0.36, 95%CI: 0.16, 0.57, p=0.0006, I^2= 24%), and depression (d=0.45, 95%CI: -0.79, -0.12, P=0.0008, I^2 = 0%); however, in the meta-analysis of the latter outcome (i.e., depression), only three studies were included[74]. Virtual reality interventions were found effective in improving overall cognition (SMD=0.42, 95%CI: 0.24, 0.60, p=0) and physical fitness (SMD=0.41, 95%CI: 0.16, 0.65, p=0.01)[69]. One review and dose-response meta-analysis assessed the impact of Mediterranean diet uptake in individuals with MCI and AD[67]. Higher adherence to Mediterranean diet was associated with a lower risk for MCI (RR=0.91, 95%CI: 0.85, 0.97, p<0.05, I^2 =0%) and lower risk for AD (RR=0.89, 95%CI: 0.84, 0.93, p<0.05, I^2 =42.1%).

Findings drawn from systematic reviews without meta-analyses

Data drawn from systematic reviews without meta-analyses showed that physical activity interventions have a positive impact on global cognition and executive function in individuals with MCI, while there was inconsistent evidence regarding the effects of physical activity interventions on cognition in individuals with a diagnosis of dementia[79]. Also, cognitive training and cognitive rehabilitation programmes were found to have positive effects on overall cognition (e.g., memory, language, executive function)[80]. One review assessed the effects of dietary interventions on cognitive outcomes in individuals with MCI with a high heterogeneity being

evident amongst the included studies[81]. Briefly, there was some evidence that uptake of certain dietary interventions (e.g., B vitamins, omega-3 fatty acids, polyphenol-rich foods) were associated with improvements in memory function, while mixed evidence were found regarding the association between dietary interventions and global cognitive functioning[81]. Also, the implementation of exercise programmes combining strength, balance, and functional mobility training was associated with improvements in gait speed and mobility, while programmes combining exercise and cognitive training were associated with gait speed and dual-task performance[50].

Findings drawn from the empirical primary studies

Amongst those empirical primary studies that assessed the effects of a wide range of cognitive-based psychological, psychotherapeutic, psycho-educational, self-management and health promotion interventions or combinations of those (see above), the following findings were drawn: cognitive training was found to improve the delayed composite memory score in individuals with MCI at immediate (Z-score=0.35, 95%CI: 0.06, 0.64, p<0.05) and short-term post-intervention follow-up (Z-score = 0.33, 95%CI: 0.03–0.64, p<0.05), while no evidence was found regarding the effect of cognitive training on depression and anxiety[83]; wellness education groups were found to be more effective than computerised cognitive training in improving QoL of individuals with MCI (effect size (ES) = 0.34, 95%CI: 0.05, 0.64; p=0.15), while wellness education and yoga compared to computerised cognitive training and support groups were found to significantly improve mood (ES=0.53; 95%CI: 0.21, 0.86; p=0.01) and memory-related activities of daily living (ES=0.43; 95%CI: 0.13, 0.72; p=0.04), respectively[85]; cognitive rehabilitation was associated with improvements in overall cognitive functioning (d=-0.439, p=0.01) in individuals with MCI and mild dementia[87]; personalized cognitive stimulation was associated with improvements in overall cognitive functioning (η^2_p= 0.014; 95%CI: 0.018, 0.107, p<0.05), global orientation, and spatial orientation in older adults with possible MCI[88]; the implementation of dignity therapy in individuals with early stage dementia was associated with improvements in depression and anxiety, physical and social QoL, spiritual well-being[90]; a tablet-based intervention consisting of dementia friendly applications was associated with improvements in well-being and self-management dimensions and self-efficacy in people with mild dementia[91]; the implementation of a cognitive virtual reality rehabilitation system treatment was associated with improvements in free and cued selective reminding test, clock drawing test, and trail making test in individuals with MCI[92]; memory training was found to be associated with improvements in overall cognitive functioning, objective and subjective compared outcomes compared to health training in individuals with MCI[93]; the implementation of an intervention aiming to promote self-management, independence and self-efficacy in people with early-stage dementia (i.e., Journeying through Dementia programme) was not associated with statistically significant differences in QoL compared to usual care[94]; the testing of speed of processing training was associated with improvements in cognitive speed of processing for visual attention tasks compared to an active control group in adults with MCI[98]; the implementation of a psychoeducational intervention was associated with increased use of services compared to control conditions in individuals with early dementia[100].

Four empirical primary studies assessing the effects of multi-component interventions that target different domains of cognition and behaviour in individuals with cognitive decline and dementia were included in this mapping review. Physical exercise combined with interactive effortful cognitive challenge was associated with improvements in executive function (ESs ranging from 0.47-0.51) and verbal memory[82]. A combined physical-cognitive training implemented in individuals with MCI was associated with improvements in neuropsychiatric symptoms (p=0.0155) and QoL (p=0.0013)[86]. An in-person home-based exercise rehabilitation

programme that promotes access to community activities was associated with improvements in fear of falling and social connection in individuals with early dementia[88]. The implementation of a multi-domain lifestyle intervention consisting of nutritional guidance, exercise, cognitive training, and management of vascular risk factors was associated with improvements in cognitive outcomes and executive functioning[96].

Two empirical primary studies that assessed the effects of exercise/physical activity interventions in individuals with MCI and early AD were included in this mapping review. The implementation of a structured exercise programme was associated with improvements on physical fitness of individuals with MCI (moderate ESs ranging from 0.4 to 0.6); however, no intervention effects were observed in their cognitive performance[97]. In a secondary analysis of trial data, aerobic exercise was associated with improvements in function independence of individuals with early AD and sustained ability of those individuals to independently perform activities of daily living[99].

One empirical primary study assessed the impact of exposure to non-invasive brain stimulation with transcranial alternating current stimulation in individuals with MCI due to AD[19]. The results showed that exposure to non-invasive brain stimulation with transcranial alternating current stimulation was associated with improvements in verbal learning test recall (MD=5.7, 95%CI: 4.0, 7.4], p<0.001) and long-delayed recall scores (MD=1.3, 95%CI: 0.4, 2.1], p=0.007)[19]. One empirical primary study assessed the impact of combined cognitive training and neurostimulation in individuals at the early stage of cognitive impairment. Combined cognitive training and neurostimulation was associated with improvements in working memory (Z = 1.168, p = 0.035, d = 0.76) and attention processing speed (Z = 2.025, p = 0.043, d = 0.67) at post-intervention and in the working memory at 6-month follow-up (Z = 2.213, p = 0.027, d = 0.72)[95].

In summary, based on data from systematic reviews and empirical primary studies, a wide range of cognitive and behavioural domains were targeted and interventions were generally effective in improving both overall and domain-specific cognitive function in the populations studied. However, evidence regarding the effects of cognitive-based interventions on psychological outcomes, such as depression and anxiety, was mixed. Even in cases where improvements were observed, these effects were often not long-lasting. Some evidence suggested that cognitive-based interventions could positively impact QoL for individuals; however, data on this aspect were limited. Brain stimulation techniques were also found to be effective in enhancing overall and domain-specific cognitive functioning, although the evidence base for these interventions was similarly limited. Online memory training demonstrated effectiveness in improving cognitive functioning and reducing depressive symptoms, but again, data in this area were sparse. Walking- and exercise-based interventions were generally effective in improving walking and exercise-related outcomes, while adherence to a Mediterranean diet was associated with a lower risk of MCI and AD. The evidence above suggests that certain interventions can have a positive impact on individuals with cognitive difficulties. However, these findings should be interpreted with caution, as in many cases, the study populations were not homogeneous in terms of their cognitive levels (e.g., MCI, early AD, early dementia, AD and SCD).

In conclusion, the volume of potentially relevant new evidence is large but pharmacological interventions evaluated in randomised controlled trials have yet to demonstrate meaningful benefits for people with preclinical or early symptomatic dementia, especially when safety concerns and associated costs are taken into account. There are large numbers of new systematic reviews and trials of non-pharmacological interventions for people with MCI but many of these are complex and/or experimental and links with population screening are lacking.

Question 3

What is the available evidence of active research or developments (including clinical trials, observational studies, evidence syntheses, patents, or opinions) investigating:

- **Innovative screening tests, diagnostic tools, care pathways or risk assessment approaches for MCI and dementia**
- **Novel interventions (both pharmacological and non-pharmacological) to prevent, delay or treat MCI and dementia**

Number of studies and designs

Overall, our horizon scanning identified 18 reports of active research or development initiatives. These included 11 on-going clinical trials, 6 published study protocols, and 1 expert review.

Nine on-going clinical trials involved treatment-based interventions, whereas 2 trials involved screening tests. Amongst the treatment interventions, 6 were pharmacological[101-106], one non-pharmacological[107], one involved a precision-medicine approach[108], and one a vaccine intervention[109].

The trials of screening tests involved cognitive assessment tools[110, 111] and both employed non-randomized diagnostic design. All studies involving treatment-based interventions were randomised controlled trials.

Amongst all on-going trials, 7 are conducted across locations in the USA[101, 103, 104, 106-109]. Three trials are conducted in Europe, including Belgium[111], Netherlands[102], and Norway[105]and 1 trial is conducted across sites in Australia and New Zealand[110].

Amongst the study protocols (n=6), 4 focused on treatment-based interventions, whereas 2 focused on screening tests. All treatment-based interventions were non-pharmacological[112-115], whereas the two screening tests involved cognitive assessment tools[116, 117]. All the study protocols involving treatment-based interventions and one screening test protocol[117] were RCT design, in addition to one diagnostic cohort study[116]. Three protocols were published in the USA[113, 115, 117]. Three were published in Europe, with one in Italy[112], one in Sweden[114], and one in Germany[116].

Population samples, conditions of interest and settings of recruitment

Those diagnosed with early symptomatic dementia[101, 105],early symptomatic dementia/MCI[103, 104, 108], AD/dementia[109] and early onset AD[102] were the target population of on-going clinical trials of treatment interventions.

These trials recruit individuals from various settings, including primary care/community[102, 104, 107], secondary care[103, 105], mixed settings[101], or the general population in case of the vaccination trial[109] and the precision medicine trial[108]. In terms of clinical trials of screening tests, these are designed for early detection of MCI/AD[111] or AD alone[110]. Consequently, these trials recruit participants from either primary care/community[110] or secondary care[111] settings.

Moving onto study protocols, treatment-based interventions target either pre-symptomatic individuals or early symptomatic AD patients[113], those diagnosed with MCI[112, 114], or those at-risk for AD[115]. These studies intend to recruit participants primarily from primary care/community settings[112, 113, 115], with a single study to recruit from secondary care[114]. The screening tests described in published protocols are intended for early detection of AD in a sample drawn from the general population[116], or cognitive impairment (including AD and related dementias) in a sample from primary care/community setting[117].

Novel interventions and screening tests used

Amongst the on-going clinical trials involving pharmacological interventions (n=6),1 trial is investigating monoclonal antibody JNJ-63733657[101]. One trial is investigating a gene therapy using adenovirus to deliver human brain-derived neurotrophic factor[103]. The remaining trials are investigating nilotinib[106], fausadil[105], ALN-APP[102], and semaglutide[104].

Amongst the on-going trials of screening tests, one is investigating a virtual reality-based spatial navigation task as potential biomarker for early detection of AD[111] and one trial investigates the feasibility and validity of an on-line motor-cognitive test for early detection of AD[110].

Turning to study protocols, treatment-based interventions included a novel psychological intervention[114], a telerehabilitation battery[112], memory support training in combination with lifestyle modifications[115], and a partnered rhythmic rehabilitation (dancing) programme[113]. For the two protocols of screening tests, these involved cognitive assessment tools. Specifically, a digital screening for the assessment of cognitive abilities for early detection of dementia amongst general population samples[116], and myCog paradigm[117].

Outcomes/findings

In addition to on-going clinical trials and study protocols, we also identified one expert opinion which offers a perspective on disease-modifying drugs in AD[118]. The authors reviewed all phase 2 and phase 3 trials using data from clinicaltrials.gov until 23 July 2018. They found that 85% of Phase 3 clinical trials for AD focus on amyloid proteins, while Phase 2 trials are more diverse. Phase 2 trials include 37% amyloid-related targets, 26% tau protein targets, and 39% other targets such as metabolic, neuroprotective, regenerative, and anti-inflammatory targets. The authors acknowledged that the Phase 3 pipeline for AD disease-modifying therapeutics is heavily focused on amyloid proteins, and a continued diversity of the global pipeline is not critical to increase the probability of emergence of successful disease-modifying drugs, which may result in multimodal treatments that will better tackle the disease.

Conclusions

Whilst there is a substantial volume of new evidence and that an evidence map does not include formal quality assessment; the findings of this evidence map appear unlikely to impact

the current recommendation not to screen for dementia as no new evidence was identified that would change this recommendation.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to screening for dementia appears insufficient to justify commissioning an evidence summary at this stage. We recommend that this topic should be re-considered in 3-years' time.

Appendix 1 — Search strategy for the evidence map

Databases and platforms searched

Question 1: What is the volume and type of evidence available on the accuracy of screening tests used to detect MCI and/or any type of dementia?

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions via Ovid

APA PsycINFO via Ovid

Embase via Ovid

Cochrane Library (CDSR and TRIALS) via Wiley

Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index – Science (CPCI-S) via Web of Science

Question 2: What is the volume and type of evidence available on the pharmacological and non-pharmacological interventions used to treat asymptomatic or pre-symptomatic adults with MCI and/or any type of dementia identified through screening?

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions via Ovid

APA PsycINFO via Ovid

Embase via Ovid

Cochrane Library CDSR and TRIALS via Wiley

Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index – Science (CPCI-S) via Web of Science

Question 3: What is the available evidence of active research or developments (including clinical trials, observational studies, evidence syntheses, patents, or opinions)

ClinicalTrials.gov https://clinicaltrials.gov/

WHO ICTRP https://trialsearch.who.int/

PROSPERO https://www.crd.york.ac.uk/prospero/

AdisInsight https://adisinsight.springer.com/

Biomedtracker https://www.biomedtracker.com/ (not searched due to access issues)

Europe PMC https://europepmc.org/

PCORI https://www.pcori.org/implementation-evidence/emerging-topics-reports-and-horizon-scans/pcori-health-care-horizon-scanning-system

Conference searches were conducted on the following sources:

Alzheimer Europe https://www.alzheimer-europe.org/

Alzheimer's Disease International https://www.alzint.org/what-we-do/adi-conference/previous-international-conferences/

Search dates

Date ranges for all searches were January 2018 to June 2024. Searches were conducted during July, August and September 2024.

Search strategies

Screening tests search

Database: Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <August 06, 2024>

Search Strategy:

1 *Cognitive Dysfunction/
2 (mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.
3 (cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)
4 *dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/
5 (dementia*1 or alzheimer*2 or lewy body).ti.
6 MCI.ti.
7 *Cognition Disorders/
8 or/1-7
9 mass screening/ or multiphasic screening/
10 diagnosis/ or delayed diagnosis/ or early diagnosis/
11 Diagnostic Tests, Routine/
12 *Prognosis/
13 (screen*3 or detect*3 or test*3 or identif*3 or predict*3 or question*5 or instrument*2 or exam*1 or examination*1 or surveillance).ti,ab.
14 (early adj2 diagnos*3).ti,ab.
15 diagnos*3.ti.
16 or/9-15
17 exp Neuropsychological Tests/
18 ((cognitive assess* or neuropsycholog*) adj2 (tool? or toolkit? or question* or instrument? or interview? or screen*3)).ti,ab.
19 ("general practitioner assessment of cognition" or gpcog or "memory impairment screen" or mis or mini-cog or "short form of the informant questionnaire on cognitive decline in the elderly" or short 1qcode or "eight-item informa interview to differentiate aging and dementia" or ad8 or "mini-mental state*exam" or mmse or clock drawing).ti,ab.

20 "Mental Status and Dementia Tests"/
21 or/17-20
22 exp Biomarkers/
23 exp Neuroimaging/
24 brain/
25 magnetic resonance imaging/ or exp tomography, emission- computed/
26 24 and 25
27 (biomarker? or biological marker?).ti,ab.
28 ((brain or neurolog*) adj5 (magnetic resonance imaging or mri or pet or tomogra*)).ti,ab.
29 (neuroimag* or neuro-imag*).ti,ab.
30 or/22-23,26-29
31 exp "Sensitivity and Specificity"/
32 sensitivity.tw.
33 specificity.tw.
34 ((pre-test or pretest) adj probability).tw.
35 post-test probability.tw.
36 predictive value$.tw.
37 likelihood ratio$.tw.
38 or/31-37
39 8 and 16 and 21 and 38
40 8 and 16 and 30 and 38
41 39 or 40
42 (editorial or comment or letter).pt.
43 41 not 42
44 exp Animals/
45 humans.sh.
46 44 not 45
47 43 not 46
48 limit 47 to english language
49 limit 48 to yr="2018 -Current"

Pharmacological and non-pharmacological intervention search

Database: Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <August 06, 2024>
Search Strategy:

1 *Cognitive Dysfunction/
2 (mild* adj2 (cognitive* impair* or cognitive dysfunction*)).ti.
3 (cognitive* impair* or cognitive dysfunction*).ti. and (adult/ or middle aged/ or young adult/)
4 *dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or *lewy body disease/
5 (dementia*1 or alzheimer*2 or lewy body).ti.
6 MCI.ti.
7 *Cognition Disorders/
8 or/1-7
9 mass screening/ or multiphasic screening/
10 diagnosis/ or delayed diagnosis/ or early diagnosis/
11 Diagnostic Tests, Routine/
12 *Prognosis/
13 (screen*3 or detect*3 or test*3 or identif*3 or predict*3 or question*5 or instrument*2 or exam*1 or examination*1 or surveillance).ti,ab.
14 (early adj2 diagnos*3).ti,ab.
15 diagnos*3.ti.
16 or/9-15
17 Cholinesterase Inhibitors/
18 ((cholinesterase or acetylcholinesterase) adj inhibitor?).ab,ti.

19 AChE inhibitor*.ab,ti.
20 Donepezil/
21 (donepezil or aricept or adlarity or eisai).ab,ti.
22 Galantamine/
23 (galantamine or reminyl or razadyne or shire).ab,ti.
24 Memantine/
25 (memantine or ebixa).ab,ti.
26 Rivastigmine/
27 (rivastigmine or exelon).ab,ti.
28 namzaric.ab,ti.
29 donanemab.ab,ti.
30 ((pharmacolog* or drug?) adj2 (therap* or treatment)).ti,ab.
31 exp Rehabilitation/
32 exp Home Nursing/
33 exp Social Support/
34 rehabilitation.ab,ti.
35 ((occupational or art or dance or music) adj therap*).ti,ab.
36 (("activity of daily living" or "activities of daily living" or adl) adj3 (support or service? or intervention? or program*)).ti,ab.
37 "social support".ti,ab.
38 home nurs*.ti,ab.
39 ((nonpharmacolog* or non-pharmacolog*) adj2 (treatment or therap*)).ti,ab.
40 (therap* or treatment or management or intervention).ti.
41 ((multicomponent or multi component or multidisciplinary or multi disciplinary or multimodal or multi modal) adj3 (treatment* or program* or intervention*)).ti,ab.
42 or/17-41
43 8 and 16 and 42
44 Cognitive Dysfunction/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy]
45 Dementia/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy]
46 Alzheimer Disease/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy]
47 Dementia, Vascular/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy]
48 Lewy Body Disease/dt, rh, th [Drug Therapy, Rehabilitation, Therapy]
49 Cognition Disorders/dh, dt, rh, th [Diet Therapy, Drug Therapy, Rehabilitation, Therapy]
50 or/44-49
51 16 and 50
52 43 or 51
53 (MEDLINE or systematic review).tw. or meta analysis.pt.
54 randomized controlled trial.pt. or randomized controlled trial.mp.
55 53 or 54
56 52 and 55
57 (editorial or comment or letter).pt.
58 56 not 57
59 exp Animals/
60 humans.sh.
61 59 not 60
62 58 not 61
63 limit 62 to english language
64 limit 63 to yr="2018 -Current"

Question 3 search strategies

For question 3, search strategies differed between different sources as follows:

ClinicalTrials.gov:

1. Condition - Dementia and screening

2. Condition - Dementia and early diagnosis
3. Condition - Dementia and pharmacological studies
4. Condition - Dementia and pharmacology treatment
5. Condition - Dementia and drug therapy
6. Condition - Dementia and diet therapy
7. Condition - Dementia and rehabilitation therapy
8. Condition - Dementia and drug treatment
9. Condition - Dementia and occupational therapy
10. Condition - Dementia and multicomponent interventions

WHO ICTRP

1. Dementia and screening
2. Dementia and early

PROSPERO

1. (dementia AND diagnosis):TI
2. (dementia AND screening):TI
3. (dementia):TI AND (Diagnostic):RT
4. (dementia AND pharmacolog*):TI
5. (dementia AND drug*):TI
6. (dementia AND diet*):TI
7. (dementia AND rehabilitation):TI
8. (dementia AND occupational therapy):TI
9. (dementia AND multicomponent):TI

AdisInsight

1. Dementia

Europe PMC

1. (TITLE:"dementia screening") AND (FIRST_PDATE:[2018 TO 2024])
2. (TITLE:"dementia and diagnosis") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
3. (TITLE:"diagnosis and dementia") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
4. (TITLE:"dementia drug") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
5. (TITLE:"dementia AND drug") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
6. (TITLE:"dementia AND diet") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
7. (TITLE:"dementia AND rehabilitation") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
8. (TITLE:"dementia AND occupational") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
9. (TITLE:"dementia AND occupational therapy") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
10. (TITLE:"dementia AND treatment") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])
11. (TITLE:"dementia AND intervention") AND (FIRST_PDATE:[2018-01-01 TO 2024-09-04])

Numbers of results for each database and question if applicable

Question 1: screening tests

Ovid MEDLINE 3558

Ovid PsycINFO 990

Ovid Embase 4444

Cochrane Library 731 (CDSR 18, TRIALS 551)

Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index – Science (CPCI-S) via Web of Science 1834

Question 2: interventions

Ovid MEDLINE 2310

Ovid PsycINFO 591

Ovid Embase 1919

Cochrane Library 423 (CDSR 16, TRIALS 407)

Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index – Science (CPCI-S) via Web of Science 1655

Question 3: horizon scanning

ClinicalTrials. gov 1352
WHO ICTRP 103
PROSPERO 247
AdisInsight 0
Europe PMC 342
PCORI 7

Inclusions and exclusions

After further exclusion when uploaded to EPPI reviewer of 20 duplicate records, 12513 records were screened in EPPI-Reviewer, of which 11518 were excluded based on the title and abstract. Following a further round of screening, with reference to full texts if required, a further 877 records were excluded from the review. A total of 116 records were included in the final map, comprising 45 for question 1 (screening tests), 51 for question 2 (interventions) and 20 for question 3 (horizon scanning).

Appendix 2 – Abstract reporting

Selected key studies included in the evidence map are summarised below using a structured template. For Question 1, we selected mainly systematic reviews of diagnostic accuracy studies (Citations 1 to 7), supplemented by diagnostic cohort studies of two novel potential screening tools (Citations 8 and 9), For Question 2, we have focused on recent randomised controlled trials of disease-modifying drugs in people with early dementia (citations 1,3,5 and 7 to 10). The other studies summarised comprise a systematic review of online cognitive interventions (citation 2); a UK-based evaluation of a home exercise programme for people with early dementia (citation 4) and a small randomised controlled trial of a different pharmacological intervention (citation 6). We have not produced any summaries for Question 3 as the included items are mainly early research, ongoing trials without published results or expert opinion of limited value for formal evidence synthesis.

Question 1

Citation 1

Karimi L, Mahboub-Ahari A, Jahangiry L, Sadeghi-Bazargani H, Farahbakhsh M. A systematic review and meta-analysis of studies on screening for mild cognitive impairment in primary healthcare. *BMC Psychiatry* 2022;**22**:97.

Study type

Systematic review

Objectives

To review evidence on the test performance of tools used in screening for mild cognitive impairment in primary care and to compare different tools in a pairwise fashion.

Components of the study

Studies were included if they evaluated screening for early cognitive disorders in a primary care setting using short questionnaires and reported sensitivity, specificity, positive and negative predictive values and area under the ROC curve (AUC). Studies published in English between January 2012 and November 2021 were included.

[Full text consulted.]

Outcomes reported

Twenty-one studies were included in the review. None of the studies evaluated feasibility or effectiveness of population screening. Heterogeneity between studies meant that pooled estimates of diagnostic accuracy could only be calculated for the MMSE (seven studies). The pooled sensitivity (random effects model) was 0.73 (95% CI 0.57 to 0.90), the pooled specificity

was 0.83 (95% CI 0.75 to 0.90), and the pooled AUC was 0.88 (95% CI 0.83 to 0.93). In pairwise comparisons, IQCODE, AD8 and GPCOG showed equal or better sensitivity and specificity relative to the MMSE.

[Full text consulted.]

Conclusions

The review found insufficient evidence to justify routine general population screening for cognitive disorders. Taking into account factors such as accuracy, time of application, ease of scoring, and charges for use, the authors concluded that tests such as IQCODE, AD8, and GPCOG seem to be good alternatives to the MMSE in screening for MCI or early dementia in primary care.

[Full text consulted.]

Citation 2

Patnode C D, Perdue L A; Rossom R C; Rushkin M C; Redmond N and Thomas RG; Lin J S;. (2020). Screening for Cognitive Impairment in Older Adults:Updated Evidence Report and Systematic Review for the US PreventiveServices Task Force. */JAMA/*, **323**(8), pp.764-785.

Study type

Systematic review

Objectives

The objectives were to systematically review the evidence base for test accuracy of cognitive screening instruments and benefits and harms of interventions to treat cognitive impairment in adults aged 65 years or older. This summary focuses on the test accuracy section of the review.

Components of the study

MEDLINE, PubMed, PsycINFO and the Cochrane Central Register of Controlled Trials were searched in January 2019, with updates to November 2019. English-language studies of cognitive impairment screening instruments, and pharmacological and non-pharmacological treatments aimed at people with MCI, mild to moderate dementia, or their caregivers were included. Studies were included if they were fair or good quality based on USPSTF design-specific criteria; studies with serious methodological shortcomings were excluded.

[Full text consulted]

Outcomes reported

Fifty-nine studies involving 38 531 participants assessed the accuracy of 49 screening instruments for the detection of cognitive impairment. The Mini-Mental State Examination was the most-studied instrument, with a pooled sensitivity of 0.89 (95% CI, 0.85 to 0.92) and specificity of 0.89 (95% CI, 0.85 to 0.93) to detect dementia using a cut-off of 23 or less or 24 or

less (15 studies, 12 796 participants). Eight very brief instruments taking 5 minutes or less to administer were examined in more than one study, with sensitivity to detect dementia usually 0.75 or more (range, 0.43 to 1.0) and specificity usually 0.80 or more (range, 0.54 to 1.0). One randomised controlled trial (4005 participants) examined the direct effect of screening for cognitive impairment on patient outcomes, including potential harms. The study found no significant differences in health-related quality of life at 12 months (effect size, 0.009 [95% CI, –0.063 to 0.080]).

Two hundred and twenty-four RCTs and 3 observational studies including more than 240 000 patients or caregivers addressed the treatment of MCI or mild to moderate dementia. None of the treatment trials were linked with a screening programme. Medications approved to treat AD produced small improvements in cognitive scores and psychoeducation interventions for caregivers were associated with small reductions in caregiver burden. Overall, intervention benefits were rated as small and of uncertain clinical importance.

[Full text consulted]

Conclusions

Screening instruments show reasonable accuracy in detection of cognitive impairment. However, there is no evidence that screening either improves patient or caregiver outcomes or causes harm. It remains unclear whether interventions for patients or caregivers provide clinically important benefits.

Citation 3

Abd Razak, M A and Ahmad N A; Chan Y Y; Mohamad Kasim ; N ; Yusof M ;Abdul Ghani ; M K A; Omar M ; Abd Aziz ; F A ; Jamaluddin R ;. (2019). Validity of screening tools for dementia and mild cognitive impairment among the elderly in primary health care: a systematic review. /*Public Health*/, **169**, pp.84-92.

Study type

Systematic review

Objectives

To provide an updated review of the accuracy of screening tools for dementia and mild cognitive impairment in primary care and their feasibility of use in practice.

Components of the study

PubMed, Embase and CENTRAL, together with reference lists of included studies, were searched for studies published in English between 2012 and 2017. Studies reporting on the validity (sensitivity and specificity) of screening tools in people aged over 60 years in primary care settings were eligible for inclusion. Screening could be performed by a healthcare provider, a self-administered questionnaire or by caregiver informant screening. A descriptive synthesis of the studies was performed.

[Full text consulted]

Outcomes reported

Thirty studies were included in the review, of which 21 involved screening by healthcare providers, eight involved self-administered tools and one involved caregiver informants. Seventeen articles covered 19 screening tools for dementia and 19 articles covered 14 tools for MCI. Most screening tools for dementia were reported to be feasible for use in community-based settings. Overall, the Montreal Cognitive Assessment (MoCA) was considered the most accurate tool for MCI screening (sensitivity 0.81 to 0.97; specificity 0.60 to 0.86%). The Addenbrooke's Cognitive Examination (ACE) was the preferable tool for dementia screening (sensitivity 0.79 to 1.00; Specificity 0.86).

[Full text consulted]

Conclusions

ACE and MoCA are recommended tools for screening for dementia and MCI, respectively.

Citation 4

Chen H H and Sun F J; Yeh T L; Liu H E; Huang H L; Kuo B I; Huang H Y;.(2018). The diagnostic accuracy of the Ascertain Dementia 8 questionnaire for detecting cognitive impairment in primary care in the community, clinics and hospitals: a systematic review and meta-analysis. /Family Practice/, 35(3), pp 239-246.

Study type

Systematic review and meta-analysis

Objectives

The early detection of cognitive impairment in primary care is of paramount importance for patients and public health decision-making. There is mixed evidence regarding the overall accuracy of Ascertain Dementia 8 (AD8) questionnaire for detecting early cognitive impairment. The aim of this systematic review was to assess the diagnostic accuracy of the AD8 for cognitive impairment in primary care.

Components of the study

Eight databases and public repositories were searched (UpToDate, Cochrane Library, PubMed/Medline, Embase, PsycINFO, PerioPath Index to Taiwan Periodical Literature, Airiti Library and Google Scholar) independently by two reviewers (sic). The QUADAS-2 tool was used to assess methodological quality in the included studies. A random-effect meta-analysis model was conducted to estimate sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR). Heterogeneity was assessed using the I^2 statistic.

Outcomes reported

Seven studies were included. The overall methodological quality of the included studies was high. The pooled sensitivity, specificity, the DOR, and the AUC of the AD8 questionnaire to differentiate normal cognition from MCI were found to be 0.72 (95%CI: 0.68, 0.75), 0.67 (95% CI: 0.63, 0.72), and 13.7 (95% CI:3.88, 48.40), 0.83, respectively. The pooled sensitivity, specificity, the DOR, and the AUC of the AD8 questionnaire to differentiate non-dementia from dementia were found to be 0.91 (95%CI: 0.89, 0.92), 0.78 (95% CI: 0.76, 0.80), 37.23 (95% CI: 21.34, 64.94), 0.92, respectively. In most of the analyses, substantial heterogeneity was evident (>90%).

Conclusions

The AD8 questionnaire could be considered an option for detecting cognitive impairment in primary care settings.

Citation 5

Park S H. (2023). Diagnostic performance of the six-item cognitive impairment test as first-step screening for dementia: a meta-analysis. /Brain Impairment/, 24(2), pp.412-423.

Study type

Systematic review and meta-analysis

Objectives

The rising prevalence of dementia poses significant health and social challenges, highlighting the need for early identification of individuals with cognitive impairment in the community. The aim of this systematic review was to assess the overall accuracy of the six-item cognitive impairment test (6-CIT) to predict sings of cognitive impairment.

Components of the study

This is a systematic review with meta-analysis of diagnostic accuracy studies and conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. Four databases were searched (MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycArticles) and the methodological quality of included studies was assessed using the QUADAS-2 tool. A random-effects meta-analysis was conducted to calculate the pooled sensitivity and specificity.

Outcomes reported

Overall, seven studies were included and the most affected categories in the risk of bias assessment were reference standards and patient selection. The pooled sensitivity and specificity of the 6-CIT to detect individuals with cognitive impairment were 0.82 (95%CI: 0.73, 0.89) and 0.87 (95%CI: 0.73, 0.95), while the sROC AUC was 0.90 (standard error (SE) = 0.04).

Conclusions

The pooled sensitivity and AUC of the 6-CIT tool was higher compared to the MMSE tool. This evidence suggests that 6-CIT tool could be used for dementia screening and can be an alternative to the MMSE

Citation 6

Seitz D P, Chan C C; Newton H T; Gill S S; Herrmann N and Smailagic N ;Nikolaou V ; Fage B A;. (2021). Mini-Cog for the detection of dementia within a primary care setting. /Cochrane Database of Systematic Reviews/, 7, pp.CD011415.

Study type

Systematic review

Objectives

To determine the accuracy of the Mini-Cog for detecting dementia in a primary care setting.

Components of the study

The Cochrane Dementia and Cognitive Improvement Register of Diagnostic Test Accuracy Studies, MEDLINE, Embase and four other databases were searched up to January 2017. Citation tracking was used and study authors contacted for unpublished data. Studies were included if they evaluated the Mini-Cog as an index test for the diagnosis of Alzheimer's disease dementia or related forms of dementia in a primary care population when compared to a reference standard. Studies had to use validated criteria for dementia. Study quality was assessed using the QUADAS-2 criteria.

Outcomes reported

Four studies (1517 participants) met the inclusion criteria. The sensitivity of the Mini-Cog ranged from 0.76 to 1.00 and its specificity ranged from 0.27 to 0.85. Meta-analysis was not performed because of significant heterogeneity in both methodologies and clinical populations. Only one study was judged to be at low risk of bias on all methodological domains. This study reported that the sensitivity of the Mini-Cog was 0.76 and its specificity was 0.73. Positive and negative predictive values were not reported. Other studies were at high risk of bias, primarily related to selection of participants.

[Full text consulted]Conclusions

Given the small number of studies, the wide range in estimates of the accuracy and methodological limitations in most of the studies, there is insufficient evidence to recommend the Mini-Cog for use as a screening test for dementia in primary care.

Citation 7

Fage B A, Chan C C; Gill S S; Noel-Storr A H; Herrmann N and Smailagic N ; Nikolaou V ; Seitz D P;. (2021). Mini-Cog for the detection of dementia within a community setting. /Cochrane Database of Systematic Reviews/, 7, pp.CD010860.

Study type

Systematic review

Objectives

The diagnosis of Alzheimer's disease (AD) is highly reliant on cognitive tests that can discriminate between individuals with dementia and those without dementia. The primary objective of this cochrane review was to evaluate the diagnostic accuracy of the Mini-Cog screening test for detecting dementia in a community setting. Secondary measures included investigating the heterogeneity of test accuracy in the included studies and potential sources heterogeneity. These potential sources included the baseline prevalence of dementia in the population sample; variations in thresholds/cut-off points for positive test results; the type of dementia (i.e., AD dementia or all-cause dementia), and the quality of individual studies included in the review.

Components of the study

Seven databaseswere searched to March 2013. All cross-sectional studies utilising the Mini-Cog as an index test for the diagnosis of dementia when compared to a reference diagnosis of dementia using standardised diagnostic criteria were included. Studies that were not conducted in community settings (i.e., general population) were excluded. The quality of the studies was assessed using the QUADAS-2 criteria. Data extraction included general information about included studies, and data pertinent to diagnostic test accuracy (sensitivity, specificity, and 95% confidence intervals). Data were summarised using forest plots and study-specific accuracy measurements were plotted in ROC space.

Outcomes reported

Overall, 3 studies met the inclusion criteria, with a total of 1620 participants. The sensitivities of the Mini-Cog in the individual studies were reported as 0.99 (0.96 to 1.00), 0.76 (0.65 to 0.85) and 0.99 (0.95 to 1.00). The specificity of the Mini-Cog varied in the individual studies and was 0.93 (0.87 to 0.97), 0.89 (0.87 to 0.91) and 0.83 (0.76 to 0.89). Positive and negative predictive values were not reported. There was clinical and methodological heterogeneity between the studies which precluded a pooled meta-analysis of the results. Methodological limitations were present in all the studies introducing potential sources of bias, specifically with respect to the methods for participant selection.

[Full text consulted]

Conclusions

The limited number of studies and the methodological limitations that are present in the current studies make it difficult to provide recommendations for or against the use of the Mini-Cog as a cognitive screening test in community settings. Additional well-designed studies comparing the Mini-Cog to other brief cognitive screening tests are required to determine the accuracy and utility of the Mini-Cog in community-based settings.

Citation 8

Groppell S, Soto-Ruiz K M and Flores B ; Dawkins W ; Smith I ; EaglemanD M; Katz Y ;. (2019). A Rapid, Mobile Neurocognitive Screening Test to Aid in Identifying Cognitive Impairment and Dementia (BrainCheck):Cohort Study. /JMIR Aging/, 2(1), pp.e12615

Study type

Diagnostic cohort study

Objectives

This study aimed to evaluate the accuracy and validity of BrainCheck Memory assessment as a diagnostic screening test for identifying age-related cognitive impairment.

Components of the study

This was a diagnostic cohort study. In total, 583 adult volunteers, aged 49 and over, were recruited from various community centres and living facilities in Houston, Texas, USA. The BrainCheck Memory assessment was administered to 398 individuals. The remaining volunteers were divided into comparison groups, including physician diagnosis (n=18), the Saint Louis University Mental Status (SLUMS) exam (n=84), the Mini-Mental State Examination (MMSE) (n=35), and the Montreal Cognitive Assessment (MoCA) (n=35). In addition to their respective assessments, each comparison group also administered the BrainCheck Memory.

Outcomes reported

The study found statistically significant correlations between BrainCheck Memory and the SLUMS, MMSE, and MoCA. The correlation coefficients with the SLUMS exam ranged from 0.5 to 0.7. The researchers developed a composite score using the BrainCheck Memory results, which demonstrated even stronger correlations with the standard assessments than the individual BrainCheck Memory. BrainCheck Memory composite score showed a sensitivity of 0.81 and a specificity of 0.94 in identifying age-related cognitive impairment when compared to physician diagnosis.

Conclusions

The study concludes that BrainCheck Memory is a sensitive and specific tool for assessing age-related cognitive impairment in older adults. The authors highlight its advantages, including its mobile and digital format, and ease of use.

Citation 9

Tolea M I, Heo J and Chrisphonte S ; Galvin J E;. (2021). A Modified CAIDE Risk Score as a Screening Tool for Cognitive Impairment in Older Adults. /Journal of Alzheimer's Disease/, 82(4), pp.1755-1768.

Study type

Diagnostic cohort study

Objectives

To develop and validate a modified version of the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) score, called mCAIDE, and assess its ability to predict the presence, severity, and etiology of cognitive impairment in older adults.

Components of the study

The study consisted of 449 participants in dementia research (community sample: N=230; 67.9±10.0 years old, 29.6% male, 13.7±4.1 years of education; clinical sample: N=219; 74.3±9.8 years old, 50.2% male, 15.5±2.6 years of education). The mCAIDE includes self-reported and performance-based measures instead of blood-derived measures, was developed in the community sample and tested in the independent clinical sample. The diagnostic ability of mCAIDE to confirm presence, severity, and etiology of cognitive impairment, including mild cognitive impairment (MCI) and dementia (both Alzheimer's disease (AD) and non-AD dementia) was investigated against Framingham, Hachinski, and CAIDE risk scores

Outcomes reported

The study found an association between higher mCAIDE score quartiles and lower performance on global and domain-specific cognitive tests. Each one-point increase in mCAIDE increased the odds of MCI by up to 65%, those of AD by 69%, and those for non-AD dementia by >85%, with highest scores in cases with vascular etiologies. Being in the highest mCAIDE risk group improved ability to discriminate dementia from MCI and controls and MCI from controls, with a cut-off of ≥7 points offering the highest sensitivity, specificity, and positive and negative predictive values.

Conclusions

Authors conclude that The mCAIDE may be a valuable tool for case ascertainment in research studies, helping flag primary care patients for cognitive testing, and identify those in need of lifestyle interventions for symptomatic control.

Question 2

Citation 1

Florian H, Wang D and Arnold S E; Boada M ; Guo Q ; Jin Z ; Zheng H ; Fisseha N ; Kalluri H V; Rendenbach-Mueller B ; Budur K ; Gold M ;. (2023). Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. *Brain*, 146(6), pp 2275-2284

Study type

Phase II, randomized, double-blind, placebo-controlled study

Objectives

The aim of this study was to investigate the efficacy of tilavonemab in slowing Alzheimer's disease (AD) progression and the long-term safety of tilavonemab in patients with early AD.

Components of the study

This was a multi-centre international phase 2, multiple-dose, randomized, double-blind, placebo-controlled study. Eligible patients were adults aged 55–85 years who met the National Institute on Aging and the Alzheimer's Association criteria for mild cognitive impairment or probable Alzheimer's disease and had a Clinical Dementia Rating (CDR) global score of 0.5 at screening Visit 1, a Mini-Mental State Examination (MMSE) score of 22 to 30. The study consisted of a 12-week screening period, 96-week double-blind treatment period, and a 20-week follow-up after administration of the last study drug. The primary efficacy analysis used a likelihood-based, mixed-effects model repeated measures (MMRM) analysis of the change from baseline for each post-baseline visit using all observed data. The primary outcome was the change from baseline to Week 96 in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score.

Outcomes reported

In total, 453 were randomized to receive one of three doses of tilavonemab: 300 mg (n = 108), 1000 mg (n = 116), or 2000 mg (n = 113), or placebo (n = 116). Overall, 392 patients completed the study. Change from baseline at Week 96 in the CDR-SB score was not significantly different between treatment groups. Similarly, through Week 96, there was no significant difference across treatment groups in any of the secondary outcomes assessed, including global clinical impact and decline in patient cognition. There was no evidence of a treatment effect on medial temporal lobe or lateral ventricle volume. Hippocampal volume was significantly less decreased at Week 28 in the tilavonemab 1000 mg group compared with placebo (−94.9 versus −121.6 mm3, respectively; p = 0.03) and was also significantly less decreased at Week 44 in the tilavonemab 2000 mg group compared with placebo (−127.9 versus −165.9 mm3, respectively; p = 0.01); however, these were the only time points with statistical significance between groups without multiplicity adjustment. Preliminary exposure-response results showed no improvement in the primary or key secondary end points with increasing tilavonemab exposures.

Conclusions

Tilavonemab was not found effective in treating patients with early Alzheimer's disease.

Citation 2

Chae H J and Lee S H;. (2023). Effectiveness of online-based cognitive intervention in community-dwelling older adults with cognitive dysfunction: A systematic review and meta-analysis. International Journal of Geriatric Psychiatry, 38(1), pp.e5853.

Study type

Systematic review and meta-analysis

Objectives

Mild cognitive impairment (MCI) has detrimental consequences for individuals cognitive functioning, imposing a significant burden on patients, families, and social systems. Information and communication technology (ICT)-based cognitive training can increase patients' quality of life and slow the progression of dementia. The aim of this review was to assess the impact of ICT-based cognitive interventions on MCI and mild dementia patients' cognitive functioning and psychosocial outcomes in community-dwelling patients with MCI or mild dementia.

Components of the study

This is a systematic review with meta-analysis of randomised controlled trials (RCTs) and conforms to the PRISMA reporting guidelines. A literature search was performed in four databases (Ovid-Medline, Ovid-EMBASE, Cochrane Library, and CINAHL). Two reviewers independently screened the studies at title/abstract and full-text screening and assessed the risk-of-bias in the included studies. A random-effects meta-analysis was conducted. Heterogeneity was assessed using the I^2 statistic.

Outcomes reported

Overall, 44 studies were included in this systematic review. Amongst the included studies, the most affected risk of bias categories were the blinding of participants and personnel, and allocation concealment. Overall, ICT-based cognitive interventions were found to improve cognitive functioning (SMD=0.37, 95%CI: 0.22, 0.51, $p < 0.00001$, $I^2 = 15\%$), verbal and semantic fluency (SMD= 0.38, 95%CI: 0.09, 0.66, $p = 0.009$, $I^2 = 40\%$), forward (SMD=0.98, 95%CI: 0.28, 1.68, $p = 0.006$, $I^2 = 71\%$) and backward digit span test (SMD=1.20, 95%CI: 0.85, 1.56, $p < 0.00001$, $I^2 = 27\%$), memory (SMD=0.85, 95%CI: 0.57, 1.13, $p < 0.00001$, $I^2 = 0\%$), depression scores (SMD= −0.90, 95%CI: −1.33, −0.46, $p < 0.0001$, $I^2 = 40\%$), and QoL (SMD=0.36, 95%CI: 0.05, 0.67, $p = 0.02$, $I^2 = 0\%$).

Conclusions

Given the beneficial impact that ICT-based interventions have on patients' health, the application of such interventions should be expanded.

Citation 3

Cohen S, van Dyck C H and Gee M ; Doherty T ; Kanekiyo M ; Dhadda S ; Li D ; Hersch S ; Irizarry M ; Kramer L D;. (2023). Lecanemab Clarity AD: Quality-of-Life Results from a Randomized, Double-Blind Phase 3 Trial in Early Alzheimer's Disease. Journal of Prevention of Alzheimer's Disease, 10(4), pp.771-777.

Study type

Randomized, Double-Blind Phase 3 Trial

Objectives

Lecanemab is a humanized IgG1 monoclonal antibody binding with high affinity to amyloid-beta protein protofibrils and has been found promising in reducing markers of amyloid in early Alzheimer's disease (AD), as well as slowing cognitive and function decline over 18-months. Based on the Clarity AD trial, a multi-centre Phase III double-blind randomized controlled trial (RCT), the aim of this study was to explore the health-related quality-of-life (HRQoL) outcomes of the trial.

Components of the study

Individuals 50 to 90 years of age with a diagnosis of mild cognitive impairment (MCI) or mild dementia due to AD were included in this study. The effects of lecanemab 10-mg/kg on individuals' HRQoL was compared against placebo.

Outcomes reported

Overall, 1795 (898 assigned to lecanemab, and 897 assigned to placebo) were randomized. A statistically significant on change from baseline to 18 months was observed in the European quality of Life-5 dimeansions scale (EQ-5D-5L) favouring lecanemab (MD= 2.017, $p<0.01$), representing 49.1% less decline ($p=0.00383$). A statistically significant difference on change from baseline to 18 months was also observed in Quality of Life in AD (QOL-AD) total score favouring lecanemab (adjusted MD=0.657), representing 55.6% less decline ($p=0.00231$). A statistically significant difference on change from baseline to 18 months was also observed in Zarit Burden Interview favouring lecanemab (-2.211), representing 38.4% less progression ($p=0.00002$).

Conclusions

Lecanemab was found to be related with a relative preservation of HRQoL in individuals with MCI or mild dementia. Lecanemab was also found to be associated with less increase in caregivers' burden.

Citation 4

Doungsong K, Hartfiel N and Gladman J ; Harwood R ; Edwards R T;. (2024). RCT-based Social Return on Investment (SROI) of a Home Exercise Program for People With Early Dementia Comparing In-Person and Blended Delivery Before and During the COVID-19 Pandemic. Inquiry, 61, pp.469580241246468.

Study type

Multi-centre, pragmatic randomized controlled trial (RCT)

Objectives

The rising prevalence of dementia poses significant health challenges, imposing a heavy financial burden on healthcare systems. Physical activity, exercise-based interventions, and community engagement could improve patients' overall health and functioning by slowing the progression of the disease. However, there is mixed evidence regarding the cost-effectiveness of such interventions. This study aimed to compare the social value generated from the in-person Promoting activity, independence and stability in early dementia (PrAISED) programme, a home exercise and community referral for people with early dementia, delivered before March 2020 with a blended PrAISED programme (i.e, telephone calls, videoconferencing and in-person visits when possible) delivered after March 2020.

Components of the study

Stakeholders were identified, a logic model was developed, outcomes were evidenced and valued, costs were calculated, and SROI ratios were estimated.

Outcomes reported

Overall, 365 individuals participated, while complete data was obtained from 205 individuals (61 and 144 participants completed the in-person and the blended program, respectively). Data were collected at baseline and at 12-month follow-up. The in-person PrAISED programme generated SROI ratios ranging from £0.58 to £2.33 for every £1 invested. In-person PrAISED individuals gained social value from improved health-related quality of life, social connection, and less fear of falling. In-person PrAISED carer participants acquired social value from less carer strain. However, the blended PrAISED programme generated lower SROI ratios ranging from a negative ratio to £0.08:£1.

Conclusions

The PrAISED in-person programme generated higher SROI ratios compared to the blended programme. However, the implementation of the former was associated with great costs.

Citation 5

Fleisher A S, Munsie L M; Perahia D G. S; Andersen S W; Higgins I A; Hauck P M; Lo A C; Sims J R; Brys M and Mintun M ;. (2024). Assessment of Efficacy and Safety of Zagotenemab: Results From PERISCOPE-ALZ, a Phase 2 Study in Early Symptomatic Alzheimer Disease. Neurology, 102(5), pp.e208061.

Study type

A multicenter phase II clinical trial (PERISCOPE-ALZ).

Objectives

The aim of this study was to determine whether zagotenemab slows disease progression relative to placebo in early symptomatic AD. The primary objective of this study was to determine whether zagotenemab would decrease the decline in cognition and function in patients with early symptomatic AD relative to placebo.

Components of the study

PERISCOPE-ALZ was a multicentre, international randomized, double-blind, placebo-controlled phase 2 study of zagotenemab. Patients with early symptomatic AD (patients with mild cognitive impairment or mild dementia due to AD) 60–85 years of age with gradual and progressive change in memory function for ≥6 months consistent with AD, a Mini-Mental State Examination (MMSE) score of 20–28, and biomarker evidence of AD-type tauopathy were eligible for inclusion. Participants who met inclusion criteria were randomized in a 1:1:1 ratio to receive IV infusions every 4 weeks for 100 weeks of 1,400 mg zagotenemab, 5,600 mg zagotenemab, or placebo. The primary endpoint was the change in the integrated AD Rating Scale (iADRS) score from baseline to 104 weeks. A Bayesian disease progression model (DPM) was chosen for the primary analyses

Outcomes reported

In total, 360 participants were randomized. The safety population (N = 360) consisted of all randomized participants who received at least 1 dose of double-blind treatment (1,400 mg [n = 126], 5,600 mg [n = 116], or placebo [n = 118]). A total of 218 participants completed treatment (1,400 mg [n = 76], 5,600 mg [n = 70], or placebo [n = 72]). Neither zagotenemab arm showed slowing in rate of clinical decline as assessed by iADRS across 104 weeks compared with placebo. The DPR comparing zagotenemab 1,400 mg with placebo and 5,600 mg with placebo was 1.10 (95% credible intervals [CrI]: 0.96, 1.27) and 1.05 (95% CrI: 0.91, 1.21), respectively. Consistent with the primary endpoint, no meaningful slowing of clinical decline rate, compared with placebo, was observed for other outcome measures MMSE using the DPM. No meaningful slowing in clinical decline at 104 weeks, compared with placebo, was observed for any clinical assessments using the MMRM-based analysis. There were no significant differences at week 104 on global or regional analyses with either zagotenemab dose group compared with placebo. Over 104 weeks, 1,400 mg and 5,600 mg groups showed a significant increase from baseline of plasma total tau compared with placebo ($p < 0.001$). Over 104 weeks, 1,400 mg and 5,600 mg groups showed a significant increase from baseline of phosphorylated tau (p-tau) 181 compared with placebo ($p < 0.001$). Neither zagotenemab-treated group resulted in significant change from baseline in neurofilament light chain compared with the placebo group. There were no statistically significant changes in brain volume in either of the zagotenemab dose groups compared with the placebo group. Four deaths occurred in the double-blind period of the study, 2 in the placebo group and 1 in each of the zagotenemab treatment groups. Treatment-emergent adverse effects were reported by 88 (74.6%) participants in the placebo group, 105 (83.3%) in the zagotenemab 1,400 mg group, and 101 (87.1%) in the zagotenemab 5,600 mg group.

Conclusions

Zagotenemab was not found effective in significantly slowing the clinical disease progression in participants with early symptomatic AD.

Citation 6

Galasko D, Farlow M R and Lucey B P; Honig L S; Elbert D ; Bateman R; Momper J ; Thomas R G; Rissman R A; Pa J ; Aslanyan V ; Balasubramanian A ; West T ; Maccecchini M ; Feldman H H;. (2024). A multicenter, randomized, double-blind, placebo-controlled ascending dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) effects of

Posiphen in subjects with early Alzheimer's Disease. Alzheimer's Research & Therapy, 16(1), pp.151.

Study type

Double-blind, randomized, ascending dose, phase 1b trial

Objectives

To evaluate the safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) effects of Posiphen on A-beta metabolism using Stable Isotope Labeling Kinetic (SILK) analysis in individuals with mild cognitive impairment or mild AD (early AD).

Components of the study

This study recruited 19 adults (aged 55-89 years) meeting the diagnostic criteria for MCI or mild AD (early AD) as confirmed by low cerebrospinal fluid (CSF) A-beta42/40. All participants had CSF samples collected prior to treatment. Included participants were then randomised within each dose arm to receive Posiphen (60 mg once/day, 60 mg twice/day, or 60 mg three times/day) or placebo for 21-23 days. Participants underwent CSF catheter placement, intravenous infusion of 13C6-leucine, and CSF sampling for 36 h after final treatment. Safety, tolerability, and PK and PD effects on amyloid beta (A-beta) metabolism using CSF SILK analysis. Amyloid precursor protein (APP), A-beta and other biomarkers were measured at baseline and day 21. The Mini-Mental State Exam (MMSE) and the AD Assessment Scale-cognitive subscale 12 were given at baseline and day 21.

NB: Full text was consulted to establish the age of participants

Outcomes reported

In total, 15 participants completed all study procedures (10 active drug and 5 placebo). Posiphen was safe and well-tolerated. Eight participants had headaches related to CSF catheterisation, and five needed blood patches. The SILK analyses of Fractional Synthesis Rate for CSF A-beta40 showed no significant overall or dose-dependent effects of Posiphen vs. placebo. Comprehensive multiparameter modelling of (APP) kinetics supported dose-dependent lowering of APP production by Posiphen. Cognitive measures and CSF biomarkers did not change significantly from baseline to 21 days in Posiphen vs. placebo groups.

Conclusions

Posiphen was safe and well-tolerated in early AD, suggesting a multicenter SILK study was feasible. Although findings were limited by small sample size, they provided additional supportive safety and PK data. Comprehensive modelling of biomarker dynamics using SILK data may reveal subtle drug effects.

Citation 7

Henley D, Sperling R A and Aisen P S; Raman R ; Donohue M C; Ernstrom K ; Shi Y ; Karcher K ; Raghavan N ; Tymofyeyev Y ; Brashear R ; Novak G P; Thipphawong J ; Saad Z ; Kolb H C;

Romano G ;. (2019). Final Efficacy, Safety and Biomarker Results of the Phase 2b/3 Randomized, Double-Blinded, Placebo-Controlled Early Trial of Atabecestat in Preclinical Alzheimer's Disease. Alzheimer's and Dementia, 15(7 Supplement), pp.P873-P874.

Study type

Double-blind, randomized, placebo-controlled, phase 2b/3 trial

Objectives

The aim of this study was to evaluate the efficacy and safety of Atabecestat, a nonselective oral beta-secretase inhibitor, for slowing cognitive decline in participants with preclinical AD, with focus on potential recovery of effects on cognition and behaviour following treatment discontinuation.

Components of the study

This study included 557 amyloid-positive, cognitively normal (Clinical Dementia Rating of 0) preclinical AD individuals, aged 60-85. Participants were randomised equally to receive either Atabecestat 5 mg (n=189), 25 mg (183), or placebo (n=185). The main outcome measures included changes from baseline in Preclinical Alzheimer Cognitive Composite (PACC) score; Cognitive Function Index (CFI); and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale score. This study was terminated early due to safety concerns. Approximately 34% of the 1650 initially enrolled participants were randomized before the trial sponsor stopped enrollment.

Outcomes reported

Atabecestat, 25 mg, showed significant cognitive worsening compared to placebo for PACC at month 6 (least-square mean difference, −1.09; 95% CI, −1.66 to −0.53; P < .001) and month 12 [least-square mean (LSM), −1.62; 95%CI, −2.49 to −0.76; P < .001].The CFI participant report showed nonsignificant worsening at month 12. Atabecestat, 25 mg, also showed significant worsening of neuropsychological status compared to placebo for RBANS at month 3 (LSM, −3.70; 95% CI, −5.76 to −1.63; P < .001).

Systemic and neuropsychiatric-related treatment-emergent adverse events (AEs) were greater in atabecestat groups vs placebo. After stopping treatment, follow-up cognitive testing and AE assessment provided evidence of reversibility of drug-induced cognitive worsening and AEs in atabecestat groups.

Conclusions

Atabecestat treatment may worsen cognitive function and lead to neuropsychiatric treatment-emergent AEs, with evidence of reversibility after 6 months off treatment.

Citation 8

Mintun M A, Lo A C; Duggan Evans and C ; Wessels A M; Ardayfio P A; Andersen S W; Shcherbinin S ; Sparks J ; Sims J R; Brys M ; Apostolova L G; Salloway S P; Skovronsky D M;.

(2021). Donanemab in Early Alzheimer's Disease. New England Journal of Medicine, 384(18), pp.1691-1704.

Study type

Double-blind, randomized, placebo-controlled phase 2 trial.

Objectives

The aim of this study was to investigate the efficacy and safety of donanemab, an antibody that targets a modified form of deposited A-beta, in the treatment of early Alzheimer's disease (AD).

Components of the study

In total, 256 patients (60 to 85 years) diagnosed with early symptomatic AD by presence of tau and amyloid deposition on positron-emission tomography (PET) were included in the study. Patients were randomised equally to receive either donanemab (700 mg for the first three doses and 1400 mg thereafter) or placebo via intravenous infusion every 4 weeks for up to 72 weeks. The primary outcome was change from baseline in the scores on Integrated Alzheimer’s Disease Rating Scale (iADRS) at 76 weeks.MMSE

NB: Full text was consulted to obtain the age of participants.

Outcomes reported

At baseline iADRS score was 106 in both groups. A change from baseline in the iADRS score at 76 weeks was -6.86 in donanemab group and -10.06 in placebo group (difference, 3.20; 95% confidence interval, 0.12 to 6.27; P = 0.04). There was no substantial difference for most secondary outcomes. However, reductions in the amyloid plaque level and the global tau load at Week 76 were 85.06 centiloids and 0.01 greater, respectively, in the donanemab group than in the placebo group. Although mostly asymptomatic, amyloid-related cerebral edema or effusions occurred in donanemab-treated individuals.

Conclusions

The study found that donanemab resulted in a more favourable composite score for cognition and activities of daily living than a placebo, although results for secondary outcomes were mixed.

Citation 9

Sims John R, Zimmer Jennifer A; Evans Cynthia D; Lu Ming and Ardayfio Paul; Sparks JonDavid ; Wessels Alette M; Shcherbinin Sergey; Wang Hong; Monkul Nery Emel Serap; Collins Emily C; Solomon Paul ; Salloway Stephen; Apostolova Liana G; Hansson Oskar; Ritchie Craig ; Brooks Dawn A; Mintun Mark ; Skovronsky Daniel M;. (2023). Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA: Journal of the American Medical Association*, 330(6), pp.512-527.

Study type

Double-blind, randomized, placebo-controlled phase 3 trial.

Objectives

This study aimed to assess the efficacy and adverse events of donanemab, an antibody that targets a modified form of deposited A-beta, in participants with early symptomatic Alzheimer disease (AD).

Components of the study

The study enrolled 1736 patients (mean age, 73.0 years) with early symptomatic AD (mild cognitive impairment/mild dementia) confirmed by amyloid and low/medium or high tau pathology on PET. Participants were randomised equally to receive either donanemab (n = 860) or placebo (n = 876) via intravenous infusion every 4 weeks for 72 weeks. If dose conditions were met, participants in the donanemab arm were switched blindly to placebo for the remaining duration of the trial. The primary outcome measure was the change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). In addition, there were 24 gated outcomes (primary, secondary, and exploratory.

Outcomes reported

The least-squares mean (LSM) change in iADRS score at 76 weeks showed a significant difference favouring the donanemab group in both the low/medium tau population and the combined population.

Similarly, LSM change in the CDR-SB score at 76 weeks also demonstrated a significant difference favouring the donanemab group in both populations.

Amyloid-related imaging abnormalities of edema/effusion were more frequent in the donanemab group, with some cases being symptomatic. Infusion-related reactions were also more common in the donanemab group. In addition, a small number of deaths were considered treatment-related in both groups.

Conclusions

This trial concluded that donanemab offers promise in slowing the clinical progression of AD in individuals with early symptoms and amyloid and tau pathology. However, these potential benefits need to be weighed against the risks of amyloid-related imaging abnormalities and infusion-related reactions.

Citation 10

Bateman R J, Smith J and Donohue M C; Delmar P ; Abbas R ; Salloway S ; Wojtowicz J ; Blennow K ; Bittner T ; Black S E; Klein G ; Boada M ; Grimmer T ; Tamaoka A ; Perry R J; Turner R S; Watson D ; Woodward M ; Thanasopoulou A ; Lane C ; Baudler M ; Fox N C; Cummings J L; Fontoura P ; Doody R S;. (2023). Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. *New England Journal of Medicine*, 389(20), pp.1862-1876.

Study type

Two double-blind, randomized, placebo-controlled phase 3 trials (GRADUATE I and II)

Objectives

The aim of this study was to evaluate the efficacy and safety of gantenerumab, a monoclonal antibodies that target amyloid-beta (A-beta) in slowing cognitive and functional decline in individuals with early Alzheimer's disease (AD).

Components of the study

Participants aged 50 to 90 years with mild cognitive impairment or mild dementia due to AD and evidence of amyloid plaques on positron-emission tomography (PET) or CSF testing. A total of 985 and 980 participants were enrolled in the GRADUATE I and II trials, respectively. Participants were randomized equally to receive either gantenerumab or placebo every 2 weeks. The primary outcome was the change from baseline in the score on the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater cognitive impairment.

Outcomes reported

Gantenerumab did not significantly slow clinical decline in participants with early AD. The change in CDR-SB scores from baseline to week 116 did not differ significantly between the gantenerumab and placebo groups in either trial [The change from baseline in the CDR-SB score at week 116 was 3.35 with gantenerumab and 3.65 with placebo in the GRADUATE I trial (difference, -0.31; 95% CI, -0.66 to 0.05; P = 0.10) and was 2.82 with gantenerumab and 3.01 with placebo in the GRADUATE II trial (difference, -0.19; 95% CI, -0.55 to 0.17; P = 0.30)]. However, those receiving gantenerumab demonstrated significantly lower amyloid levels on PET and a higher proportion achieved amyloid-negative status compared to the placebo group. At week 116, the difference in the amyloid level on PET between the gantenerumab group and the placebo group was -66.44 and -56.46 centiloids in the GRADUATE I and II trials, respectively, and amyloid-negative status was attained in 28.0% and 26.8% of the participants receiving gantenerumab in the two trials. Participants receiving gantenerumab showed lower CSF levels of phosphorylated tau 181 and higher levels of A-beta42, but the accumulation of aggregated tau on PET was similar between groups.

Importantly, a significant percentage experienced symptomatic amyloid-related imaging abnormalities with edema (ARIA-E), highlighting the potential safety concerns associated with this treatment.

Conclusions

Gantenerumab successfully reduced amyloid plaque burden in individuals with early Alzheimer's disease, this did not translate into a clinically meaningful slowing of cognitive decline. The study also underscored the potential for ARIA-E, including symptomatic cases, with gantenerumab treatment.

References

1. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F*, et al.* Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health* 2022;**7**:e105-e25. 10.1016/S2468-2667(21)00249-8
2. National Institute for Health and Care Excellence. *Dementia: assessment, management and support for people living with dementia and their carers (NG97)*. London: National Institute for Health and Care Excellence; 2018.
3. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Syst Rev* 2022;**18**:e1230. 10.1002/cl2.1230
4. Aiello EN, Esposito A, Appollonio I, Bolognini N. Diagnostic properties of the Frontal Assessment Battery (FAB) in Italian healthy adults. *Aging Clin Exp Res* 2022;**34**:1021-6. https://dx.doi.org/10.1007/s40520-021-02035-2
5. Balogh N, Astrand R, Wallin A, Rolstad S. The five-items memory screen-extended variant: A tool for assessing memory. *Acta Neurol Scand* 2020;**141**:162-7. https://dx.doi.org/10.1111/ane.13188
6. Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages: Implications for Clinical Alzheimer Trials. *Neurology* 2022;**99**:e1142-e53. https://dx.doi.org/10.1212/WNL.0000000000200817
7. Echevarria-Cooper SL, Ho EH, Gershon RC, Weintraub S, Kahnt T. Evaluation of the NIH Toolbox Odor Identification Test across normal cognition, amnestic mild cognitive impairment, and dementia due to Alzheimer's disease. *Alzheimer's dement* 2024;**20**:288-300. https://dx.doi.org/10.1002/alz.13426
8. Groppell S, Soto-Ruiz KM, Flores B, Dawkins W, Smith I, Eagleman DM*, et al.* A Rapid, Mobile Neurocognitive Screening Test to Aid in Identifying Cognitive Impairment and Dementia (BrainCheck): Cohort Study. *JMIR Aging* 2019;**2**:e12615. https://dx.doi.org/10.2196/12615
9. Logue MW, Panizzon MS, Elman JA, Gillespie NA, Hatton SN, Gustavson DE*, et al.* Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. *Mol Psychiatry* 2019;**24**:421-30. https://dx.doi.org/10.1038/s41380-018-0030-8
10. Macoir J, Tremblay P, Hudon C. The Use of Executive Fluency Tasks to Detect Cognitive Impairment in Individuals with Subjective Cognitive Decline. *Behavioral Sciences* 2022;**12**. 10.3390/bs12120491
11. Mukaetova-Ladinska EB, Abdullah S, Critchfield M, Maltby J. Suspected Dementia in Young Adults: Cognitive Screening Tools for Use in Primary Care. *J Alzheimers Dis* 2022;**86**:333-41. https://dx.doi.org/10.3233/JAD-215514
12. O'Caoimh R, Coghlan P, O'Donovan MR, Mohd Zaki N, Daly B, Gao Y*, et al.* Screening for Cognitive Impairment with the Quick Memory Check: Validation of a Caregiver Administered Cognitive Screen. *J Alzheimers Dis* 2022;**90**:1417-27. https://dx.doi.org/10.3233/JAD-220339
13. Rossi M, Baiardi S, Teunissen CE, Quadalti C, van de Beek M, Mammana A*, et al.* Diagnostic Value of the CSF alpha-Synuclein Real-Time Quaking-Induced Conversion Assay at the Prodromal MCI Stage of Dementia With Lewy Bodies. *Neurology* 2021;**97**:e930-e40. https://dx.doi.org/10.1212/WNL.0000000000012438
14. Salvatore C, Cerasa A, Castiglioni I. MRI Characterizes the Progressive Course of AD and Predicts Conversion to Alzheimer's Dementia 24 Months Before Probable Diagnosis. *Front Aging Neurosci* 2018;**10**:135. https://dx.doi.org/10.3389/fnagi.2018.00135

15. Shwartz SK, Morris RD, Penna S. Psychometric properties of the Saint Louis University Mental Status Examination. *Applied Neuropsychology: Adult* 2019;**26**:101-10. https://dx.doi.org/10.1080/23279095.2017.1362407
16. Stein AL, Tolle KA, Stover AN, Shidler MD, Krikorian R. Detecting mild cognitive impairment remotely with the modified memory impairment screen by telephone. *Neuropsychol* 2024;**31**:404-16. https://dx.doi.org/10.1080/13825585.2023.2189688
17. Tolea MI, Heo J, Chrisphonte S, Galvin JE. A Modified CAIDE Risk Score as a Screening Tool for Cognitive Impairment in Older Adults. *J Alzheimers Dis* 2021;**82**:1755-68. https://dx.doi.org/10.3233/JAD-210269
18. Alegret M, Munoz N, Roberto N, Rentz DM, Valero S, Gil S*, et al.* A computerized version of the Short Form of the Face-Name Associative Memory Exam (FACEmemory R) for the early detection of Alzheimer's disease. *Alzheimers Res Ther* 2020;**12**:25. https://dx.doi.org/10.1186/s13195-020-00594-6
19. Benussi A, Cantoni V, Cotelli MS, Cotelli M, Brattini C, Datta A*, et al.* Exposure to gamma tACS in Alzheimer's disease: A randomized, double-blind, sham-controlled, crossover, pilot study. *Brain Stimulation* 2021;**14**:531-40. https://dx.doi.org/10.1016/j.brs.2021.03.007
20. Curiel Cid RE, Crocco EA, Kitaigorodsky M, Beaufils L, Pena PA, Grau G*, et al.* A Novel Computerized Cognitive Stress Test to Detect Mild Cognitive Impairment. *Journal of Prevention of Alzheimer's Disease* 2021;**8(2)**:135-41. https://dx.doi.org/10.14283/jpad.2021.1
21. Ferre-Gonzalez L, Pena-Bautista C, Alvarez-Sanchez L, Ferrer-Cairols I, Baquero M, Chafer-Pericas C. Assessment of Screening Approach in Early and Differential Alzheimer's Disease Diagnosis. *Antioxidants (Basel)* 2021;**10**:22. https://dx.doi.org/10.3390/antiox10111662
22. Jiskoot LC, Panman JL, van Asseldonk L, Franzen S, Meeter LHH, Donker Kaat L*, et al.* Longitudinal cognitive biomarkers predicting symptom onset in presymptomatic frontotemporal dementia. *J Neurol* 2018;**265**:1381-92. https://dx.doi.org/10.1007/s00415-018-8850-7
23. Murray MM, Eardley AF, Edginton T, Oyekan R, Smyth E, Matusz PJ. Sensory dominance and multisensory integration as screening tools in aging. *Sci* 2018;**8**:8901. https://dx.doi.org/10.1038/s41598-018-27288-2
24. Nortunen T, Puustinen J, Luostarinen L, Huhtala H, Hanninen T. Validation of the finnish version of the montreal cognitive assessment test. *Acta Neuropsychologica* 2018;**16(4)**:353-60. https://dx.doi.org/10.5604/01.3001.0012.7964
25. O'Bryant SE, Zhang F, Petersen M, Hall JR, Johnson LA, Yaffe K*, et al.* A blood screening tool for detecting mild cognitive impairment and Alzheimer's disease among community-dwelling Mexican Americans and non-Hispanic Whites: A method for increasing representation of diverse populations in clinical research. *Alzheimer's dement* 2022;**18**:77-87. https://dx.doi.org/10.1002/alz.12382
26. Pillemer S, Papandonatos GD, Crook C, Ott BR, Tremont G. The Modified Telephone-Administered Minnesota Cognitive Acuity Screen for Mild Cognitive Impairment. *J Geriatr Psychiatry Neurol* 2018;**31**:123-8. https://dx.doi.org/10.1177/0891988718776131
27. Rao SM, Galioto R, Sokolowski M, Pierce M, Penn L, Sturtevant A*, et al.* Cleveland Clinic Cognitive Battery (C3B): Normative, Reliability, and Validation Studies of a Self-Administered Computerized Tool for Screening Cognitive Dysfunction in Primary Care. *J Alzheimers Dis* 2023;**92(3)**:1051-66. https://dx.doi.org/10.3233/JAD-220929
28. Saiyed N, Yilmaz A, Vishweswariah S, Maiti AK, Ustun I, Bartolone S*, et al.* Urinary Cytokines as Potential Biomarkers of Mild Cognitive Impairment and Alzheimer's Disease: A Pilot Study. *JAD Rep* 2023;**7**:649-57. https://dx.doi.org/10.3233/ADR-220081
29. Saxon JA, Thompson JC, Harris JM, Ealing J, Hamdalla H, Chaouch A*, et al.* The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) in frontotemporal dementia. *Amyotroph Lateral Scler Frontotemporal Degener* 2020;**21**:606-13. https://dx.doi.org/10.1080/21678421.2020.1797090

30. Abd Razak MA, Ahmad NA, Chan YY, Mohamad Kasim N, Yusof M, Abdul Ghani MKA*, et al.* Validity of screening tools for dementia and mild cognitive impairment among the elderly in primary health care: a systematic review. *Public Health* 2019;**169**:84-92. https://dx.doi.org/10.1016/j.puhe.2019.01.001
31. Karimi L, Mahboub-Ahari A, Jahangiry L, Sadeghi-Bazargani H, Farahbakhsh M. A systematic review and meta-analysis of studies on screening for mild cognitive impairment in primary healthcare. *BMC Psychiatry* 2022;**22**:97. https://dx.doi.org/10.1186/s12888-022-03730-8
32. Seitz DP, Chan CC, Newton HT, Gill SS, Herrmann N, Smailagic N*, et al.* Mini-Cog for the detection of dementia within a primary care setting. *Cochrane Database Syst Rev* 2021;**7**:CD011415. https://dx.doi.org/10.1002/14651858.CD011415.pub3
33. Fage BA, Chan CC, Gill SS, Noel-Storr AH, Herrmann N, Smailagic N*, et al.* Mini-Cog for the detection of dementia within a community setting. *Cochrane Database Syst Rev* 2021;**7**:CD010860. https://dx.doi.org/10.1002/14651858.CD010860.pub3
34. Burton JK, Stott DJ, McShane R, Noel-Storr AH, Swann-Price RS, Quinn TJ. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the early detection of dementia across a variety of healthcare settings. *Cochrane Database Syst Rev* 2021;**7**:CD011333. https://dx.doi.org/10.1002/14651858.CD011333.pub3
35. Chen HH, Sun FJ, Yeh TL, Liu HE, Huang HL, Kuo BI*, et al.* The diagnostic accuracy of the Ascertain Dementia 8 questionnaire for detecting cognitive impairment in primary care in the community, clinics and hospitals: a systematic review and meta-analysis. *Fam Pract* 2018;**35**:239-46. https://dx.doi.org/10.1093/fampra/cmx098
36. Patnode CD, Perdue LA, Rossom RC, Rushkin MC, Redmond N, Thomas RG*, et al.* Screening for Cognitive Impairment in Older Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama* 2020;**323**:764-85. https://dx.doi.org/10.1001/jama.2019.22258
37. Fowler NR, Perkins AJ, Gao S, Sachs GA, Boustani MA. Risks and Benefits of Screening for Dementia in Primary Care: the Indiana University Cognitive Health Outcomes Investigation of the Comparative Effectiveness of Dementia Screening (IU CHOICE)Trial. *J Am Geriatr Soc* 2020;**68**:535-43. https://dx.doi.org/10.1111/jgs.16247
38. Zhuang L, Yang Y, Gao J. Cognitive assessment tools for mild cognitive impairment screening. *J Neurol* 2021;**268**:1615-22. https://dx.doi.org/10.1007/s00415-019-09506-7
39. Abayomi SN, Sritharan P, Yan E, Saripella A, Alhamdah Y, Englesakis M*, et al.* The diagnostic accuracy of the Mini-Cog screening tool for the detection of cognitive impairment-A systematic review and meta-analysis. *PLoS ONE* 2024;**19**:e0298686. https://dx.doi.org/10.1371/journal.pone.0298686
40. Glynn K, Coen R, Lawlor BA. Is the Quick Mild Cognitive Impairment Screen (QMCI) more accurate at detecting mild cognitive impairment than existing short cognitive screening tests? A systematic review of the current literature. *Int J Geriatr Psychiatry* 2019;**34**:1739-46. https://dx.doi.org/10.1002/gps.5201
41. Park SH. Diagnostic performance of the six-item cognitive impairment test as first-step screening for dementia: a meta-analysis. *Brain Impair* 2023;**24**:412-23. https://dx.doi.org/10.1017/BrImp.2022.22
42. Elliott E, Green C, Llewellyn DJ, Quinn TJ. Accuracy of Telephone-Based Cognitive Screening Tests: Systematic Review and Meta-Analysis. *Curr Alzheimer Res* 2020;**17**:460-71. https://dx.doi.org/10.2174/1567205017999200626201121
43. Bat BKK, Chan JYC, Chan TK, Huo Z, Yip BHK, Wong MCS*, et al.* Comparing drawing under instructions with image copying for mild cognitive impairment (MCI) or dementia screening: a meta-analysis of 92 diagnostic studies. *Aging Ment Health* 2022;**26**:1019-26. https://dx.doi.org/10.1080/13607863.2021.1922599

44. Ding Z, Lee TL, Chan AS. Digital Cognitive Biomarker for Mild Cognitive Impairments and Dementia: A Systematic Review. *Journal of Clinical Medicine* 2022;**11(14) (no pagination)**. https://dx.doi.org/10.3390/jcm11144191
45. Teh SK, Rawtaer I, Tan HP. Predictive Accuracy of Digital Biomarker Technologies for Detection of Mild Cognitive Impairment and Pre-Frailty Amongst Older Adults: A Systematic Review and Meta-Analysis. *IEEE j* 2022;**26**:3638-48. https://dx.doi.org/10.1109/JBHI.2022.3185798
46. Thabtah F, Peebles D, Retzler J, Hathurusingha C. Dementia medical screening using mobile applications: A systematic review with a new mapping model. *J Biomed Inform* 2020;**111(no pagination)**. https://dx.doi.org/10.1016/j.jbi.2020.103573
47. Arruda JE, McInnis MC, Steele J. The flash visual evoked potential-P2 and the detection of amnestic mild cognitive impairment: A review of empirical literature. *Int J Psychophysiol* 2020;**155**:162-7. https://dx.doi.org/10.1016/j.ijpsycho.2020.05.012
48. Quimas Molina da Costa R, Pompeu JE, Pereira de Viveiro LA, Brucki SMD. Spatial orientation tasks show moderate to high accuracy for the diagnosis of mild cognitive impairment: A systematic literature review. *Arq Neuropsiquiatr* 2020;**78(11)**:713-23. https://dx.doi.org/10.1590/0004-282X20200043
49. Yang Q, Tian C, Tseng B, Zhang BB, Huang S, Jin S*, et al.* Gait Change in Dual Task as a Behavioral Marker to Detect Mild Cognitive Impairment in Elderly Persons: A Systematic Review and Meta-analysis. *Archives of Physical Medicine and Rehabilitation* 2020;**101**:1813-21. 10.1016/j.apmr.2020.05.020
50. Zhang W, Low LF, Gwynn JD, Clemson L. Interventions to Improve Gait in Older Adults with Cognitive Impairment: A Systematic Review. *J Am Geriatr Soc* 2019;**67**:381-91. https://dx.doi.org/10.1111/jgs.15660
51. Terao I, Kodama W. Comparative Efficacy, Tolerability, and Acceptability of Donanemab, Lecanemab, Aducanumab, Melatonin, and Aerobic Exercise for a Short Time on Cognitive Function in Mild Cognitive Impairment and Mild Alzheimer's Disease: A Systematic Review and Network Meta-Analysis. *J Alzheimers Dis* 2024;**98**:825-35. https://dx.doi.org/10.3233/JAD-230911
52. Dantas JM, Mutarelli A, Navalha DD, Dagostin CS, Romeiro PH, Felix N*, et al.* Efficacy of anti-amyloid-s monoclonal antibody therapy in early Alzheimer's disease: A systematic review and meta-analysis. *Neurol Sci* 2024;**45**:2461-9. https://dx.doi.org/10.1007/s10072-023-07194-w
53. Hort J, Duning T, Hoerr R. Ginkgo biloba extract EGb 761 in the treatment of patients with mild neurocognitive impairment: A systematic review. *Neuropsychiatric Disease and Treatment* 2023;**19**:647-60. https://dx.doi.org/10.2147/NDT.S401231
54. Bateman RJ, Smith J, Donohue MC, Delmar P, Abbas R, Salloway S*, et al.* Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. *N Engl J Med* 2023;**389**:1862-76. https://dx.doi.org/10.1056/NEJMoa2304430
55. Cohen S, van Dyck CH, Gee M, Doherty T, Kanekiyo M, Dhadda S*, et al.* Lecanemab Clarity AD: Quality-of-Life Results from a Randomized, Double-Blind Phase 3 Trial in Early Alzheimer's Disease. *Journal of Prevention of Alzheimer's Disease* 2023;**10(4)**:771-7. https://dx.doi.org/10.14283/jpad.2023.123
56. Fleisher AS, Munsie LM, Perahia DGS, Andersen SW, Higgins IA, Hauck PM*, et al.* Assessment of Efficacy and Safety of Zagotenemab: Results From PERISCOPE-ALZ, a Phase 2 Study in Early Symptomatic Alzheimer Disease. *Neurology* 2024;**102**:e208061. https://dx.doi.org/10.1212/WNL.0000000000208061
57. Florian H, Wang D, Arnold SE, Boada M, Guo Q, Jin Z*, et al.* Tilavonemab in early Alzheimer's disease: results from a phase 2, randomized, double-blind study. *Brain* 2023;**146**:2275-84. https://dx.doi.org/10.1093/brain/awad024

58. Galasko D, Farlow MR, Lucey BP, Honig LS, Elbert D, Bateman R*, et al.* A multicenter, randomized, double-blind, placebo-controlled ascending dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) effects of Posiphen in subjects with early Alzheimer's Disease. *Alzheimers Res Ther* 2024;**16**:151. https://dx.doi.org/10.1186/s13195-024-01490-z
59. Henley D, Sperling RA, Aisen PS, Raman R, Donohue MC, Ernstrom K*, et al.* Final Efficacy, Safety and Biomarker Results of the Phase 2b/3 Randomized, Double-Blinded, Placebo-Controlled Early Trial of Atabecestat in Preclinical Alzheimer's Disease. *Alzheimer's and Dementia* 2019;**15(7 Supplement)**:P873-P4. https://dx.doi.org/10.1016/j.jalz.2019.06.4621
60. Mintun M, Ritchie C, Solomon P, Sims JR, Salloway S, Hansson O*, et al.* Donanemab in early symptomatic Alzheimer's Disease: Efficacy and safety in TRAILBLAZER-ALZ 2, Phase 3 Randomized Clinical Trial. *Age and Ageing* 2024;**53(Supplement 1)**:i30-i1. https://dx.doi.org/10.1093/ageing/afad246.112
61. Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW*, et al.* Donanemab in Early Alzheimer's Disease. *N Engl J Med* 2021;**384**:1691-704. https://dx.doi.org/10.1056/NEJMoa2100708
62. Prins ND, Harrison JE, Chu HM, Blackburn K, Alam JJ, Scheltens P. A phase 2 double-blind placebo-controlled 24-week treatment clinical study of the p38 alpha kinase inhibitor neflamapimod in mild Alzheimer's disease. *Alzheimers Res Ther* 2021;**13**:106. https://dx.doi.org/10.1186/s13195-021-00843-2
63. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J*, et al.* Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA: Journal of the American Medical Association* 2023;**330**:512-27. https://dx.doi.org/10.1001/jama.2023.13239
64. Sperling RA, Donohue MC, Raman R, Rafii MS, Johnson K, Masters CL*, et al.* Trial of Solanezumab in Preclinical Alzheimer's Disease. *N Engl J Med* 2023;**389**:1096-107. https://dx.doi.org/10.1056/NEJMoa2305032
65. Bishnoi A, Hernandez ME. Dual task walking costs in older adults with mild cognitive impairment: a systematic review and meta-analysis. *Aging Ment Health* 2021;**25**:1618-29. 10.1080/13607863.2020.1802576
66. Chae HJ, Lee SH. Effectiveness of online-based cognitive intervention in community-dwelling older adults with cognitive dysfunction: A systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2023;**38**:e5853. https://dx.doi.org/10.1002/gps.5853
67. Garcia-Casares N, Fuentes PG, Barbancho MA, Lopez-Gigosos R, Garcia-Rodriguez A, Gutierrez-Bedmar M. Alzheimer's disease, mild cognitive impairment and mediterranean diet. A systematic review and dose-response meta-analysis. *Journal of Clinical Medicine* 2021;**10(20) (no pagination)**. https://dx.doi.org/10.3390/jcm10204642
68. Gomez-Soria I, Marin-Puyalto J, Peralta-Marrupe P, Latorre E, Calatayud E. Effects of multi-component non-pharmacological interventions on cognition in participants with mild cognitive impairment: A systematic review and meta-analysis. *Archives of Gerontology and Geriatrics* 2022;**103**:1-14. https://dx.doi.org/10.1016/j.archger.2022.104751
69. Kim O, Pang Y, Kim JH. The effectiveness of virtual reality for people with mild cognitive impairment or dementia: a meta-analysis. *BMC Psychiatry* 2019;**19**. 10.1186/s12888-019-2180-x
70. Leow Y, Rashid N, Klainin-Yobas P, Zhang Z, Wu XV. Effectiveness of mindfulness-based interventions on mental, cognitive outcomes and neuroplastic changes in older adults with mild cognitive impairment: A systematic review and meta-analysis. *J Adv Nurs* 2023;**79**:4489-505. https://dx.doi.org/10.1111/jan.15720

71. Li F, Parsons J, Peri K, Yu A, Cheung G. Effects of cognitive interventions on quality of life among adults with mild cognitive impairment: A systematic review and meta-analysis of randomised controlled trials. *Geriatric Nursing* 2022;**47**:39-50. 10.1016/j.gerinurse.2022.06.009
72. Li S, Tang Y, Zhou Y, Ni Y. Effects of Transcranial Direct Current Stimulation on Cognitive Function in Older Adults with and without Mild Cognitive Impairment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Gerontology* 2024;**70**:544-60. https://dx.doi.org/10.1159/000537848
73. Lin JC, Chen IH, Cheng FY. Review articles (Meta-Analyses) effects of walking on cognitive function in individuals with mild cognitive impairment: a systematic review and meta-analysis. *BMC geriatr* 2023;**23**:500. https://dx.doi.org/10.1186/s12877-023-04235-z
74. Pang SH, Lim SF, Siah CJ. Online memory training intervention for early-stage dementia: A systematic review and meta-analysis. *J Adv Nurs* 2021;**77**:1141-54. https://dx.doi.org/10.1111/jan.14664
75. Sung CM, Jen HJ, Liu D, Kustanti CY, Chu H, Chen R*, et al.* The effect of cognitive training on domains of attention in older adults with mild cognitive impairment and mild dementia: A meta-analysis of randomised controlled trials. *Journal of Global Health* 2023;**13**:04078. https://dx.doi.org/10.7189/jogh.13.04078
76. Teselink J, Bawa KK, Koo GK, Sankhe K, Liu CS, Rapoport M*, et al.* Efficacy of non-invasive brain stimulation on global cognition and neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review. *Ageing Res Rev* 2021;**72**:101499. https://dx.doi.org/10.1016/j.arr.2021.101499
77. Tulliani N, Bissett M, Fahey P, Bye R, Liu KPY. Efficacy of cognitive remediation on activities of daily living in individuals with mild cognitive impairment or early-stage dementia: a systematic review and meta-analysis. *Syst* 2022;**11**:156. https://dx.doi.org/10.1186/s13643-022-02032-0
78. Yi LRS, Jing SJ, Hammoda A, Jonathan B. Effects of mindfulness-based interventions on neuropsychiatric symptoms and psychological well-being on people with subjective cognitive decline and mild cognitive impairment: A meta-analysis. *Int J Geriatr Psychiatry* 2023;**38**. 10.1002/gps.5986
79. Gkotzamanis V, Magriplis E, Panagiotakos D. The effect of physical activity interventions on cognitive function of older adults: A systematic review of clinical trials. *Psuhiatrike* 2022;**33**:291-300. https://dx.doi.org/10.22365/jpsych.2022.060
80. Gomez-Soria I, Peralta-Marrupe P, Calatayud-Sanz E, Latorre E. Efficacy of cognitive intervention programs in amnesic mild cognitive impairment: A systematic review. *Arch Gerontol Geriatr* 2021;**94**:104332. https://dx.doi.org/10.1016/j.archger.2020.104332
81. McGrattan AM, McEvoy CT, McGuinness B, McKinley MC, Woodside JV. Effect of dietary interventions in mild cognitive impairment: a systematic review. *Br J Nutr* 2018;**120**:1388-405. https://dx.doi.org/10.1017/S0007114518002945
82. Anderson-Hanley C, Barcelos NM, Zimmerman EA, Gillen RW, Dunnam M, Cohen BD*, et al.* The Aerobic and Cognitive Exercise Study (ACES) for Community-Dwelling Older Adults With or At-Risk for Mild Cognitive Impairment (MCI): Neuropsychological, Neurobiological and Neuroimaging Outcomes of a Randomized Clinical Trial. *Front Aging Neurosci* 2018;**10**. 10.3389/fnagi.2018.00076
83. Belleville S, Hudon C, Bier N, Brodeur C, Gilbert B, Grenier S*, et al.* MEMO+: Efficacy, Durability and Effect of Cognitive Training and Psychosocial Intervention in Individuals with Mild Cognitive Impairment. *J Am Geriatr Soc* 2018;**66**:655-63. https://dx.doi.org/10.1111/jgs.15192
84. Benussi A, Premi E, Grassi M, Alberici A, Cantoni V, Gazzina S*, et al.* Diagnostic accuracy of research criteria for prodromal frontotemporal dementia. *Alzheimer's Research and Therapy* 2024;**16(1) (no pagination)**. https://dx.doi.org/10.1186/s13195-024-01383-1

85. Chandler MJ, Locke DE, Crook JE, Fields JA, Ball CT, Phatak VS*, et al.* Comparative Effectiveness of Behavioral Interventions on Quality of Life for Older Adults With Mild Cognitive Impairment: A Randomized Clinical Trial. *JAMA netw* 2019;**2**:e193016. https://dx.doi.org/10.1001/jamanetworkopen.2019.3016
86. Cintoli S, Radicchi C, Noale M, Maggi S, Meucci G, Tognoni G*, et al.* Effects of combined training on neuropsychiatric symptoms and quality of life in patients with cognitive decline. *Aging Clin Exp Res* 2021;**33**:1249-57. https://dx.doi.org/10.1007/s40520-019-01280-w
87. Diaz Baquero AA, Franco-Martin MA, Parra Vidales E, Toribio-Guzman JM, Bueno-Aguado Y, Martinez Abad F*, et al.* The Effectiveness of GRADIOR: A Neuropsychological Rehabilitation Program for People with Mild Cognitive Impairment and Mild Dementia. Results of a Randomized Controlled Trial After 4 and 12 Months of Treatment. *J Alzheimers Dis* 2022;**86**:711-27. https://dx.doi.org/10.3233/JAD-215350
88. Doungsong K, Hartfiel N, Gladman J, Harwood R, Edwards RT. RCT-based Social Return on Investment (SROI) of a Home Exercise Program for People With Early Dementia Comparing In-Person and Blended Delivery Before and During the COVID-19 Pandemic. *Inquiry* 2024;**61**:469580241246468. https://dx.doi.org/10.1177/00469580241246468
89. Gomez-Soria I, Brandin-de la Cruz N, Cuenca Zaldivar JN, Calvo S, Herrero P, Calatayud E. Effectiveness of Personalized Cognitive Stimulation in Older Adults with Mild Possible Cognitive Impairment: A 12-month Follow-up Cognitive Stimulation in Mild Cognitive Impairment. *Clin Gerontol* 2022;**45**:878-90. https://dx.doi.org/10.1080/07317115.2021.1937764
90. Jenewein J, Moergeli H, Meyer-Heim T, Muijres P, Bopp-Kistler I, Chochinov HM*, et al.* Feasibility, Acceptability, and Preliminary Efficacy of Dignity Therapy in Patients With Early Stage Dementia and Their Family. A Pilot Randomized Controlled Trial. *Front Psychiatr* 2021;**12**:795813. https://dx.doi.org/10.3389/fpsyt.2021.795813
91. Kerkhof Y, Kohl G, Veijer M, Mangiaracina F, Bergsma A, Graff M*, et al.* Randomized controlled feasibility study of FindMyApps: first evaluation of a tablet-based intervention to promote self-management and meaningful activities in people with mild dementia. *Disabil* 2022;**17**:85-99. https://dx.doi.org/10.1080/17483107.2020.1765420
92. Manenti R, Gobbi E, Baglio F, Macis A, Ferrari C, Pagnoni I*, et al.* Effectiveness of an Innovative Cognitive Treatment and Telerehabilitation on Subjects With Mild Cognitive Impairment: A Multicenter, Randomized, Active-Controlled Study. *Front Aging Neurosci* 2020;**12**:585988. https://dx.doi.org/10.3389/fnagi.2020.585988
93. McDougall GJ, McDonough IM, LaRocca M. Memory training for adults with probable mild cognitive impairment: a pilot study. *Aging Ment Health* 2019;**23**:1433-41. https://dx.doi.org/10.1080/13607863.2018.1484884
94. Mountain G, Wright J, Cooper CL, Lee E, Sprange K, Beresford-Dent J*, et al.* An intervention to promote self-management, independence and self-efficacy in people with early-stage dementia: the Journeying through Dementia RCT. *Health Technol Assess* 2022;**26**:1-152. https://dx.doi.org/10.3310/KHHA0861
95. Rodella C, Bernini S, Panzarasa S, Sinforiani E, Picascia M, Quaglini S*, et al.* A double-blind randomized controlled trial combining cognitive training (CoRe) and neurostimulation (tDCS) in the early stages of cognitive impairment. *Aging Clinical and Experimental Research* 2022;**34**:73-83. 10.1007/s40520-021-01912-0
96. Rosenberg A, Ngandu T, Rusanen M, Antikainen R, Backman L, Havulinna S*, et al.* Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: The FINGER trial. *Alzheimer's dement* 2018;**14**:263-70. https://dx.doi.org/10.1016/j.jalz.2017.09.006
97. Stuckenschneider T, Sanders ML, Devenney KE, Aaronson JA, Abeln V, Claassen J*, et al.* NeuroExercise: The Effect of a 12-Month Exercise Intervention on Cognition in Mild

Cognitive Impairment-A Multicenter Randomized Controlled Trial. *Front Aging Neurosci* 2020;**12**:621947. https://dx.doi.org/10.3389/fnagi.2020.621947
98. Valdes EG, Andel R, Lister JJ, Gamaldo A, Edwards JD. Can Cognitive Speed of Processing Training Improve Everyday Functioning Among Older Adults With Psychometrically Defined Mild Cognitive Impairment? *J Aging Health* 2019;**31**:595-610. https://dx.doi.org/10.1177/0898264317738828
99. Vidoni ED, Perales J, Alshehri M, Giles AM, Siengsukon CF, Burns JM. Aerobic Exercise Sustains Performance of Instrumental Activities of Daily Living in Early-Stage Alzheimer Disease. *J Geriatr Phys Ther* 2019;**42**:E129-E34. https://dx.doi.org/10.1519/JPT.0000000000000172
100. Whitlatch CJ, Heid AR, Femia EE, Orsulic-Jeras S, Szabo S, Zarit SH. The Support, Health, Activities, Resources, and Education program for early stage dementia: Results from a randomized controlled trial. *Dementia-International Journal of Social Research and Practice* 2019;**18**:2122-39. 10.1177/1471301217743033
101. NCT04619420. A Study of JNJ-63733657 in Participants With Early Alzheimer's Disease. 2020.
102. NL-OMON51311. A Randomized, Double-blind, Placebo-controlled Single Ascending Dose and Open-label Multi-dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ALN-APP in Adult Patients with Early-onset Alzheimer*s Disease (EOAD). In; 2022.
103. Tuszynski MH. A Phase I Study to Assess the Safety, Tolerability and Preliminary Efficacy of AAV2-BDNF [Adeno-Associated Virus (AAV)-Based, Vector-Mediated Delivery of Human Brain Derived Neurotrophic Factor] in Subjects With Early Alzheimer's Disease and Mild Cognitive Impairment. In: Ohio State U, ed.; 2021.
104. Novo Nordisk A/S. A Randomised Double-blind Placebo-controlled Clinical Trial Investigating the Effect and Safety of Oral Semaglutide in Subjects With Early Alzheimer´s Disease (EVOKE Plus). In; 2021.
105. Helse Stavanger HF. A Placebo Controlled Randomized Double-blind Parallel Group 12-month Trial of Fasudil for the Treatment of Early Alzheimer's Disease (FEAD). In: University of E, ed.; 2024.
106. KeifeRx L. A Multicenter, Phase III, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Nilotinib BE in Subjects With Early Alzheimer's Disease (NILEAD). In: Worldwide Clinical T, Life Molecular Imaging Gmb H, Sun Pharmaceuticals Industries L, eds.; 2021.
107. Nicholson JS, Hudak EM, Phillips CB, Chanti-Ketterl M, O'Brien JL, Ross LA*, et al.* The Preventing Alzheimer's with Cognitive Training (PACT) randomized clinical trial. *Contemp Clin Trials* 2022;**123**:106978. https://dx.doi.org/10.1016/j.cct.2022.106978
108. NCT05894954. Precision Medicine Approach for Early Dementia & Mild Cognitive Impairment. In; 2023.
109. Institute for Molecular Medicine. A Phase I, Randomized, Double-Blind Study to Evaluate Safety and Tolerability of Amyloid-β Vaccine, AV-1959D, in Patients With Early Alzheimer's Disease. In: National Institute on A, Clinartis, eds.; 2022.
110. University of Tasmania. TAS Test: Determining the Feasibility and Validity of Online Motor-cognitive Testing for Early Detection of Alzheimer's Disease. In: National H, Medical Research Council A, University of S, University of L, eds.; 2021.
111. University Hospital Ghent. An Immersive Virtual Reality Spatial Navigation Task as Potential Biomarker for the Early Detection of Alzheimer's Disease. In; 2024.
112. Caminiti SP, Bernini S, Bottiroli S, Mitolo M, Manca R, Grillo V*, et al.* Exploring the neural and behavioral correlates of cognitive telerehabilitation in mild cognitive impairment with three

distinct approaches. *Front Aging Neurosci* 2024;**16**:1425784. https://dx.doi.org/10.3389/fnagi.2024.1425784
113. Cao K, Bay AA, Hajjar I, Wharton W, Goldstein F, Qiu D*, et al.* Rationale and Design of the PARTNER Trial: Partnered Rhythmic Rehabilitation for Enhanced Motor-Cognition in Prodromal Alzheimer's Disease. *J Alzheimers Dis* 2023;**91**:1019-33. https://dx.doi.org/10.3233/JAD-220783
114. Ekman U, Kemani MK, Wallert J, Wicksell RK, Holmström L, Ngandu T*, et al.* Evaluation of a Novel Psychological Intervention Tailored for Patients With Early Cognitive Impairment (PIPCI): Study Protocol of a Randomized Controlled Trial. *Front Psychol* 2020;**11**. 10.3389/fpsyg.2020.600841
115. Tomaszewski Farias S, Fox J, Dulaney H, Chan M, Namboodiri S, Harvey DJ*, et al.* Memory support training and lifestyle modifications to promote healthy aging in persons at risk for Alzheimer's disease: a digital application supported intervention (Brain Boosters). *BMC geriatr* 2023;**23**:881. https://dx.doi.org/10.1186/s12877-023-04574-x
116. DRKS00033764. Digital screening for the Assessment of Cognitive Abilities (digiDEM-SCREEN). In; 2024.
117. Lovett R, Bonham M, Yoshino Benavente J, Hosseinian Z, Byrne GJ, Varela Diaz M*, et al.* Primary care detection of cognitive impairment leveraging health and consumer technologies in underserved US communities: protocol for a pragmatic randomised controlled trial of the MyCog paradigm. *BMJ Open* 2023;**13**:e080101. 10.1136/bmjopen-2023-080101
118. Cole MA, Seabrook GR. On the horizon-the value and promise of the global pipeline of Alzheimer's disease therapeutics. *Alzheimers Dement (N Y)* 2020;**6**:e12009. https://dx.doi.org/10.1002/trc2.12009