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Continuing Education for the Prevention of Mild Cognitive Impairment and Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic Reviews.

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ABSTRACT

Objective: To summarize evidence on the preventive effects of continuing education on mild cognitive impairment and Alzheimer's-type dementia.

Design: Systematic review and overview of systematic reviews.

Data sources: We systematically searched MEDLINE, PsycINFO, EMBASE, CENTRAL, CINAHL and Scopus for published studies and gray literature databases for unpublished studies from January 1990 to April 2018.

Methods: To assess evidence directly addressing our objectives, we conducted a systematic review. Because we were aware of a dearth of direct evidence, we also performed an overview of systematic reviews on leisure activities that mimic formal continuing education. We a priori established inclusion and exclusion criteria. Two authors independently assessed inclusion and exclusion on abstract and full-text level, rated risk of bias, and determined the certainty of evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation). We resolved all discrepancies by consensus. We synthesized the available evidence narratively.

Results: Our searches identified 4933 citations. For the systematic review, two publications on the same prospective cohort study (Tasmanian Healthy Brain Project) met inclusion criteria; for the overview of reviews we included five systematic reviews. Based on 459 participants, preliminary data of the ongoing cohort study indicated that cognitive reserve statistically significantly increased in persons attending university classes compared to the control group (92.5% vs. 55.7%). Likewise, language processing capacities statistically significantly improved. Episodic memory, working memory, and executive function did not differ significantly between groups.

Systematic reviews consistently reported a positive association between participation in cognitively stimulating leisure activities and reduced incidence of dementia and improved cognitive test performance.

Conclusion: Available results demonstrate that cognitive reserve increases through continuing education and show a positive association of cognitive leisure activities with both improved cognitive

function and lower dementia incidence. Healthcare providers and policymakers should promote a healthy lifestyle, which also includes being cognitively active throughout life.

Systematic review registration: PROSPERO CRD42017063944

Strengths and Limitations of this study:

- This is the first systematic review assessing the benefits and harms of continuing education on the prevention of mild cognitive impairment or Alzheimer's type dementia.
- This is the first overview of systematic reviews presenting an up-to-date summary of currently available research in the field of cognitive leisure activities and dementia.
- The certainty of evidence is low, indicating that future studies might have a substantial impact on results of our review.
- Measurements and types of cognitive leisure activities differed widely across studies and quantitative analysis were often not possible.
- The majority of included systematic reviews have serious methodological shortcomings.

INTRODUCTION

In 2012, the World Health Organization (WHO) named the prevention and control of neurocognitive disorders such as mild cognitive impairment or Alzheimer's-type dementia a global public health priority.[1] Alzheimer's-type dementia is the most common form of dementing illnesses.[1] In 2015, 47.5 million people worldwide lived with Alzheimer's disease or another closely related dementing illness.[2] As a consequence of the rapidly aging world population, the prevalence is projected to rise up to 135.5 million patients in 2050.[2]

The progressive loss of independent functioning of patients with Alzheimer's-type dementia, leads to an enormous social and economic burden. In 2017, the U.S. economic burden associated with Alzheimer's type dementia was estimated to be 259 billion U.S. Dollars[3] the total global costs for dementia were 818 billion in 2015.[4]

The Diagnostic and Statistical Manual (DSM-5) characterizes Alzheimer's disease as a significant decline of intellectual abilities in one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual motor function, social cognition) outside the context of delirium.[5]

Any dementia diagnosis, however, is frequently preceded by a long period of subclinical neuropathological disorder with subjective cognitive disorder (SCI) and mild cognitive disorder (MCI) as a transition phase before diagnostic criteria for dementia are fulfilled.[6] If cognitive decline progresses to a degree that a person's capability of carrying out everyday activities is significantly affected, this state is called major neurocognitive disorder.[5 6]

The risk of developing neurocognitive disorders increases substantially with age. The prevalence of Alzheimer's type dementia is 3.5% in persons aged 75 or older and 46.3% in those 95 years or older.[7] Other risk factors contributing to the development of the disease are not yet thoroughly understood. In recent years, epidemiological studies have linked the development of dementia with risk factors such as low educational level, unhealthy diet, decreased physical activity, and smoking.[8 9] In addition, potential predictors of dementia are chronic medical conditions such as

cardiovascular diseases, diabetes, obesity, cancers, depression, thyroid disorder, or genetic factors.[10] However, some studies found a protective association of cognitively stimulating activities, such as learning a new language in middle age, with a slower cognitive decline during late life.[11-15] Such results underpin the "cognitive reserve hypothesis".[16-18] According to this theory, through every activity that stimulates the brain, the cognitive reserve gets boosted and the resistance towards any dementia-related brain pathology increases.[19] In animal trials, an enriched environment was associated with increased cortical thickness.[20] Epidemiological research on humans has shown that education[21] and probably also other forms of intellectual stimulation, during the whole lifespan, is associated with a lower risk to develop dementia.[22 23] A larger cognitive reserve acquired by continuing education activities, thus, might protect against cognitive decline.[19 24]

For this systematic review, we define continuing education as structured learning activities and programs provided by formal and non-formal educational institutions for persons beyond the age of compulsory schooling. These activities are designed to help individuals satisfy learning needs and interests, to enrich knowledge, to develop and improve abilities and skills, and to foster personality, social competences, families, networks, health, and professional life. Continuing education is voluntary, and based on topics and courses that are not directly connected to any special job position or vocational training.[25-30]

Rationale

To date, the preventive effect of continuing education on cognitive impairment and Alzheimer's-type dementia has not been assessed in an objective and systematic way. The aim of our review was to summarise the evidence investigating the preventive effects of continuing education on the development of cognitive impairment and Alzheimer's-type dementia.

Our systematic review addressed the following questions:

Key question 1a: In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment, does continuing education lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type dementia compared with no continuing education?

Key question 1b: (In case no evidence on continuing education is available or the evidence is sparse): In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment, do leisure activities lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type dementia compared with no continuing education?

Key question 2: What are potential harms of continuing education?

Key question 3: Do benefits and harms differ by subgroups based on age, sex/gender, race or ethnicities, level of education, or duration of intervention?

Key question 4: What is the optimal age to start continuing education to prevent mild cognitive impairment or dementia?

METHODS

Design

Throughout this manuscript we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[31] (See supplementary file 1). The protocol of this systematic review was published[32] and registered in PROSPERO (International Prospective Register of Systematic Reviews) (Registration number CRD42017063944). Figure 1 depicts the analytic framework that guided our systematic review.

[Figure 1 about here]

We addressed our research questions with two different methodological approaches:

1) We performed a systematic review of primary studies to assess the preventive effects and potential harms of continuing education provided by formal and non-formal institutions (key questions 1a, 2, 3, and 4)

2) We conducted an overview of systematic reviews to determine the preventive effects and potential harms of related leisure activities (e.g. playing cards, reading books, etc., key question 1b).

We chose this two-step approach because studies in the field of continuing education and dementia are very rare. Certain leisure activities, however, are able to mimic continuing education regarding content (e.g. learning a new language privately versus learning a new language as an organized educational activity). Leisure activities are not our primary focus of interest but can be considered as surrogate interventions for continuing education in some circumstances.

Study selection

Eligibility criteria for the systematic review

The population of interest were adults 45 years or older, without a clinical diagnosis of cognitive impairment at the time of study recruitment, which included people with subjective cognitive impairment. Eligible interventions comprised of all cognitive activities that are provided by formal and non-formal educational institutions. These activities include classes, courses, and trainings that are based on individual interests and that are attended voluntarily. We included randomized controlled trials, nonrandomized controlled trials, prospective controlled cohort studies, retrospective controlled cohort studies, and case-control studies. All nonrandomized studies needed to have a minimum sample size of 300 or more participants.

Eligible studies had a minimum follow up time of 1 year and a minimum duration of intervention of 3 months. We excluded studies that investigated formal (vocational) education (e.g. School or College), physical activities, and all job-related courses and trainings.

Outcomes of interest included patient-relevant health outcomes such as incidence of dementia, incidence of MCI, psychological wellbeing, functional capacity, quality of life, and other relevant health outcomes; in addition, we included intermediate outcomes such as cognitive functioning, cognitive (test) performance, or social inclusion. For the purpose of our study, mild

cognitive impairment refers to "amnestic" mild cognitive impairment (aMCI), meaning that memory loss is the predominant symptom.[33]

Eligibility criteria for the overview of systematic reviews

Eligibility criteria for population and outcomes for the overview of systematic reviews were the same as for the systematic review. Eligible interventions were leisure activities that are cognitively stimulating and mimic the content of continuing education but in an informal setting. Just as in the systematic review, we excluded physical activities. Eligible study designs were exclusively systematic reviews and meta-analyses. We excluded reviews with searches conducted before 2013.

Further details about our inclusion and exclusion criteria can be found in our protocol[32] and in the supplementary file 2.

Search strategy

We systematically searched Ovid MEDLINE, Cochrane Library, Embase, PsycINFO, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ALOIS (the Cochrane Dementia and Cognitive Improvement Group Specialized Register), and ERIC (Education Resources Information Center) from January 1990 to April 2018 to identify relevant publications (see supplementary file 3 for the search strategy). For the overview of reviews, we searched Epistemonikos from inception to April 2018 in addition to the above mentioned databases (see supplementary file 4).

An experienced information specialist developed an appropriate search strategy using a combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the search to human-only studies without applying any language limitations. The electronic Ovid Medline search strategy was peer-reviewed by another information specialist following the PRESS (peer review of the electronic search strategy) statement.[34] For the systematic review, we searched for gray literature in ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, web pages of relevant organizations, and a dissertation database ("Digital Access to Research Theses", DART-Europe). Additionally, in an attempt to avoid retrieval bias, we manually

searched the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed. We imported all citations into an electronic database (EndNote X.8) and deleted duplicates.

Study selection

Two review authors independently screened abstracts and relevant full text articles for eligibility, using Covidence Software.[35] They resolved disagreements by discussion or by consultation with a third author.

Data abstraction

We designed, pilot-tested, and used a data abstraction form to gather pertinent information from each article. One author extracted relevant data from each study that met our inclusion criteria. A second author of the team cross-checked data abstractions for completeness and accuracy. We extracted study information (author, publication year, years covered by searches, location/setting, number of included studies and included study designs), sample size, study characteristics (population, interventions, and comparators), outcome measurements, and results. For systematic reviews we abstracted summary estimates of meta-analyses whenever available.

Risk of bias assessment

Two investigators independently assessed the risk of bias of included studies. They resolved any disagreements by consensus or by consulting a third team member. For eligible non-randomized studies we used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool.[36] For the assessment of eligible systematic reviews, we used the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool.[37] Detailed risk of bias ratings of included articles are given in supplementary file 5.

Data synthesis and statistical analysis

We narratively summarized evidence from included studies. If available, we present effect estimates of systematic reviews. For the incidence of dementia we present hazard ratios (HR), odds

ratios (OR), and risk ratios (RR). A value below 1 represents a lower risk for the intervention, a value greater than 1 indicates a lower risk for the control group; an estimate of 1 means no difference between intervention and control. For the assessment of cognitive test performance we use standardized mean differences because scales for measurements differed in the individual studies. A standardized mean difference of 0 indicates that both groups had the same cognitive test performance.

Certainty of evidence

We followed the recommendations of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group for rating the certainty of evidence for each outcome.[38]

Patient involvement

No patients were involved in the development of this research paper.

RESULTS

Our search identified in total 4933 citations after exclusion of duplicates. Based on title and abstract review, we considered 58 primary studies and 28 systematic reviews for full-text review. After scrutinising the full-text articles, we included two primary studies[39 40] and five systematic reviews.[41-45] Figure 2 and figure 3 depict the study selection process. Supplementary file 6 provides a list of excluded studies at full-text level.

[Figure 2 and figure 3 about here]

Study characteristics

Systematic Review

We included two publications[39 40] that present interim findings of the same medium risk of bias prospective cohort study, namely the Tasmanian Healthy Brain Project that plans to follow participants for 10-20 years.[46] The two publications analysed different aspects of cognitive

functioning of the same 459 participants who did or did not engage in a 12 month, part-time or full-time university-level education. Participants' mean age was 59.6±7 (mean±SD) years in the intervention group and 62.4±6 years in the control group with a follow-up period of 4 years. Participants completed a neuropsychological test battery, consisting of 14 tests each year.[46]

In this study, selection bias is likely because participants voluntarily opted for university courses or no further education. It is not clear if investigators used appropriate methods to adjust for potential confounders (See supplementary file 5 for risk of bias ratings).

Overview of Reviews

All five included systematic reviews investigated the benefits of cognitive leisure activities in adults over the age of 45 years.[41-45] Four studies included any cognitive leisure activities in their analyses (e.g. reading books, doing crosswords, attending cultural events, knitting, painting), one study[44] specifically focused on the benefits of playing video games in older adults. The number of participants investigated in the reviews ranged from 913[44] to 24,554.[42]

We rated three of the included systematic reviews[41 43 44] as high and two studies[42 45] as medium risk of bias. Reasons for the high risk of bias ratings were lack of critical appraisal of included studies, single review of the literature, and insufficient literature searches (See supplementary file 5).

We graded the evidence for all meta-analysis outcomes with low certainty of evidence mostly because of high inconsistency and indirectness among studies (See supplementary file 7).

We present characteristics of included studies [41-45] in Table 1.

Reference	Risk of Bias	Search	Study design	Population	Interventions	Control	Outcomes	k of studies on cognitive leisure activities n of participants
Primary Studies								
Lenhan et al., 2016[40]	Medium		Prospective cohort study, Tasmanian Healthy Brain Project (2011-2016)	50-79 years, healthy older adults	Minimum of 12 months of part-time or full-time university study Follow-up: 4 years	No further education	55,7% in the control group vs 92,5% in the university education group showed a significant increase of **cognitive reserve**	n = 459 (359 in the Intervention group, 100 control group)
Thow et al., 2018[39]	Medium		Prospective cohort study, Tasmanian Healthy Brain Project (2011-2018)	50-79 years, healthy older adults	Minimum of 12 months of part-time or full-time university study Follow-up: 4 years	No further education	Statistically significant improvement of **language processing capacity.** No significant improvement of episodic memory, working memory, executive function.	n = 459 (359 in the Intervention group, 100 control group)
Systematic Reviews								
Di Marco et al., 2014[41]	High	NR to 2013	NR	≥65 years, non-demented adults at baseline	Cognitive leisure activities (assessed with self-reported questionnaires) Time period: Past 12 months		No quantitative analysis Cognitive leisure activities might be associated with **reduced incidence of all-cause dementia**	k = 6 n = NR
Opdebeeck et al., 2016[42]	High	NR to 2014	31 Cross-sectional studies	≥60 years (at least 80% of study participants)	Cognitive leisure activities (assessed with self-reported questionnaires) Time period: currently, mid-life, late-life		SMD 0.26 (95% CI 0.21-0.32) Participating in cognitive leisure activities is associated with **improved cognitive functions** (including memory, working memory, executive function, visuospatial ability, and language)	k = 31 n = 24561
Sajeev et al., 2016[43]	Medium	NR to June 2014	10 prospective cohort studies; 2 nested case-control studies	≥45 years	Leisure activities that require information seeking and processing (assessed with self-reported questionnaires) Time period: current, early, mid and late life		No quantitative analysis Late-life cognitive activity might be associated with **lower AD and/or all-cause dementia incidence**	k = 12 n = 13939 (dementia: 1663 AD: 565)
Toril et al., 2014[44]	High	1986-2013	18 controlled studies 2 uncontrolled studies	50 - 86 years, healthy older adults	Video Game training Games: Medal of Honor, Pac Man, Donkey Kong, Tetris, Crystal castle, Nintendo Brain Training, Brain Age, Big Brain Academy, etc. Pre- and post training measures	active and passive control groups	SMD 0.37 (95% CI 0.26 – 0.48) Video game training is associated with **improved cognitive functions** in older adults (including memory, attention, reaction time, cognitive function, executive functions)	k = 20 n = 913 (474 trained, 439 healthy controls)
Yates et	Medium	2004 -	17 Cohort studies	≥ 46 years,	Unstructured leisure activities		**All-cause dementia incidence:**	k = 19

al., 2016[45]		2014	2 Case control studies	cognitively healthy adults (i.e. no diagnosis of impairment or dementia)	which elicit a “mental response” from the Participant.		RR 0.61 (95%CI 0.42 – 0.90), k=3, RE HR 0.58 (95%CI 0.46 – 0.74), k=2, RE OR 0.78 (95%CI 0.67 – 0.90), k=2, FE **Cognitive impairment incidence:** OR 0.69 (95%CI 0.56 – 0.85), k=5, RE HR 0.85 (95% CI 0.71 – 1.02), k=3, RE, n.s.	n = 32546

NR = Not reported, AD = Alzheimer’s-type dementia, k = studies that assessed cognitive activities only, n= number of participants, RE = random-effects model, FE = fixed effects model, n.s. = not significant

Table 1: Study Characteristics of included primary studies and systematic reviews

Outcomes

Key question 1a: Continuing education

Two interim analyses of the Tasmanian Healthy Brain Project focused on language processing[39] and cognitive reserve[40] after 4 years of follow-up. To date, no results on the incidence of mild cognitive impairment or Alzheimer's-type dementia are available yet. Both studies reported beneficial effects of continuing education. Thow and colleagues[39] showed that attending university courses over a period of 12 months statistically significantly ($p<0.05$) improved language processing capacity in the intervention group compared to the control group. No statistically significant differences were detected for episodic memory, working memory, and executive function between groups. In all analyses, authors accounted for age and prior cognitive reserve (education, pre-existing intellectual capacity, life-experience).

Lenehan and coworkers[40] demonstrated by conducting growth mixture modeling that the cognitive reserve statistically significantly increased in 92.5% of participants in the intervention group (n=359) compared to 55.7% of participants in the control group (n=100). Investigators created a proxy measure of "current cognitive reserve" to capture dynamic changes in cognitive reserve over time, including intellectual capacity and academic ability.[47]

Key question 1b: Cognitive leisure activities

Overall, the five included systematic reviews showed consistently that participation in cognitive stimulating leisure activities can reduce the risk of developing mild cognitive impairment or Alzheimer's-type dementia and improves cognitive functioning of healthy older adults.

Two systematic reviews[41 43] investigated the impact of cognitive leisure activities on the incidence of Alzheimer's-type dementia. Both studies concluded that leisure activities protect against dementia. Due to different categorization of cognitive leisure activities and a high heterogeneity between studies, quantitative analyses were not possible in the two reviews. The effect estimates of included studies ranged from hazard ratios [HR] of 0.39 (95% CI: 0.21 - 0.71)[48] to HR of 0.93 (95% CI: 0.88 – 0.98)[49] showing a reduced risk of Alzheimer's-type dementia when carrying out leisure

activities. Sajeev et al.[43] performed an extensive bias analysis showing that it is unlikely that the observed positive effects of cognitively stimulating activities on dementia incidence are exclusively explained by unmeasured confounders or reverse causation.

One review[45] assessed both incidence of mild cognitive impairment and Alzheimer's-type dementia and cognitive test performance. The authors conducted five meta-analyses based on groups for outcomes and reported effect estimates (risk ratio [RR], odds ratio [OR], and hazard ratio [HR]). Four out of five meta-analyses revealed statistically significant results showing that cognitive leisure activities were associated with a reduction of dementia incidence (RR = 0.61, 95% CI: 0.42-0.90, p=0.01; HR = 0.58, 95% CI: 0.46-0.74, p=0.00, OR = 0.78, 95% CI: 0.67 – 0.90) and a reduction of cognitive impairment incidence (OR = 0.69, 95% CI: 0.56 – 0.85, p=0.00). However, one meta-analysis, combining three cohort studies did not reach statistical significance (HR = 0.85, 95% CI: 0.71-1.02, p=0.08) for reduction of cognitive impairment. A narrative analysis of primary studies assessing cognitive test performance showed a statistically significant improvement of memory, speed of processing, language, and executive functioning and overall later life cognition.

Two other included studies[42 44], both rated as high risk of bias, focused on cognitive test performance. Opdebeeck et al.[42] reported a benefit in overall cognitive abilities for the group involving in cognitive leisure activities (standardized mean difference [SMD] of 0.26 (95% confidence interval [CI]: 0.21-0.32). The cognitive domains included memory, working memory, executive function, visuospatial ability, and language. According to the review by Toril et al. [44], playing video games enhances several cognitive functions. They observed a SMD of 0.37 (95% CI 0.26 – 0.48) for global cognitive function (combining results for memory, attention, reaction time and executive functions), showing a benefit for the intervention group.

Key question 2: Harms

We found no evidence regarding harms of continuing education or cognitive leisure activities.

Key question 3: Subgroups

Toril and colleagues[44] performed several subgroup analyses. The study revealed that the age of the participants and the number of video game training sessions significantly changed the effect size. Older participants (between 71 and 80 years) seemed to benefit more from computer training than younger participants (60 to 70 years). For the improvement of cognitive test performance, shorter training sessions (1-6 weeks) seemed to show an advantage over longer training interventions (7-12 weeks). By contrast, for incidence of Alzheimer's-type dementia, DiMarco et al.[41] and Sajeev et al.[43] infer from their data that greater participation in cognitive leisure activities over a longer period of time contributes positively to the protective effect.

Key question 4: Optimal age

No study specifically discussed the optimal age to start with continuing education activities or cognitive leisure activities to prevent mild cognitive impairment or dementia.

DISCUSSION

The evidence assessing the impact of continuing education on the risk of MCI or Alzheimer-type dementia is limited. The only eligible primary study is still ongoing and reports findings on intermediate outcomes only after 4 years of follow-up. Cognitive leisure activities can be viewed as proxies for formal continuing education and provide the best available evidence on the prevention of MCI and Alzheimer's-type dementia. Overall, the available evidence consistently indicates beneficial effects of cognitive leisure activities by reducing incidence of MCI and Alzheimer's-type dementia and improving cognitive function of older adults. The certainty of evidence, however, is low which means that future studies are likely to have a substantial impact on these findings.

The ongoing Tasmanian Healthy Brain project[46] was the only cohort study that met the eligibility criteria of our systematic review. So far, after 4 years of follow-up, this study has not yielded results about the impact of continuing education on the incidence of MCI or Alzheimer's-type dementia but reports promising findings on cognitive function. It demonstrated the dynamic nature of cognitive reserve that permits changes through education even at an advanced age. Previous studies revealed that individuals with high cognitive reserve were able to better cope with age-related brain damage[17 50] and had a 46% lower risk to develop dementia.[18] Nevertheless, these early findings of the Tasmanian Healthy Brain Project have to be viewed cautiously because selection bias could potentially distort results. Participants voluntarily opted for university courses or no further education. From the available publications, it wasn't explained sufficiently how baseline differences such as comorbid diseases were taken into consideration during the analyses.

The five included systematic reviews investigating cognitive leisure activities demonstrated both a reduction of MCI and Alzheimer's-type dementia incidence[41 43 45] and improvements in several cognitive domains.[42 44 45] Four reviews assessed the involvement in leisure activities during the past 12 months or a much longer period. The study of Toril[44], which assessed video game trainings, however had a much shorter follow-up time and showed significant improvements in cognitive functions, even after very short training sessions (1-6 weeks). These results could be explained by the neuroplasticity of the human brain, which refers to the ability of the brain to adapt to every new

stimulus by forming dendritic connections, creating morphological changes and increasing cognitive reserve.[51-53]

As far as we know, our study was the first assessing the impact of continuing education on MCI and Alzheimer's-type dementia. It is also the first overview of systematic reviews presenting an up-to-date summary of currently available research in the field of cognitive leisure activities and dementia. It has several limitations, however. First of all, there is a lack of evidence in our systematic review, directly addressing our research question. Inferences from indirect evidence such as studies on leisure activities have to be viewed cautiously. Second, in the overview of systematic reviews we had to rely on the quality of included systematic reviews. Several methodological shortcomings were detected (e.g. no risk of bias assessment, no dual screening etc.) thus our confidence in the robustness of some findings is low. Third, most of the included studies were observational studies, which are prone to selection bias because participants self-select the group. Risk factors for MCI or dementia in participants selecting leisure activities or further education might be systematically different from participants in the control group. For example, people who eventually suffer from preclinical dementia stages might be more likely to avoid cognitive leisure activities, which would lead to reverse causation. Fourth, many primary studies within the reviews used self-reported questionnaires that could be challenging for people who start having cognitive deficits. Finally, the variation of leisure activity categorization across studies made meta-analysis difficult and sometimes impossible. For example, "visiting a library" was classified as a cognitive activity by one author but as a physical activity by another. Some studies assessed current participation in activities, others participation at younger ages. Additionally, some studies assessed the frequency of participation, others the time devoted to activities and some the total number of leisure activities. Consequently, due to these limitations, the comparability of results among studies was limited. A standardization of measures and methods would be necessary to help synthesize evidence in the future and make more reliable recommendations.

Implication for future research, policy and practice

Based on preliminary results of a long-term cohort study and indirect evidence from studies on leisure activities, continuing education might be a promising option to help prevent dementia. A recent study suggests that modifiable risk factors (low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression) might be responsible for about a third of Alzheimer's-type dementia cases.[54] Hence, considering our results, a campaign promoting to "actively use the brain by participating in the wide range of continuing education" could be added to the list of preventive options and could have an impact on the reduction of Alzheimer's-type dementia cases. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[55], randomized controlled trial, with a multi-domain approach (diet, exercise, cognitive training, vascular risk monitoring) supports the hypothesis that simultaneous changes in several risk factors can lead to a protective effect on cognition. In light of previously published studies, we agree that in order to prevent Alzheimer's-type dementia in the future, a multi-domain prevention approach seems to be the most promising solution.

Further research is needed to address the evidence gap regarding continuing education and the extent to which it acts as a protective factor. A study similar to the Tasmanian Healthy Brain Project[40], but conducted as a randomized controlled trial, would be ideal because it would adequately handle known and unknown confounders. Computers and Internet could play a more significant role in future prevention trials. Instead of "sending your grandparents to university," older adults could, for instance, be randomized to attend online courses and communicate with professors and other students in virtual classrooms. This approach could save time, money, and increase the potential participant pool.

Conclusion

Although no firm conclusions about the effects of continuing education to prevent MCI and dementia can be drawn, data from preliminary and indirect evidence indicate that continuing education could potentially have important preventive effects. Physicians and policymakers should promote a healthy lifestyle, which also includes being cognitively active throughout late life.

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Competing interests: All authors declare that they have no competing interest.

Author Contributions: All authors made substantial contribution to the conception and design of this study. GG, NM, MK, CG and SA developed the concept of the study. As an information specialist, IK developed the search strategy. GW, FKA, NM and BT conducted the literature review, abstracted data and graded the strength of evidence. NM wrote the first draft of the manuscript; all authors reviewed the manuscript and provided comments. All authors have given approval for this version to be published.

Figure Legends:

Figure 1: Analytic framework for continuing education to prevent mild cognitive impairment and Alzheimer's-type dementia

Figure 2: Flow diagram of systematic review of continuing education for the prevention of mild cognitive impairment and Alzheimer's-type dementia

Figure 3: Flow diagram of overview of systematic reviews of cognitive leisure activities for the prevention of mild cognitive impairment and Alzheimer's-type dementia

List of abbreviations

AD = Alzheimer Disease
aMCI = Amnestic Mild Cognitive Impairment
AMSTAR = Assessing the Methodological Quality of Systematic Reviews
CEDEFOP = European Centre for the Development of Vocational Training
CENTRAL = Cochrane Central Register of Controlled Trials
DSM = Diagnostic and Statistical Manual of Mental Disorders
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HR = Harzard Ratio
ICD = International Classification of Diseases
MCI = Mild Cognitive Impairment
MMSE = Mini-Mental State Examination
OECD = Organisation for Economic Co-operation and Development
OR = Odds Ratio
PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-I = Risk of Bias in non-randomized studies – of interventions
RR = Relative Risk
SD = Standard Deviation
SMD = Standardized mean difference
UNESCO = United Nations Educational, Scientific and Cultural Organization
WHO = World Health Organisation

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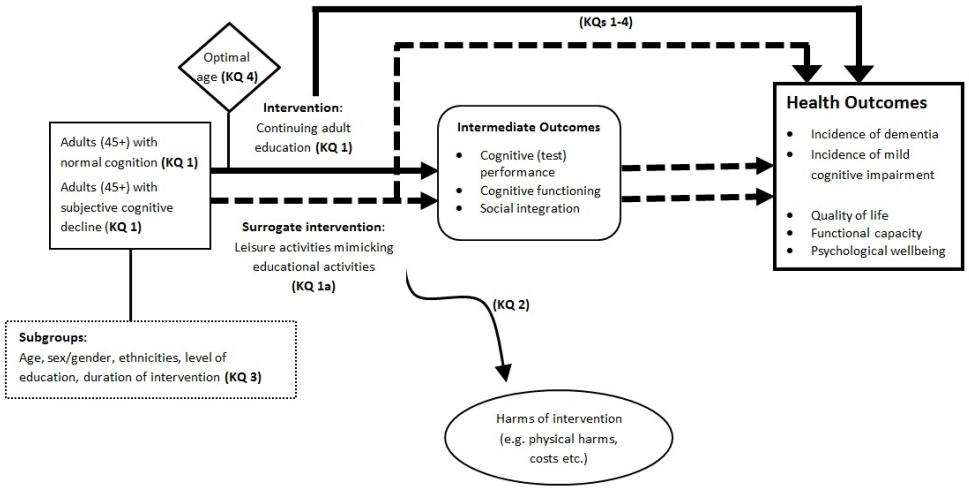
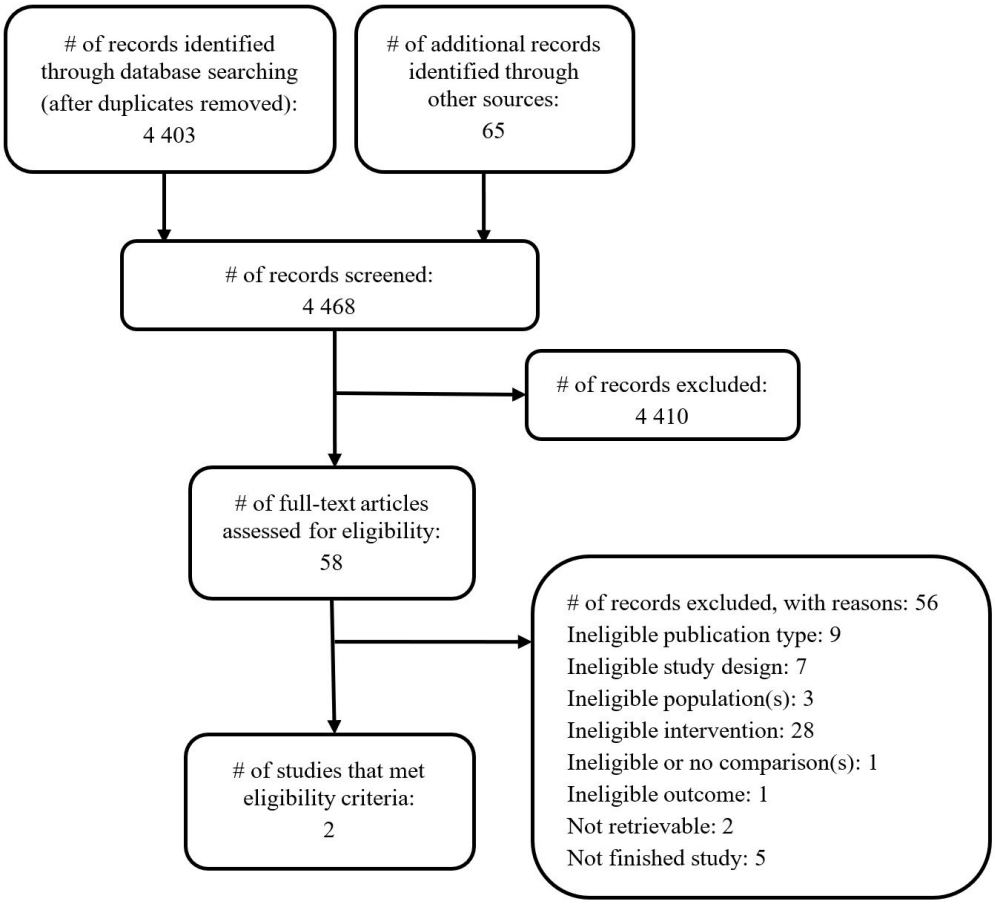


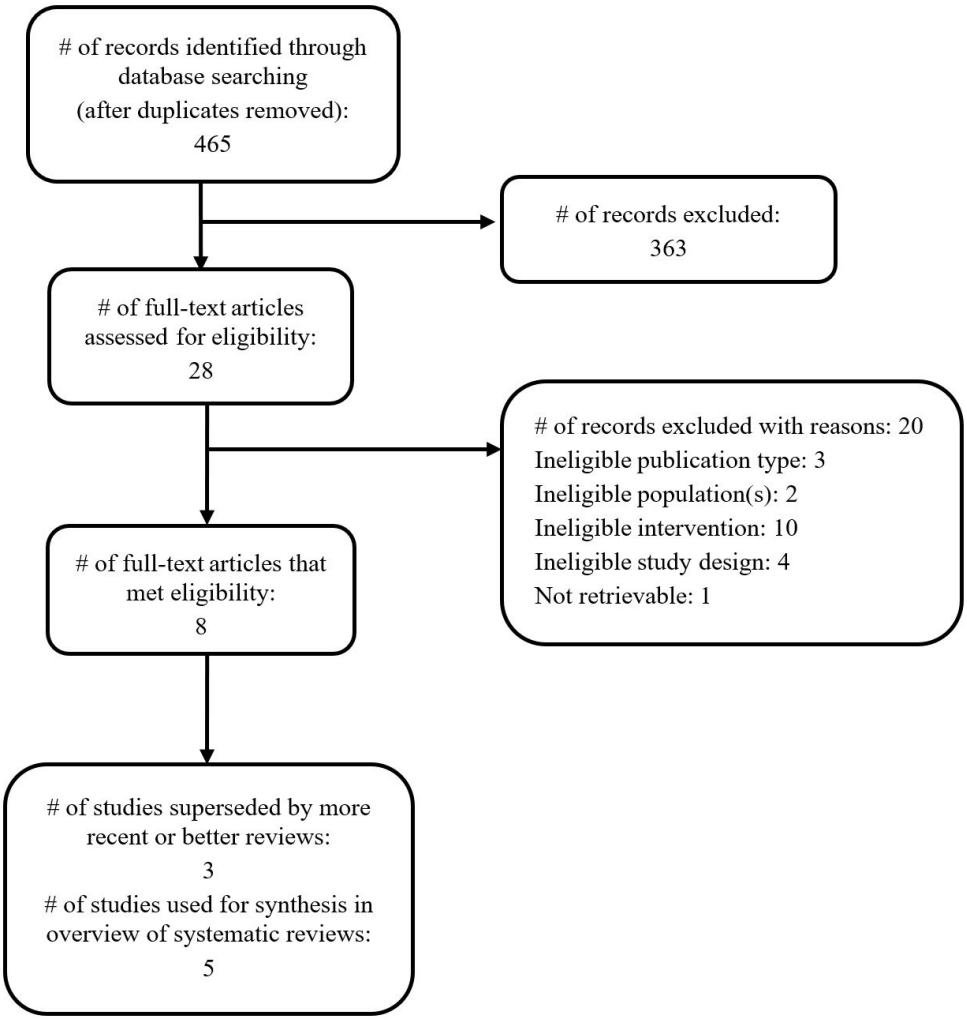
Analytic framework for continuing education to prevent mild cognitive impairment and Alzheimer's-type dementia

240x139mm (120 x 120 DPI)



Flow diagram of systematic review of continuing education for the prevention of mild cognitive impairment and Alzheimer's-type dementia

178x162mm (192 x 192 DPI)



Flow diagram of overview of systematic reviews of cognitive leisure activities for the prevention of mild cognitive impairment and Alzheimer's-type dementia

167x170mm (192 x 192 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 (line 1-3)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4 (line 33-72)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-7 (line 118-122)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7 (line 124-135)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 7 (line 142)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8-9 (line 159 - 184)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9 (line 186-202)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 3 and 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10 (line 203 – 206)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10 (line 207-210)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10 (line 210 -

PRISMA 2009 Checklist

			214)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10 (line 215-221)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 10-11 (line 222-230)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 10-11 (line 222-230)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11 (238-243) Figure 2 and 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-12 (246-268) table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13-14, table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-17, table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12 (line 263 – 268, line 254 – 256) Supplementary file 5

PRISMA 2009 Checklist

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21 (line 419-421)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e100(doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary File 2: Inclusion and exclusion criteria

	Criteria	
Category	**Inclusion**	**Exclusion**
Population	- Adults (45 years or older) without a clinical diagnosis of cognitive impairment; this includes people with subjective cognitive impairment	- People younger than 45 years - People with a clinical diagnosis of impaired cognition (e.g., MMSE < 24) -Populations comprised exclusively of patients with primary diseases with an increased risk for dementia such as Parkinson disease, HIV infection, multiple sclerosis, stroke, post traumatic brain injuries, infectious diseases, psychiatric conditions (e.g. alcohol abuse, drug abuse, major depressive disorder)
Subgroups	- Age - Sex/gender - Race/ethnicity - Level of education - Duration of intervention	
Geography	No limit	No limit
Date of search	Searches will go back until 1990	
Settings	Community-dwelling adults	Institutionalized people, e.g., people in nursing homes
Interventions	**For systematic review** - all cognitive activities that are provided by formal and non-formal educational institutions - classes/courses/trainings that are based on individual interests and that are attended voluntarily **For overview of systematic reviews** Leisure activities that are cognitively stimulating and mimic the content of continuing education but in an informal setting.	Formal (vocational) education and training; physical activities, topics and courses that are related to any special job position and/or occupation
Control Interventions	No continuing education	Any educational activities, physical activities
Outcomes	**Health Outcomes** - Incidence of dementia - Incidence of MCI - Psychological wellbeing - Functional capacity - Quality of life - Other relevant health outcomes **Intermediate Outcomes** - Cognitive functioning - Cognitive (test) performance - Social inclusion	
Timing	Minimum duration of the intervention: 3 months Minimum follow up time: 1 year	
Publication language	No language restrictions	
Study design	**For systematic reviews** - RCTs - Nonrandomized controlled trials - Prospective controlled cohort studies - Retrospective controlled cohort studies - Case-control studies - Nonrandomized studies must have a minimum sample size of 300 or more participants **For overview of systematic reviews** -systematic reviews and meta-analyses	- Case series - Case reports - Cross over trials - Nonsystematic reviews - Studies without a control group - Nonrandomized studies with fewer than 300 participants

Supplementary file 3: Search Strategies of Systematic Review, by database

Medline (via PubMed):10 July 2017

Medline

Search	Query	Hits
1	Dementia/ or exp Alzheimer Disease/	117464
2	Cognitive Dysfunction/	5918
3	Cognition/	81481
4	(dementia or alzheimer*).ti,ab.	174908
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	166793
6	or/1-5	370522
7	Primary Prevention/	16883
8	prevent*.ti,ab.	1207345
9	(protect* or reduc* or delay* or improv*).ti.	710454
10	or/7-9	1858549
11	6 and 10	39070
12	Dementia/pc or exp Alzheimer Disease/pc or Cognitive Dysfunction/pc [Prevention & Control]	4039
13	11 or 12	41057
14	exp Education, Continuing/	60977
15	((continuing or adult) adj2 (education or training)).af.	80639
16	(lifelong learning or life-long learning).af.	2396
17	education/ or exp curriculum/ or exp education, distance/ or exp education, nonprofessional/ or exp educational measurement/ or exp international educational exchange/ or mentoring/ or exp schools/ or exp teaching/	500562
18	Learning/	56308
19	Students/	47445
20	exp Educational Status/	47641
21	(learn* or class or classes or course? or educat* or school* or train* or seminar* or tutor*).ti.	569072
22	education.fs. not exp Health Personnel/ed	200448
23	(cognitiv* adj2 (stimulat* or activit*)).ti.	742
24	or/14-23	1075912
25	13 and 24	3357
26	exp Dementia/dt [Drug Therapy]	17955
27	25 not 26	3243
28	exp animals/ not exp humans/	4438320
29	27 not 28	2497
30	exp age groups/ not (exp aged/ or middle aged/)	3709828
31	29 not 30	1838
32	limit 31 to yr="1990 -Current"	1805
33	remove duplicates from 32	1695

Medline (via PubMed): updated 5 April 2018

Search	Query	Results
1	Dementia/ or exp Alzheimer Disease/	118649
2	Cognitive Dysfunction/	7920
3	Cognition/	82659
4	(dementia or alzheimer*).ti,ab.	178991
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	171636
6	or/1-5	378202
7	Primary Prevention/	16649
8	prevent*.ti,ab.	1222908
9	(protect* or reduc* or delay* or improv* or increas* or decreas*).ti.	1008130
10	or/7-9	2152629
11	6 and 10	46477
12	Dementia/pc or exp Alzheimer Disease/pc or Cognitive Dysfunction/pc or Cognition Disorders/pc [Prevention & Control]	6391
13	Cognitive Reserve/	388
14	cognitive reserve.ti,ab.	949
15	or/11-14	50722
16	exp Education, Continuing/	58777
17	((continuing or adult) adj2 (education or training)).af.	77985
18	(lifelong learning or life-long learning).af.	2438
19	education/ or exp curriculum/ or exp education, distance/ or exp education, nonprofessional/ or exp educational measurement/ or exp international educational exchange/ or mentoring/ or exp schools/ or exp teaching/	561833
20	Learning/	57102
21	Students/	48337
22	exp Educational Status/	47241
23	(learn* or class or classes or course? or educat* or school* or train* or seminar* or tutor*).ti.	571948
24	education.fs. not exp Health Personnel/ed	199668
25	(cognitiv* adj2 (stimulat* or activit*)).ti.	773
26	(late-life adj2 (activity or activities or learn* or school* or educat* or training)).ti,ab.	93
27	or/16-26	1135186
28	15 and 27	4360
29	exp Dementia/dt [Drug Therapy]	18096
30	28 not 29	4227
31	exp animals/ not exp humans/	4439627
32	30 not 31	3347
33	exp age groups/ not (exp aged/ or middle aged/)	3685655
34	32 not 33	2546
35	(201707* or 201708* or 201709* or 20171* or 2018*).ed.	749049
36	("2017/07*" or "2017/08*" or "2017/09*" or "2017/1*" or 2018*).dt.	942206
37	35 or 36	1540516
38	34 and 37	364
39	limit 34 to yr="2017 -Current"	348
40	38 or 39	435

Cochrane Library (10 July 2017)

Cochrane Library

Search	Query	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4053
#2	[mh ^"Cognitive Dysfunction"]	0
#3	[mh ^Cognition]	6276
#4	(dementia or alzheimer*):ti,ab,kw	11882
#5	((cognit* or memory or mental) near/3 (impair* or decline* or deficit* or reduc* or function*)):ti,ab	16173
#6	{or #1-#5}	27711
#7	[mh ^"Primary Prevention"]	1008
#8	prevent*:ti,ab,kw	107750
#9	(protect* or reduc* or delay* or improv*):ti	77161
#10	{or #7-#9}	175365
#11	#6 and #10	4432
#12	[mh Dementia/pc] or [mh ^"Cognitive Dysfunction"/pc]	208
#13	#11 or #12	4532
#14	[mh "Education, Continuing"]	1168
#15	((continuing or adult) near/2 (education or training)):ti,ab,kw	2819
#16	("lifelong learning" or "life-long learning"):ti,ab,kw	19
#17	[mh ^education] or [mh curriculum] or [mh "education, distance"] or [mh "education, nonprofessional"] or [mh "educational measurement"] or [mh "international educational exchange"] or [mh ^mentoring] or [mh schools] or [mh teaching]	21839
#18	[mh ^Learning]	1809
#19	[mh ^Students]	2041
#20	[mh "Educational Status"]	1348
#21	(learn* or class or classes or course or courses or educat* or school* or train* or seminar* or tutor*):ti	45060
#22	(cognitiv* near/2 (stimulat* or activit*)):ti	212
#23	(learning or ((education or training) near/2 (nonprofessional or non-professional or distance)) or teaching):kw	12784
#24	{or #14-#23}	67085
#25	#13 and #24	784
#26	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	104635
#27	#25 not #26	691
#28	#27 Publication Year from 1990 to 2017	691

Cochrane Library (updated 9 April 2018)

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4263
#2	[mh ^"Cognitive Dysfunction"]	450
#3	[mh ^Cognition]	6675
#4	(dementia or alzheimer*):ti,ab,kw	13099
#5	((cognit* or memory or mental) near/3 (impair* or decline* or deficit* or reduc* or function*)):ti,ab	18089
#6	{or #1-#5}	30564
#7	[mh ^"Primary Prevention"]	1065
#8	prevent*:ti,ab,kw	115159
#9	(protect* or reduc* or delay* or improv* or increas* or decreas*):ti	102653
#10	{or #7-#9}	205354
#11	#6 and #10	5434
#12	[mh Dementia/pc] or [mh ^"Cognitive Dysfunction"/pc] or [mh ^"Cognition Disorders"/pc]	603
#13	[mh ^"Cognitive Reserve"]	8
#14	cognitive reserve:ti,ab,kw	51
#15	{or #11-#14}	5791
#16	[mh "Education, Continuing"]	1209
#17	((continuing or adult) near/2 (education or training)):ti,ab,kw	3051
#18	("lifelong learning" or "life-long learning"):ti,ab,kw	21
#19	[mh ^education] or [mh curriculum] or [mh "education, distance"] or [mh "education, nonprofessional"] or [mh "educational measurement"] or [mh "international educational exchange"] or [mh ^mentoring] or [mh schools] or [mh teaching]	26602
#20	[mh ^Learning]	1962
#21	[mh ^Students]	2250
#22	[mh "Educational Status"]	1407
#23	(learn* or class or classes or course or courses or educat* or school* or train* or seminar* or tutor*):ti	48313
#24	(cognitiv* near/2 (stimulat* or activit*)):ti	246
#25	(learning or ((education or training) near/2 (nonprofessional or non-professional or distance)) or teaching):kw	14622
#26	(late-life near/2 (activity or activities or learn* or school* or educat* or training)):ti,ab,kw	8
#27	{or #16-#26}	75572
#28	#15 and #27	1055
#29	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
#30	#28 not #29	937
#31	#30 Publication Year from 2017 to 2018	106

Embase (10 July 2017)

Embase

Search	Query	Hits
#1	'dementia'/de	97110
#2	'alzheimer disease'/exp	156558
#3	'mild cognitive impairment'/exp	17067
#4	dementia:ti,ab OR alzheimer*:ti,ab	226442
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	221649
#6	#1 OR #2 OR #3 OR #4 OR #5	432689
#7	'primary prevention'/exp	33540
#8	'preventive medicine'/exp	25875
#9	prevent*:ti,ab	1469112
#10	protect*:ti OR reduc*:ti OR delay*:ti OR improv*:ti	850362
#11	#7 OR #8 OR #9 OR #10	2260166
#12	#6 AND #11	49357
#13	'dementia'/dm_pc	1833
#14	'mild cognitive impairment'/exp/dm_pc	90
#15	'alzheimer disease'/exp/dm_pc	4342
#16	#12 OR #13 OR #14 OR #15	52112
#17	'continuing education'/exp OR 'continuing education provider'/exp	29360
#18	((continuing OR adult) NEAR/2 (education OR training)):ti,ab	24617
#19	lifelong learning':ti,ab OR 'life-long learning':ti,ab	1695
#20	'education'/de OR 'adult education'/exp OR 'lifelong learning'/exp OR 'mentoring'/exp OR 'masters education'/exp OR 'postdoctoral education'/exp OR 'postgraduate education'/exp OR 'community college'/exp OR 'university'/exp	466817
#21	learn*:ti OR class:ti OR classes:ti OR course*:ti OR educat*:ti OR school*:ti OR train*:ti OR seminar*:ti OR tutor*:ti	633869
#22	(cognitiv* NEAR/2 (stimulat* OR activit*)):ti	930
#23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	1006895
#24	#16 AND #23	3837
#25	'animal'/exp NOT 'human'/exp	4833576
#26	#24 NOT #25	2924
#27	'groups by age'/exp NOT ('middle aged'/exp OR 'aged'/exp)	5653684
#28	#26 NOT #27	2223
#29	#28 AND [1990-2017]/py	2199
#30	'medication therapy management'/exp OR 'dementia'/exp/dm_dt OR 'pharmaceutical vehicles and additives'/exp	1386295
#31	#29 NOT #30	2022
#32	#31 NOT 'conference abstract'/it	996

Embase (updated 9 April 2018)

No.	Query	Hits
#1	'dementia'/exp	308108
#2	'alzheimer disease'/exp	167836
#3	'mild cognitive impairment'/exp	19554
#4	dementia:ti,ab OR alzheimer*:ti,ab	245698
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	244483
#6	#1 OR #2 OR #3 OR #4 OR #5	519886
#7	'primary prevention'/exp	35604
#8	'preventive medicine'/exp	26670
#9	prevent*:ti,ab	1576370
#10	protect*:ti OR reduc*:ti OR delay*:ti OR improv*:ti OR increas*:ti OR decreas*:ti	1272239
#11	#7 OR #8 OR #9 OR #10	2758722
#12	#6 AND #11	66376
#13	'dementia'/dm_pc	1929
#14	'mild cognitive impairment'/exp/dm_pc	101
#15	'alzheimer disease'/exp/dm_pc	4515
#16	'cognitive reserve'/exp	1346
#17	'cognitive reserve':ti,ab	1463
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	70716
#19	'continuing education'/exp OR 'continuing education provider'/exp	30115
#20	((continuing OR adult) NEAR/2 (education OR training)):ti,ab	25787
#21	'lifelong learning':ti,ab OR 'life-long learning':ti,ab	1820
#22	'education'/de OR 'adult education'/exp OR 'lifelong learning'/exp OR 'mentoring'/exp OR 'masters education'/exp OR 'postdoctoral education'/exp OR 'postgraduate education'/exp OR 'community college'/exp OR 'university'/exp	492706
#23	learn*:ti OR class:ti OR classes:ti OR course*:ti OR educat*:ti OR school*:ti OR train*:ti OR seminar*:ti OR tutor*:ti	669572
#24	(cognitiv* NEAR/2 (stimulat* OR activit*)):ti	1040
#25	('late life' NEAR/2 (activity OR activities OR learn* OR school* OR educat* OR training)):ti,ab	131
#26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1064036
#27	#18 AND #26	5231
#28	'animal'/exp NOT 'human'/exp	5020589
#29	#27 NOT #28	4140
#30	'groups by age'/exp NOT ('middle aged'/exp OR 'aged'/exp)	6115551
#31	#29 NOT #30	3114
#32	'medication therapy management'/exp OR 'dementia'/exp/dm_dt OR 'pharmaceutical vehicles and additives'/exp	1465869
#33	#31 NOT #32	2862
#34	#33 NOT 'conference abstract'/it	1380
#35	#34 AND [1-7-2017]/sd NOT [9-4-2018]/sd	131
#36	#34 AND [2017-2018]/py	174
#37	#35 OR #36	189

CINHAL (10 July 2017)

Search	Query	Limiters/Expanders	Hits
S1	(MH "Dementia") OR (MH "Alzheimer's Disease")	Search modes - Find all my search terms	37751
S2	dementia OR alzheimer*	Search modes - Find all my search terms	46604
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	29346
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	67725
S5	(MH "Preventive Health Care")	Search modes - Find all my search terms	1075
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	170718
S7	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	124328
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	290518
S9	S4 AND S8	Search modes - Find all my search terms	6261
S10	(MH "Dementia/PC") OR (MH "Alzheimer's Disease/PC")	Search modes - Find all my search terms	2009
S11	S9 OR S10	Search modes - Find all my search terms	7692
S12	(MH "Education, Continuing") OR (MH "Continuing Education Providers") OR (MH "Education, Diploma Programs") OR (MH "Education, Continuing (Credit)") OR (MH "Education, Masters") OR (MH "Education, Post-Doctoral")	Search modes - Find all my search terms	87064
S13	(MH "Learning") OR (MH "Lifelong Learning")	Search modes - Find all my search terms	10771
S14	(MH "Education, Nonprofessional") OR (MH "Adult Education") OR (MH "Education, Non-Traditional+")	Search modes - Find all my search terms	7406
S15	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*) OR TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	180228

S16	"lifelong learning" OR "life-long learning" OR ((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	106290
S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	27,763
S18	S11 AND S17	Search modes - Find all my search terms	667
S19	MH "Animal Studies"	Search modes - Find all my search terms	39763
S20	S18 NOT S19	Search modes - Find all my search terms	618
S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	55371
S22	S20 NOT S21	Search modes - Find all my search terms	552
S23	S22	Limiters - Published Date: 19900101-20171231	557

CINHAL (8 April 2018)

Search	Query	Limiters/Expanders	Results
S1	(MH "Dementia") OR (MH "Alzheimer's Disease")	Search modes - Find all my search terms	40,224
S2	dementia OR alzheimer*	Search modes - Find all my search terms	50,090
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	32,856
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	73,809
S5	(MH "Preventive Health Care")	Search modes - Find all my search terms	11,313
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	186,284
S7	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	134,37
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	315,336
S9	S4 AND S8	Search modes - Find all my search terms	7,002
S10	(MH "Dementia/PC") OR (MH "Alzheimer's Disease/PC")	Search modes - Find all my search terms	2,127
S11	S9 OR S10	Search modes - Find all my search terms	8,479
S12	(MH "Education, Continuing") OR (MH "Continuing Education Providers") OR (MH "Education, Diploma Programs") OR (MH "Education, Continuing (Credit)") OR (MH "Education, Masters") OR (MH "Education, Post-Doctoral")	Search modes - Find all my search terms	89,104
S13	(MH "Learning") OR (MH "Lifelong Learning")	Search modes - Find all my search terms	11,971
S14	(MH "Education, Nonprofessional") OR (MH "Adult Education") OR (MH "Education, Non-Traditional+")	Search modes - Find all my search terms	7,799
S15	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*) OR TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	191,967
S16	"lifelong learning" OR "life-long learning" OR ((continuing OR adult) N2 (education OR training)) OR ("late life" N1 (activity OR activities OR learn* OR school* OR educat* OR training))	Search modes - Find all my search terms	109,49

S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	290,595
S18	S11 AND S17	Search modes - Find all my search terms	753
S19	MH "Animal Studies"	Search modes - Find all my search terms	43,810
S20	S18 NOT S19	Search modes - Find all my search terms	691
S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	595,044
S22	S20 NOT S21	Search modes - Find all my search terms	617
S23	S22	Limiters - Published Date: 20170101-	78
S24	S22 AND EM 20170701-	Search modes - Find all my search terms	66
S25	S23 OR S24	Search modes - Find all my search terms	95

ERIC (10 July 2017)

Search	Query	Limiters/Expanders	Hits
S1	DE "Dementia" OR DE "Alzheimers Disease"	Search modes - Find all my search terms	1036
S2	DE "Cognitive Ability"	Search modes - Find all my search terms	8133
S3	dementia OR alzheimer*	Search modes - Find all my search terms	1286
S4	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	6424
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	14489
S6	(DE "Early Intervention" OR DE "Prevention") OR (DE "Preventive Medicine")	Search modes - Find all my search terms	22132
S7	TI prevent* OR AB prevent*	Search modes - Find all my search terms	33142
S8	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	30866
S9	S6 OR S7 OR S8	Search modes - Find all my search terms	71745
S10	S5 AND S9	Search modes - Find all my search terms	828
S11	DE "Adult Education" OR DE "Adult Basic Education" OR DE "Continuing Education" OR DE "Migrant Adult Education" OR DE "Preretirement Education" OR DE "Public School Adult Education" OR DE "Veterans Education"	Search modes - Find all my search terms	56528
S12	DE "Adult Learning" OR DE "Adult Programs" OR DE "Adult Reading Programs" OR DE "High School Equivalency Programs" OR DE "Evening Programs" OR DE "Part Time Students" OR DE "Distance Education" OR DE "Extension Education" OR DE "External Degree Programs" OR DE "Rural Extension" OR DE "Urban Extension"	Search modes - Find all my search terms	35681
S13	(DE "Adult Students") OR (DE "Evening Students")	Search modes - Find all my search terms	7787
S14	((DE "Nonschool Educational Programs") OR (DE "Community Education")) OR (DE "Postsecondary Education" OR DE "Higher Education")	Search modes - Find all my search terms	431319

S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8046
S16	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	555016
S17	TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	94
S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	76187
S19	"lifelong learning" or "life-long learning"	Search modes - Find all my search terms	10135
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	Search modes - Find all my search terms	851728
S21	S10 AND S20	Search modes - Find all my search terms	286
S22	S21	Limiters - Date Published: 19900101-20171231	234

ERIC (8 April 2018)

Search	Query	Limiters/Expanders	Results
S1	DE "Dementia" OR DE "Alzheimers Disease"	Search modes - Find all my search terms	1,075
S2	DE "Cognitive Ability"	Search modes - Find all my search terms	8,553
S3	dementia OR alzheimer*	Search modes - Find all my search terms	1,332
S4	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	6,684
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	15,155
S6	(DE "Early Intervention" OR DE "Prevention") OR (DE "Preventive Medicine")	Search modes - Find all my search terms	22,911
S7	TI prevent* OR AB prevent*	Search modes - Find all my search terms	34,284
S8	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	32,348
S9	S6 OR S7 OR S8	Search modes - Find all my search terms	74,665
S10	S5 AND S9	Search modes - Find all my search terms	873
S11	DE "Adult Education" OR DE "Adult Basic Education" OR DE "Continuing Education" OR DE "Migrant Adult Education" OR DE "Preretirement Education" OR DE "Public School Adult Education" OR DE "Veterans Education"	Search modes - Find all my search terms	57,669
S12	DE "Adult Learning" OR DE "Adult Programs" OR DE "Adult Reading Programs" OR DE "High School Equivalency Programs" OR DE "Evening Programs" OR DE "Part Time Students" OR DE "Distance Education" OR DE "Extension Education" OR DE "External Degree Programs" OR DE "Rural Extension" OR DE "Urban Extension"	Search modes - Find all my search terms	36,853
S13	(DE "Adult Students") OR (DE "Evening Students")	Search modes - Find all my search terms	8,01
S14	((DE "Nonschool Educational Programs") OR (DE "Community Education")) OR (DE "Postsecondary Education" OR DE "Higher Education")	Search modes - Find all my search terms	452,212
S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8,311
S16	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	579,695

S17	TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	102
S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	77,861
S19	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	17
S20	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	10,521
S21	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Find all my search terms	887,984
S22	S10 AND S21	Search modes - Find all my search terms	309
S23	S22	Limiters - Date Published: 20170101-	16
S24	S22 AND EM 20170701-	Search modes - Find all my search terms	0
S25	S23 OR S24	Search modes - Find all my search terms	16

PsycINFO (11 July 2017)

Search	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	39,900
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	30,409
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	65,198
S5	DE "Prevention" OR DE "Preventive Medicine" OR DE "Primary Mental Health Prevention"	Search modes - Find all my search terms	30,316
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	186,041
S7	TI protect* OR reduc* OR delay* OR improv*	Search modes - Find all my search terms	743,335
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	869,214
S9	S4 AND S8	Search modes - Find all my search terms	21,587
S10	DE "Adult Education" OR DE "Continuing Education"	Search modes - Find all my search terms	4,126
S11	TI (learning OR education OR educational OR training)	Search modes - Find all my search terms	259,848
S12	TI cognitiv* N1 (stimulat* OR activit*)	Search modes - Find all my search terms	751
S13	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	2,995
S14	(continuing OR adult) N2 (education OR training)	Search modes - Find all my search terms	15,241
S15	S9 AND S11	Search modes - Find all my search terms	826
S16	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,626,731
S17	S15 NOT S16	Search modes - Find all my search terms	683
S18	(DE "Health Education") OR (DE "Drug Therapy") OR (DE "Animals") OR DE "Animal Models" OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	454,796
S19	S17 NOT S18	Search modes - Find all my search terms	414
S20	S17 NOT S18	Limiters - Published Date: 19900101-20171231	403

PsycINFO (9 April 2018)

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	41,992
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	32,064
S4	dementia OR alzheimer*	Search modes - Find all my search terms	99,018
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	146,484
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	210,638
S7	DE "Prevention" OR DE "Preventive Medicine" OR DE "Primary Mental Health Prevention"	Search modes - Find all my search terms	31,621
S8	TI prevent* OR AB prevent*	Search modes - Find all my search terms	195,469
S9	TI protect* OR reduc* OR delay* OR improv*	Search modes - Find all my search terms	783,317
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	914,878
S11	S6 AND S10	Search modes - Find all my search terms	71,575
S12	DE "Cognitive Reserve"	Search modes - Find all my search terms	353
S13	"Cognitive Reserve"	Search modes - Find all my search terms	985
S14	S11 OR S12 OR S13	Search modes - Find all my search terms	72,193
S15	DE "Adult Education" OR DE "Continuing Education"	Search modes - Find all my search terms	4,2
S16	TI (learning OR education OR educational OR training)	Search modes - Find all my search terms	269,992
S17	TI cognitiv* N1 (stimulat* OR activit*)	Search modes - Find all my search terms	794
S18	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	3,169
S19	(continuing OR adult) N2 (education OR training)	Search modes - Find all my search terms	15,885
S20	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	159
S21	S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Find all my search terms	281,675

S22	S14 AND S21	Search modes - Find all my search terms	4,549
S23	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,695,649
S24	S22 NOT S23	Search modes - Find all my search terms	3,295
S25	(DE "Health Education") OR (DE "Drug Therapy") OR (DE "Animals") OR DE "Animal Models" OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	465,312
S26	S24 NOT S25	Search modes - Find all my search terms	2,094
S27	S26	Limiters - Publication Year: 2017-	276
S28	S26 AND RD 201707-	Search modes - Find all my search terms	197
S29	S27 OR S28	Search modes - Find all my search terms	299

ClinicalTrials.gov (16 May 2017)

280 studies found for: (prevention OR reduction OR risk OR improvement) AND (dementia OR alzheimer OR "cognitive impairment" OR "cognitive decline") | healthy OR aged OR adult OR cognitive | education OR learning OR lesson OR educational OR class OR mental OR cognitive | Adult, Senior | Studies that accept healthy volunteers

ClinicalTrials.gov (9 April 2018)

58 Studies found for: (prevention OR reduction OR risk OR improvement) AND (dementia OR alzheimer OR "cognitive impairment" OR "cognitive decline") | healthy OR aged OR adult OR cognitive | education OR learning OR lesson OR educational OR class OR mental OR cognitive | Adult, Senior | Studies that accept healthy volunteers | First posted from 05/01/2017 to 04/09/2018

ICTRP (16 May 2017)

ICTRP		
Search 1	21 records for 20 trials found for:	dementia AND education* AND prevent* OR alzheimer AND education* AND prevent* OR cognitive impairment AND education* AND prevent*
Search 2	3 records for 3 trials found for:	dementia AND mental activ* AND prevent* OR alzheimer AND mental activ* AND prevent* OR cognitive impairment AND mental activ* AND prevent*
Search 3	3 records for 3 trials found for:	dementia AND cognitive stimulat* AND prevent* OR alzheimer AND cognitive stimulat* AND prevent* OR cognitive impairment AND cognitive stimulat* AND prevent*
Search 4	11 records for 11 trials found for:	dementia AND learning AND prevent* OR alzheimer AND learning AND prevent* OR cognitive impairment AND learning AND prevent*
Search 5	No results were found for:	dementia AND lesson* AND prevent* OR alzheimer AND lesson* AND prevent* OR cognitive impairment AND lesson* AND prevent*
Search 6	45 records for 45 trials found for:	dementia AND training AND prevent* OR alzheimer AND training AND prevent* OR cognitive impairment AND training AND prevent*
SUM	**82**	

ICTRP (9 April 2018)

Search 1	20	dementia AND education* AND prevent* OR alzheimer AND education* AND prevent* OR cognitive impairment AND education* AND prevent*
Search 2	3	dementia AND mental activ* AND prevent* OR alzheimer AND mental activ* AND prevent* OR cognitive impairment AND mental activ* AND prevent*
Search 3	5	dementia AND cognitive stimulat* AND prevent* OR alzheimer AND cognitive stimulat* AND prevent* OR cognitive impairment AND cognitive stimulat* AND prevent*
Search 4	27	dementia AND learning AND prevent* OR alzheimer AND learning AND prevent* OR cognitive impairment AND learning AND prevent*
Search 5	1	dementia AND lesson* AND prevent* OR alzheimer AND lesson* AND prevent* OR cognitive impairment AND lesson* AND prevent*
Search 6	64	dementia AND training AND prevent* OR alzheimer AND training AND prevent* OR cognitive impairment AND training AND prevent*
SUM	120	

ALOIS (15 May 2017)

ALOIS		
Study Aim:	Cognitive Enhancement (healthy); Primary Prevention	
Intervention type:	Non-pharmacological	
Intervention:	Contains any word	learning education educational

18 Studies found

ALOIS (9 April 2018)

Not searched website down

DART-Europe (16 May 2017)

search	reults
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimualtion") AND (prevent* OR improve*)	43

DART-Europe (8 April 2018)

search	reults
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimualtion") AND (prevent* OR improve*)	56
YEAR: 2017	4

Supplementary file 4: Search Strategies of Overview of Systematic Reviews, by database

Medline (via PubMed): 10 July 2017

#	Suchen	Ergebnisse
1	Dementia/ or exp Alzheimer Disease/	117573
2	Cognitive Dysfunction/	5969
3	Cognition/	81563
4	(dementia or alzheimer*).ti,ab.	175194
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	167110
6	or/1-5	371089
7	exp Leisure Activities/	209051
8	leisure.ti,ab.	13073
9	(hobby or hobbies).ti,ab.	1465
10	free time.ti,ab.	1405
11	Recreation.ti,ab.	4826
12	(in-door or out-door or indoor or outdoor).ti.	8929
13	(garden* or horticultur*).ti.	3216
14	(play* or game? or gaming).ti.	46562
15	(creativ* or painting or drawing or reading).ti.	24387
16	(voluntary or volunteer* or extracurricular).ti.	32266
17	or/7-16	321695
18	6 and 17	9189
19	exp age groups/ not (exp aged/ or middle aged/)	3712487
20	18 not 19	6496
21	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	118333
22	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.	15710
23	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.	145368
24	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	117882
25	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.	171997

26	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.	167686
27	21 or 22 or 23 or 24 or 25 or 26	412039
28	27 not (case report/ or letter.pt.)	401602
29	20 and 28	243
30	remove duplicates from 29	229

Medline (via PubMed): 4 April 2018

#	Searches	Results
1	Dementia/ or exp Alzheimer Disease/	118622
2	Cognitive Dysfunction/	7904
3	Cognition/	82628
4	Cognitive Reserve/	388
5	(dementia or alzheimer*).ti,ab.	179042
6	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	171766
7	or/1-6	378437
8	exp Leisure Activities/	207917
9	leisure.ti,ab.	13201
10	(hobby or hobbies).ti,ab.	1472
11	free time.ti,ab.	1429
12	Recreation.ti,ab.	4900
13	(in-door or out-door or indoor or outdoor).ti.	9232
14	(garden* or horticultur*).ti.	3312
15	(play* or game? or gaming).ti.	47658
16	(creativ* or painting or drawing or reading).ti.	24235
17	(voluntary or volunteer* or extracurricular).ti.	32218
18	(cognitiv* adj2 (activity or activities)).ti.	521
19	or/8-18	322366
20	7 and 19	9826
21	exp age groups/ not (exp aged/ or middle aged/)	3685197
22	20 not 21	6996
23	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	126873
24	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.	15689
25	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.	151505
26	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	125835
27	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.	184250

28	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.	168915
29	23 or 24 or 25 or 26 or 27 or 28	425049
30	29 not (case report/ or letter.pt.)	414173
31	22 and 30	283
32	("2017/07*" or "2017/08*" or "2017/09*" or "2017/1*" or 2018*).dt.	947449
33	(201707* or 201708* or 201709* or 20171* or 2018*).ed.	745570
34	32 or 33	1543513
35	31 and 34	53
36	remove duplicates from 35	52

Embase: 17 Juli 2017

No.	Query	Results
#1	'alzheimer disease'/exp	158632
#2	'mild cognitive impairment'/exp	17483
#3	'dementia'/de	98402
#4	dementia:ti,ab OR alzheimer*:ti,ab	230453
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	226651
#6	#1 OR #2 OR #3 OR #4 OR #5	440912
#7	'recreation'/exp	57806
#8	leisure:ti,ab	16016
#9	hobby:ti,ab OR hobbies:ti,ab	2028
#10	'free time':ti,ab	1939
#11	recreation:ti,ab	6442
#12	'in door':ti OR 'out door':ti OR indoor:ti OR outdoor:ti	11551
#13	garden*:ti OR horticultur*:ti	3581
#14	play*:ti OR game:ti OR games:ti OR gaming:ti	52543
#15	creativ*:ti OR painting:ti OR drawing:ti OR reading:ti	25887
#16	voluntary:ti OR volunteer*:ti OR extracurricular:ti	38793
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	196912
#18	#6 AND #17	5027
#19	'groups by age'/exp AND ('middle aged'/exp OR 'aged'/exp)	3258589
#20	#18 NOT #19	3277
#21	systematic review'/exp OR 'meta analysis'/exp	211886
#22	meta analys*':ti,ab OR metaanalys*:ti,ab OR 'meta synth*':ti,ab OR metasynth*:ti,ab OR ((systematic* OR quantitativ* OR methodologic*) NEAR/5 (review* OR overview* OR synthes*)):ti,ab	239389
#23	systematic:ti OR structured:ti OR evidence:ti OR trials:ti AND (review:ti OR overview:ti OR look:ti OR examination:ti OR update*:ti OR summary:ti)	98173
#24	#21 OR #22 OR #23	306796
#25	#24 NOT ('case report'/exp OR 'case study'/exp)	301911
#26	#20 AND #25	128

Embase: 4 April 2018

No.	Query	Results
#1	'alzheimer disease'/exp	167669
#2	'mild cognitive impairment'/exp OR 'dementia'/de	115768
#3	'cognitive reserve'/de	1341
#4	dementia:ti,ab OR alzheimer*:ti,ab	245434
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	244167
#6	#1 OR #2 OR #3 OR #4 OR #5	470026
#7	'recreation'/exp	61588
#8	leisure:ti,ab	16979
#9	hobby:ti,ab OR hobbies:ti,ab	2145
#10	'free time':ti,ab	2061
#11	recreation:ti,ab	6767
#12	'in door':ti OR 'out door':ti OR indoor:ti OR outdoor:ti	12183
#13	garden*:ti OR horticultur*:ti	3745
#14	play*:ti OR game:ti OR games:ti OR gaming:ti	55639
#15	creativ*:ti OR painting:ti OR drawing:ti OR reading:ti	26738
#16	voluntary:ti OR volunteer*:ti OR extracurricular:ti OR ((cognitiv* NEAR/2 (activity OR activities)):ti)	39956
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	207154
#18	#6 AND #17	5442
#19	'groups by age'/exp AND ('middle aged'/exp OR 'aged'/exp)	3451202
#20	#18 NOT #19	3533
#21	'systematic review'/exp OR 'meta analysis'/exp	239710
#22	'meta analys*':ti,ab OR metaanalys*:ti,ab OR 'meta synth*':ti,ab OR metasynth*:ti,ab OR (((systematic* OR quantitativ* OR methodologic*) NEAR/5 (review* OR overview* OR synthes*)):ti,ab)	267896
#23	(systematic:ti OR structured:ti OR evidence:ti OR trials:ti) AND (review:ti OR overview:ti OR look:ti OR examination:ti OR update*:ti OR summary:ti)	112383
#24	#21 OR #22 OR #23	342728
#25	#24 NOT ('case report'/exp OR 'case study'/exp)	337160
#26	#20 AND #25	145
#27	#26 AND [1-7-2017]/sd NOT [5-4-2018]/sd	26
#28	#26 AND [2017-2018]/py	30
#29	#27 OR #28	35

CINAHL (Ebsco): 17 July 2017

#	Query	Limiters/Expanders	Results
S1	(MH "Alzheimer's Disease") OR (MH "Dementia")	Search modes - Find all my search terms	38,358
S2	dementia OR alzheimer*	Search modes - Find all my search terms	47,332
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	30,037
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	68,971
S5	(MH "Leisure Activities+")	Search modes - Find all my search terms	36,998
S6	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	11,096
S7	TI in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular	Search modes - Find all my search terms	31,628
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	69,497
S9	S4 AND S8	Search modes - Find all my search terms	2,053
S10	MH "Animal Studies"	Search modes - Find all my search terms	41,599
S11	S9 NOT S10	Search modes - Find all my search terms	2,051
S12	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	564,745
S13	S11 NOT S12	Search modes - Find all my search terms	1,855
S14	(MH "Systematic Review") OR (MH "Meta Analysis")	Search modes - Find all my search terms	42,089
S15	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	31,338
S16	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Boolean/Phrase	55,272
S17	TI (systematic OR structured OR evidence OR trials) AND (review OR overview OR look OR examination OR update* OR summary)	Search modes - Boolean/Phrase	27,392
S18	S14 OR S15 OR S16 OR S17	Search modes - Find all my search terms	72,333
S19	S13 AND S18	Search modes - Find all my search terms	71

CINAHL (Ebsco): 4 April 2018

#	Query	Limiters/Expanders	Results
S1	(MH "Alzheimer's Disease") OR (MH "Dementia")	Search modes - Find all my search terms	40,163
S2	dementia OR alzheimer*	Search modes - Find all my search terms	50,045
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	32,819
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	73,730
S5	(MH "Leisure Activities+")	Search modes - Find all my search terms	39,894
S6	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	11,740
S7	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR oluntary OR volunteer* OR extracurricular) OR TI (cognitiv* W1 (activity OR activities))	Search modes - Find all my search terms	33,266
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	73,940
S9	S4 AND S8	Search modes - Find all my search terms	2,298
S10	MH "Animal Studies"	Search modes - Find all my search terms	43,752
S11	S9 NOT S10	Search modes - Find all my search terms	2,295
S12	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	594,058
S13	S11 NOT S12	Search modes - Find all my search terms	2,079
S14	(MH "Systematic Review") OR (MH "Meta Analysis")	Search modes - Find all my search terms	50,503
S15	meta-analys* OR meta analys* OR metaanalys* OR	Search modes - Boolean/Phrase	34,556

	meta synth* OR meta-synth* OR metasynth*		
S16	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Boolean/Phrase	63,373
S17	TI (systematic OR structured OR evidence OR trials) AND (review OR overview OR look OR examination OR update* OR summary)	Search modes - Boolean/Phrase	30,586
S18	S14 OR S15 OR S16 OR S17	Search modes - Find all my search terms	81,245
S19	S13 AND S18	Search modes - Find all my search terms	93
S20		Limiters - Published Date: 20170701- Search modes - Find all my search terms	156,794
S21	EM 20170701-	Search modes - Find all my search terms	208,855
S22	S20 OR S21	Search modes - Find all my search terms	253,372
S23	S22 AND S19	Search modes - Find all my search terms	27

PsycINFO (Ebsco): 18 July 2017

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	39,908
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	30,416
S4	dementia OR alzheimer*	Search modes - Find all my search terms	94,008
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	138,651
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	200,033
S7	(((((DE "Leisure Time") OR (DE "Hobbies")) AND (DE "Recreation" OR DE "Clubs (Social Organizations)" OR DE "Traveling" OR DE "Vacationing")) OR (DE "Gambling")) AND (DE "Games" OR DE "Chess" OR DE "Computer Games"))	Search modes - Find all my search terms	347
S8	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	37,212
S9	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular) OR SU (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)	Search modes - Find all my search terms	175,457
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	207,264
S11	S6 AND S10	Search modes - Find all my search terms	5,662
S12	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,627,211
S13	S11 NOT S12	Search modes - Find all my search terms	3,357
S14	(DE "Animals") OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	311,593
S15	S13 NOT S14	Search modes - Find all my search terms	3,212

S16	(DE "Drug Therapy")	Search modes - Find all my search terms	127,11
S17	S15 NOT S16	Search modes - Find all my search terms	3,161
S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,026
S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	27,695
S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	27,454
S21	TI (systematic OR structured OR evidence OR trials) AND TI (review OR overview OR look OR examination OR update* OR summary)	Search modes - Find all my search terms	16,949
S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	51,681
S23	S17 AND S22	Search modes - Find all my search terms	73

PsycINFO (Ebsco): 5 April 2018

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	41,959
S2	DE "Senile Dementia" OR DE "Cognitive Impairment"	Search modes - Find all my search terms	33,077
S3	DE "Cognitive Reserve"	Search modes - Find all my search terms	353
S4	dementia OR alzheimer*	Search modes - Find all my search terms	98,945
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	146,379
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	210,573
S7	(((((DE "Leisure Time") OR (DE "Hobbies")) AND (DE "Recreation" OR DE "Clubs (Social Organizations)" OR DE "Traveling" OR DE "Vacationing")) OR (DE "Gambling")) AND (DE "Games" OR DE "Chess" OR DE "Computer Games"))	Search modes - Find all my search terms	358
S8	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	39,017
S9	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular OR (cognitiv* W1 activit*)) OR SU (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular OR (cognitiv* W1 activit*))	Search modes - Find all my search terms	182,299
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	215,667
S11	S6 AND S10	Search modes - Find all my search terms	6,166
S12	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,695,146

S13	S11 NOT S12	Search modes - Find all my search terms	3,706
S14	(DE "Animals") OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	318,343
S15	S13 NOT S14	Search modes - Find all my search terms	3,539
S16	(DE "Drug Therapy")	Search modes - Find all my search terms	129,812
S17	S15 NOT S16	Search modes - Find all my search terms	3,481
S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,152
S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	30,127
S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	30,748
S21	TI (systematic OR structured OR evidence OR trials) AND TI (review OR overview OR look OR examination OR update* OR summary)	Search modes - Find all my search terms	19,166
S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	56,448
S23	S17 AND S22	Search modes - Find all my search terms	84
S24	RD 201707-	Search modes - Find all my search terms	148,956
S25	DT 201707-	Search modes - Find all my search terms	100,982
S26	S24 OR S25	Search modes - Find all my search terms	159,715
S27	S23 AND S26	Search modes - Find all my search terms	13

Epistemonikos 18. Juli 2017

Search	Results
(dementia OR alzheimer* OR cognitiv*) AND (leisure OR recreation OR "free time" OR hobby OR hobbies OR (title:(in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)))	273
Filter: Systematic Review	64

Epistemonikos 18. Juli 2017

Search	Results
(dementia OR alzheimer* OR cognitiv*) AND (leisure OR recreation OR "free time" OR hobby OR hobbies OR (title:(in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)))	368
Filter: Systematic Review	146
Added to database: 01-07-17 to 05-04-18	25

Cochrane Library: 18. Juli 2017

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4053
#2	[mh ^"Cognitive Dysfunction"]	181
#3	[mh ^Cognition]	6276
#4	(dementia or alzheimer*):ti,ab,kw	11879
#5	((cognit* or memory or mental) next (impair* or decline* or deficit* or reduc* or function*)):ti,ab,kw	12722
#6	{or #1-#5}	25014
#7	[mh "Leisure Activities"]	15395
#8	leisure:ti,ab,kw	1481
#9	(hobby or hobbies):ti,ab,kw	55
#10	"free time":ti,ab,kw	162
#11	Recreation:ti,ab,kw	615
#12	(in-door or out-door or indoor or outdoor):ti,kw	478
#13	(garden* or horticultur*):ti,kw	106
#14	(play* or game* or gaming):ti,kw	3280
#15	(creativ* or painting or drawing or reading):ti,kw	2913
#16	(voluntary or volunteer* or extracurricular):ti,kw	17942
#17	{or #7-#16}	39978
#18	#6 and #17	1551
#19	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	104634
#20	#18 not #19 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	38

Cochrane Library: 5. April 2018

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4263
#2	[mh ^"Cognitive Dysfunction"]	450
#3	[mh ^Cognition]	6675
#4	[mh ^"Cognitive Reserve"]	8
#5	(dementia or alzheimer*):ti,ab,kw	13099
#6	((cognit* or memory or mental) next (impair* or decline* or deficit* or reduc* or function*)):ti,ab,kw	14315
#7	{or #1-#6}	27581
#8	[mh "Leisure Activities"]	16504
#9	leisure:ti,ab,kw	1683
#10	(hobby or hobbies):ti,ab,kw	59
#11	free time:ti,ab,kw	169
#12	Recreation:ti,ab,kw	674
#13	(in-door or out-door or indoor or outdoor):ti,kw	541

#14	(garden* or horticultur*):ti,kw	125
#15	(play* or game* or gaming):ti,kw	3653
#16	(creativ* or painting or drawing or reading):ti,kw	3482
#17	(voluntary or volunteer* or extracurricular):ti,kw	20037
#18	(cognitiv* near/2 (activity or activities)):ti,kw	80
#19	{or #8-#18}	44252
#20	#7 and #19	1838
#21	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
#22	#20 not #21 Publication Year from 2017 to 2018, in Cochrane Reviews (Reviews and Protocols) and Technology Assessments	1

Supplementary file 5: Risk of Bias of included studies

Systematic reviews

Author, Year	RISK OF BIAS	Dual Screening and Extraction	Comprehensive literature search	Study quality assessed	'A priori' design	Grey literature included	List of studies	Study characteristics provided	Scientific quality used appropriately	Appropriate methods to combine findings	Publication bias	Conflict of interest included	Reason for High Risk of Bias Decision
Di Marco et al., 2014 [41]	High	NR	Yes	No	Yes	No	No	No	NA	Yes	No	No	No information on screening methods or dual extraction No risk of bias assessment
Opdebeeck et al., 2016 [42]	High	Yes	Yes	No	Yes	Yes	No	Yes	NA	Yes	No	No	No risk of bias assessment No assessment of Publication bias
Sajeev et al., 2016 [43]	Medium	NR	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No information on dual screening or dual extraction
Toril et al., 2014 [44]	High	NR	Yes	No	Yes	No	No	Yes	NA	Yes	Yes	No	No information on screening methods or dual extraction No risk of bias assessment
Yates et al., 2016 [45]	Medium	NR	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No (too few studies)	Yes	No information on dual screening or dual extraction

NA = not applicable, NR = not reported

Supplementary file 6: List of excluded studies during full text screening

Systematic review:

Study	Title	Reason for Exclusion
Canadian Nursing Home, 2007	Studies confirm link between late-life cognitive activities and reduced risk of dementia	Not retrievable
Adam et al., 2013	Occupational activity and cognitive reserve: implications in terms of prevention of cognitive aging and Alzheimer's disease	Ineligible study design
GM: Midlife & Beyond, 2017	Study finds education does not protect against cognitive decline in later life	Ineligible study design
Dowd et al., 2003	Can mental and physical activities such as chess and gardening help in the prevention and treatment of Alzheimer's? Healthy aging through stimulation of the mind	Ineligible study design
Beydoun et al., 2014	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Ineligible study design
Gilland, 2007	Continuing education topic 4: dementia	Ineligible study design
Nursing Standard, 2010	Clinical digest. Cognitive stimulation delays dementia but later decline is faster	Ineligible publication type
Albert et al., 2007	Changing the trajectory of cognitive decline?	Ineligible publication type
Bak et al., 2016	Language lessons to help protect against dementia	Ineligible publication type
Bauer et al., 2002	RN news watch: clinical highlights. Mentally stimulating activities seem to cut Alzheimer's risk	Ineligible publication type
Burgener et al., 2009	Effectiveness of community-based, nonpharmacological interventions for early-stage dementia: conclusions and recommendations	Ineligible publication type
Gatz et al., 2005	Educating the brain to avoid dementia: can mental exercise prevent Alzheimer disease?	Ineligible publication type
Rosenberg et al., 2017	Influence of apoe, age, sex, education and baseline cognition on intervention effects on cognition in the finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)	Ineligible publication type
Summers et al., 2013	The Tasmanian Healthy Brain Project (THBP): a prospective longitudinal examination of the effect of university-level education in older adults in preventing age-related cognitive	Ineligible publication type
Wahlund et al., 2006	[Life-long mental exercise can prevent Alzheimer disease]	Ineligible publication type
ACTRN126120001 47886, 2012	The Body, Brain, Life Program â€“a prevention trial to reduce risk of Alzheimer's Disease	Ineligible intervention
Anon et al., 2008	The Study of Mental Activity and Regular Training for the Prevention of Cognitive Decline in at Risk Individuals: The SMART Trial Or The Study of Mental Activity and Regular	Ineligible intervention
Brenes et al., 2003	Cognitive training may improve targeted cognitive functions in older adults	Ineligible intervention
Fratiglioni et al., 2007	Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project	Ineligible intervention
Gatz et al., 2006	Lifestyle risk and delaying factors	Ineligible intervention
Hall et al., 2009	Cognitive activities delay onset of memory decline in persons who develop dementia	Ineligible intervention
Harmanci et al., 2003	Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey	Ineligible intervention
Harmanci et al., 2003	Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey	Ineligible intervention
Kwok et al., 2011	Effectiveness of coordination exercise in improving cognitive function in older adults: a prospective study	Ineligible intervention
Le Carret et al., 2003	The effect of education on cognitive performances and its implication for the constitution of the cognitive reserve	Ineligible intervention
Merom et al., 2016	Cognitive benefits of social dancing and walking in old age: The dancing mind randomized controlled trial	Ineligible intervention
Roberts et al., 2015	Risk and protective factors for cognitive impairment in persons aged 85 years and older	Ineligible intervention
Sandro et al., 2008	Risk-reducing effect of education in Alzheimer's disease	Ineligible intervention
Sattler et al., 2012	Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease	Ineligible intervention
Schultz et al., 2015	Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease	Ineligible intervention
Soubelet et al., 2011	Engaging in cultural activities compensates for educational differences in cognitive abilities	Ineligible intervention

Standford University, 2012	Activities for Cognitive Enhancement of Seniors	Ineligible intervention
Then et al., 2016	Education as protector against dementia, but what exactly do we mean by education?	Ineligible intervention
University Hospital 2016	Long-term Effects of Interventional Strategies to Prevent Cognitive Decline in Elderly	Ineligible intervention
VanDijk et al., 2008	No protective effects of education during normal cognitive aging: results from the 6-year follow-up of the Maastricht Aging Study	Ineligible intervention
Vemuri et al., 2014	Association of lifetime intellectual enrichment with cognitive decline in the older population	Ineligible intervention
Wang et al., 2002	Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project	Ineligible intervention
Yaffe et al., 2009	Predictors of maintaining cognitive function in older adults: the Health ABC study	Ineligible intervention
Kliegel et al., 2004	Life-long intellectual activities mediate the predictive effect of early education on cognitive impairment in centenarians: A retrospective study	Ineligible populations
Jonaitis et al., 2013	Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease	Ineligible populations
Friedland et al., 2001	Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members	No information about the intervention
National University,	Choral Singing For the Prevention of Dementia	not finished study
Marquez et al., 2017	Regular Latin Dancing and Health Education may Improve Cognition of Late Middle-Aged and Older Latinos	Ineligible comparison;
University Hospital 2018	Prospective Population Based Cohort Study on Cognitive and Cardiovascular Aging (MonaLisaPredor)	not finished study;
Janssen Research Development 2018	Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research: Prospective Readiness Cohort Study	not finished study
ACTRN126170008 58392 2017	Ageing and Folk Dances from the Basque Country: Functional and neuropsychological changes. A controlled trial.	Ineligible intervention
Biasutti et al., 2018	Assessing a cognitive music training for older participants: a randomised controlled trial	Ineligible population
Centre de Recherche del'Institut Universitaire de Geriatriede. 2018	Impact of a Cognitive Intervention Enriched With Leisure Activities in Persons With Subjective Cognitive Decline	Not finished study
Chan et al., 2016	Training Older Adults to Use Tablet Computers: Does It Enhance Cognitive Function?	Ineligible study design
Ihle et al., 2017	The relation of education and cognitive activity to mini-mental state in old age: The role of functional fitness status	Ineligible intervention
Krell-Roesch et al., 2017	Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE epsilon4 Genotype	Ineligible intervention
NCT02919748, 2016	Choral Singing For the Prevention of Dementia	Not finished study
Ramos et al., 2017	Does learning a language in the elderly enhance switching ability?	Ineligible outcome
Wang et al., 2017	Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study	Ineligible intervention
Zanesco et al., 2018	Mental training of attention through intensive meditation: Longitudinal behavioral and electrophysiological investigations of visual sustained attention and response inhibition	Not retreivable
Zhu et al., 2017	Leisure activities, education, and cognitive impairment in Chinese older adults: A population-based longitudinal study	Ineligible intervention
2017	Study suggests late-life activities reduce the risk of mild cognitive impairment	Ineligible study design

Overview of Systematic Reviews

Study	Title	Reason for Exclusion
Bernhardt et al., 2002	[The effect of psychosocial factors on risk of dementia]	Ineligible intervention
Bleakley et al., 2015	Gaming for health: a systematic review of the physical and cognitive effects of interactive computer games in older adults	Ineligible intervention
Conti et al., 2009	The potential role of leisure in the prevention of dementia	Not retreivable
Fratiglioni et al., 2004	An active and socially integrated lifestyle in late life might protect against dementia	Ineligible study design
Karkou et al., 2017	Dance movement therapy for dementia	Ineligible population
Lee et al., 2019	Systematic review of health behavioral risks and cognitive health in older adults	Ineligible intervention
Liapis et al., 2017	Meaningful use of computers has a potential therapeutic and preventative role in dementia care: A systematic review	Ineligible intervention
Munn et al., 2010	Review summaries: evidence for nursing practice. Cognitive leisure activities and their role in preventing dementia: a systematic review	Ineligible publication type
Opdebeeck et al., 2014	Cognitive reserve and cognitive function: A meta-analysis	Ineligible publication type
Stephen et al., 2017	Physical Activity and Alzheimer's Disease: A Systematic Review	Ineligible intervention
Stern et al., 2010	Cognitive leisure activities and their role in preventing dementia: a systematic review	Study superseeded by more recent study
Stern et al., 2009	Cognitive leisure activities and their role in preventing dementia: a systematic review	Ineligible publication type
Wang et al., 2012	Leisure activities, cognition and dementia	Study superseeded by more recent study
Wayne et al., 2014	Effect of tai chi on cognitive performance in older adults: systematic review and meta-analysis	Ineligible intervention
Zheng et al., 2015	Tai Chi and the Protection of Cognitive Ability: A Systematic Review of Prospective Studies in Healthy Adults	Ineligible intervention
Fallahpour et al., 2016	Leisure-activity participation to prevent later-life cognitive decline: a systematic review	Study superseeded by more recent study (search only till 2011)
Bediou et al., 2018	Meta-Analysis of Action Video Game Impact on Perceptual, Attentional, and Cognitive Skills	Ineligible population
Howes et al., 2017	Gaming for Health: Systematic Review and Meta-analysis of the Physical and Cognitive Effects of Active Computer Gaming in Older Adults	Inelgiible intervention
Klimova et al., 2017	Cognitive decline in normal aging and its prevention: a review on non-pharmacological lifestyle strategies	Ineligible intervention
Schneider et al., 2018	Potential Cognitive Benefits From Playing Music Among Cognitively Intact Older Adults: A Scoping Review	Ineligible study design
Solloway et al., 2016	An evidence map of the effect of Tai Chi on health outcomes	Ineligible study design
Wouters et al., 2013	A meta-analysis of the cognitive and motivational effects of serious games	Ineligible study design
Zhang et al., 2016	Physical and Cognitive Impacts of Digital Games on Older Adults: A Meta-Analytic Review	Ineligible intervention

GRADE of Recommendations:

Cognitive leisure activities compared to no cognitive leisure activities for the prevention of dementia (OPDEBEEK et al.)

Patient or population: over 60 years, non-demented adults at baseline

Intervention: cognitive leisure activities

Comparison: no cognitive leisure activities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no cognitive leisure activities	**Risk with cognitive leisure activities**				
Overall cognitive functioning	The mean overall cognitive functioning was **0** SD	The mean overall cognitive functioning in the intervention group was 0,26 SD higher (0,21 higher to 0,31 higher)	-	(31 observational studies)	⨁◯◯◯ VERY LOW [a,b]	

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

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

Explanations

a. $I^2 = 94\%$, b. Interventions vary between studies

Video Games compared to no Video Games for the prevention of dementia (TORIL et al.)

Patient or population: 50-86 years, healthy older adults

Intervention: Video Games

Comparison: no Video Games

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no Video Games	Risk with Video Games				
Cognitive Function	-	-	-	913 (20 observational studies)	⨁◯◯◯ VERY LOW [a]	

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

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

Explanations

a. Mixing various different interventions and study designs

Cognitive leisure activities compared to no cognitive leisure activities for healthy older adults (YATES et al.)

Patient or population: over 46 years, healthy older adults, **Intervention**: cognitive leisure activities, **Comparison**: no cognitive leisure activities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no cognitive leisure activities	**Risk with cognitive leisure activities**				
Incidence of AD	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 0.610** (0.418 to 0.900)	(3 observational studies)	⨁◯◯◯ VERY LOW [a,b]	
Incidence of AD	0 per 1.000	**NaN per 1.000** (NaN to NaN)	**HR 0.584** (0.462 to 0.739)	(2 observational studies)	⨁◯◯◯ VERY LOW [b]	
Incidence of AD	**Low**		**OR 0.775** (0.668 to 0.899)	0 cases 0 controls (2 observational studies)	⨁◯◯◯ VERY LOW [b,c]	
	0 per 1.000	**0 per 1.000** (0 to 0)				
Incidence of cognitive impairment	0 per 1.000	**0 per 1.000** (0 to 0)	**OR 0.685** (0.550 to 0.845)	(5 observational studies)	⨁◯◯◯ VERY LOW [b]	
Incidence of cognitive impairment	0 per 1.000	**NaN per 1.000** (NaN to NaN)	**HR 0.853** (0.711 to 1.022)	(3 observational studies)	⨁◯◯◯ VERY LOW [b,c]	

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

Explanations

a. moderate heterogeneity, x^2 test p=0.09, b. differences in interventions (definition of cognitive leisure activities varies across studies), c. high heterogeneity, x^2 test p=0.00, confidence intervals do not overlap

BMJ Open

Continuing Education for the Prevention of Mild Cognitive Impairment and Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic Reviews.

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Continuing Education for the Prevention of Mild Cognitive Impairment and Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic Reviews.

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ABSTRACT

Objective: To summarize evidence on the preventive effects of continuing education on mild cognitive impairment and Alzheimer's-type dementia in adults 45 years or older.

Design: Systematic review and overview of systematic reviews.

Data sources: We systematically searched MEDLINE, PsycINFO, EMBASE, CENTRAL, CINAHL and Scopus for published studies and gray literature databases for unpublished studies from January 1990 to April 2018.

Methods: To assess evidence directly addressing our objectives, we conducted a systematic review. Because we were aware of a dearth of direct evidence, we also performed an overview of systematic reviews on leisure activities that mimic formal continuing education. We a priori established inclusion and exclusion criteria. Two authors independently assessed inclusion and exclusion on abstract and full-text level, rated risk of bias, and determined the certainty of evidence using GRADE. We resolved all discrepancies by consensus. We synthesized the available evidence narratively.

Results: Our searches identified 4933 citations. For the systematic review, only two publications on the same prospective cohort study (Tasmanian Healthy Brain Project) met inclusion criteria; for the overview of reviews we included five systematic reviews. Based on 459 participants, preliminary data of the ongoing cohort study indicated that cognitive reserve statistically significantly increased in persons attending university classes compared to the control group (92.5% vs. 55.7%). Likewise, language processing capacities statistically significantly improved. Episodic memory, working memory, and executive function did not differ significantly between groups.
Systematic reviews consistently reported a positive association between participation in cognitively stimulating leisure activities and reduced incidence of dementia and improved cognitive test performance.

Conclusion: Available results demonstrate that cognitive reserve increases through continuing education and show a positive association of cognitive leisure activities with both improved cognitive

function and lower dementia incidence. Healthcare providers and policymakers should promote a healthy lifestyle, which also includes being cognitively active throughout life.

Systematic review registration: PROSPERO CRD42017063944

Strengths and Limitations of this study:

- This is the first systematic review assessing the benefits and harms of continuing education on the prevention of mild cognitive impairment or Alzheimer's type dementia.
- This is the first overview of systematic reviews presenting an up-to-date summary of currently available research in the field of cognitive leisure activities and dementia.
- The certainty of evidence is low, indicating that future studies might have a substantial impact on results of our review.
- Measurements and types of cognitive leisure activities differed widely across studies and quantitative analysis were often not possible.
- The majority of included systematic reviews have serious methodological shortcomings.

INTRODUCTION

In 2012, the World Health Organization (WHO) named the prevention and control of neurocognitive disorders such as mild cognitive impairment or Alzheimer's-type dementia a global public health priority.[1] Alzheimer's-type dementia is the most common form of dementia.[1] In 2018, 50 million people worldwide lived with Alzheimer's disease or another closely related form of dementia.[2] As a consequence of the rapidly aging world population, the prevalence of dementia is projected to rise up to 152 million people in 2050.[2]

The progressive loss of independent functioning of people with Alzheimer's-type dementia, leads to an enormous social and economic burden. In 2018, the U.S. economic burden associated with Alzheimer's type dementia was estimated to be 277 billion U.S. Dollars.[3] The total global costs for dementia were about a trillion US dollar in 2018.[2]

The Diagnostic and Statistical Manual (DSM-5) characterizes Alzheimer's disease as a significant decline of intellectual abilities in one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual motor function, social cognition) outside the context of delirium.[4]

Any dementia diagnosis, however, is frequently preceded by a long period of subclinical neuropathological disorder with subjective cognitive disorder and mild cognitive disorder as a transition phase before diagnostic criteria for dementia are fulfilled.[5] If cognitive decline progresses to a degree that a person's capability of carrying out everyday activities is significantly affected, this state is called major neurocognitive disorder.[4 5]

The risk of developing neurocognitive disorders increases substantially with age. The prevalence of Alzheimer's type dementia is 3.5% in persons aged 75 or older and 46.3% in those 95 years or older.[6] It is estimated that 15 to 20 percent of people age 65 or older are living with mild cognitive impairment.[3] Other risk factors than age contributing to the development of dementia are not yet thoroughly understood. In recent years, epidemiological studies have linked the development of dementia with risk factors such as low educational level, unhealthy diet, decreased physical

activity, and smoking.[7 8] In addition, potential predictors of dementia are chronic medical conditions such as cardiovascular diseases, diabetes, obesity, cancers, depression, thyroid disorder, or genetic factors.[9] Some studies, however, found a protective association of cognitively stimulating activities, such as learning a new language in middle age, with a slower cognitive decline during late life.[10-14] Such results underpin the "cognitive reserve hypothesis".[15-17] According to this theory, through every activity that stimulates the brain, the cognitive reserve gets boosted and the resistance towards any dementia-related brain pathology increases.[18] In animal trials, an enriched environment was associated with increased cortical thickness.[19] Epidemiological research on humans has shown that education[20] and probably also other forms of intellectual stimulation, during the whole lifespan, are associated with a lower risk to develop dementia.[21 22] A larger cognitive reserve acquired by continuing education activities, thus, might protect against cognitive decline.[18 23]

Continuing education activities are structured learning activities offered by educational institutes. These activities are designed to help individuals satisfy learning needs and interests after compulsory schooling, to enrich knowledge, to develop and improve abilities and skills, and to foster personality, social competences, families, networks, health, and professional life. Continuing education is voluntary, based on topics and courses that are not directly connected to any special job position or vocational training.[24-29] Cognitive leisure activities (e.g., learning a new language) often mimic continuing education activities but are not taking place within the framework of an educational institution.

Rationale

To date, the preventive effect of continuing education on cognitive impairment and Alzheimer's-type dementia has not been assessed in an objective and systematic way. The aim of our review was to summarize the evidence investigating the preventive effects of continuing education on the development of cognitive impairment and Alzheimer's-type dementia.

Our systematic review addressed the following questions:

Key question 1a: In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment, does continuing education lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type dementia compared with no continuing education?

Key question 1b: (In case no evidence on continuing education is available or the evidence is sparse): In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment, do cognitive leisure activities lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type dementia compared with no cognitive leisure activities?

Key question 2: What are potential harms of continuing education?

Key question 3: Do benefits and harms differ by subgroups based on age, sex/gender, race or ethnicities, level of education, or duration of intervention?

Key question 4: What is the optimal age to start continuing education to prevent mild cognitive impairment or dementia?

METHODS

Design

Throughout this manuscript we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[30] (see supplementary file 1). The protocol of this systematic review was registered in PROSPERO (International Prospective Register of Systematic Reviews) (Registration number CRD42017063944) and published previously.[31] Figure 1 depicts the analytic framework that guided our systematic review.

[Figure 1 about here]

For this systematic review, we define continuing education as structured learning activities and programs provided by formal and non-formal educational institutions for persons beyond the age of compulsory schooling (in most countries 16 years and older).[24-29]

We addressed our research questions with two different methodological approaches:

1) We performed a systematic review of primary studies to assess the preventive effects and potential harms of continuing education provided by formal and non-formal institutions (key questions 1a, 2, 3, and 4).

2) We conducted an overview of systematic reviews to determine the preventive effects and potential harms of related leisure activities (e.g. playing cards, reading books, etc., key question 1b).

We chose this two-step approach because studies in the field of continuing education and dementia are very rare. Certain leisure activities, however, are able to mimic continuing education regarding content (e.g. learning a new language privately versus learning a new language as an organized educational activity). Leisure activities are not our primary focus of interest but can be considered as proxy interventions for continuing education in some circumstances.

Study selection

Eligibility criteria for the systematic review

The population of interest were adults 45 years or older, without a clinical diagnosis of cognitive impairment at the time of study recruitment, which included people with subjective cognitive impairment. Eligible interventions comprised of all cognitive activities that are provided by formal and non-formal educational institutions. These activities include classes, courses, and trainings that are based on individual interests and that are attended voluntarily. We included randomized controlled trials, nonrandomized controlled trials, prospective controlled cohort studies, retrospective controlled cohort studies, and case-control studies. All nonrandomized studies needed to have a minimum sample size of 300 or more participants.

Eligible studies had a minimum follow up time of 1 year and a minimum duration of intervention of 3 months. We excluded studies that investigated formal (vocational) education (e.g. School or College), physical activities, and all job-related courses and trainings.

Outcomes of interest included patient-relevant health outcomes such as incidence of dementia, incidence of MCI, psychological wellbeing, functional capacity, quality of life, and other relevant health outcomes; in addition, we included intermediate outcomes such as cognitive functioning, cognitive (test) performance, or social inclusion. For the purpose of our study, mild cognitive impairment refers to "amnestic" mild cognitive impairment (aMCI), meaning that memory loss is the predominant symptom.[32]

Eligibility criteria for the overview of systematic reviews

Eligibility criteria for population and outcomes for the overview of systematic reviews were the same as for the systematic review. Eligible interventions were leisure activities that are cognitively stimulating and mimic the content of continuing education but in an informal setting. Just as in the systematic review, we excluded physical activities. Eligible study designs were exclusively systematic reviews and meta-analyses. We excluded reviews with searches conducted before 2013.

Further details about our inclusion and exclusion criteria can be found in our protocol[31] and in the supplementary file 2.

Search strategy

We systematically searched Ovid MEDLINE, Cochrane Library, Embase, PsycINFO, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ALOIS (the Cochrane Dementia and Cognitive Improvement Group Specialized Register), and ERIC (Education Resources Information Center) from January 1990 to April 2018 to identify relevant publications (see supplementary file 3 for the search strategy). For the overview of reviews, we searched Epistemonikos from inception to April 2018 in addition to the above mentioned databases (see supplementary file 4).

An experienced information specialist developed an appropriate search strategy using a combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the search to human-only studies without applying any language limitations. The electronic Ovid Medline search strategy was peer-reviewed by another information specialist following the PRESS (peer

review of the electronic search strategy) statement.[33] For the systematic review, we searched for gray literature in ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, web pages of relevant organizations, and a dissertation database ("Digital Access to Research Theses", DART-Europe). Additionally, in an attempt to avoid retrieval bias, we manually searched the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed. We imported all citations into an electronic database (EndNote X.8) and deleted duplicates.

Study selection

Two review authors independently screened abstracts and relevant full text articles for eligibility, using Covidence Software.[34] They resolved disagreements by discussion or by consultation with a third author.

Data abstraction

We designed, pilot-tested, and used a data abstraction form to gather pertinent information from each article. One author extracted relevant data from each study that met our inclusion criteria. A second author of the team cross-checked data abstractions for completeness and accuracy. We extracted study information (author, publication year, years covered by searches, location/setting, number of included studies and included study designs), sample size, study characteristics (population, interventions, and comparators), outcome measurements, and results. For systematic reviews we abstracted summary estimates of meta-analyses whenever available.

Risk of bias assessment

Two investigators independently assessed the risk of bias of included studies. They resolved any disagreements by consensus or by consulting a third team member. For eligible non-randomized studies we used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool.[35] For the assessment of eligible systematic reviews, we used the AMSTAR (Assessing the Methodological

Quality of Systematic Reviews) tool.[36] Detailed risk of bias ratings of included articles are given in supplementary file 5.

Data synthesis and statistical analysis

We narratively summarized evidence from included studies. If available, we present effect estimates of systematic reviews. For the incidence of dementia we present hazard ratios (HR), odds ratios (OR), and risk ratios (RR). For the assessment of cognitive test performance we use standardized mean differences because scales for measurements differed in the individual studies. A standardized mean difference of 0 indicates that both groups had the same cognitive test performance.

Certainty of evidence

We followed the recommendations of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group for rating the certainty of evidence for each outcome.[37]

Patient involvement

No patients were involved in the development of this research paper.

RESULTS

Our search identified in total 4933 citations after exclusion of duplicates. Based on title and abstract review, we considered 58 primary studies and 28 systematic reviews for full-text review. After scrutinising the full-text articles, we included two publications of one primary study[38 39] and five systematic reviews.[40-44] Figure 2 and figure 3 depict the study selection process. Supplementary file 6 provides a list of excluded studies at full-text level.

[Figure 2 and figure 3 about here]

Study characteristics

Systematic Review

We included two publications[38 39] that present interim findings of the same medium risk of bias prospective cohort study, namely the Tasmanian Healthy Brain Project that plans to follow participants for 10-20 years.[45] The two publications analysed different aspects of cognitive functioning of the same 459 participants who did or did not engage in a 12 month, part-time or full-time university-level education. Participants' mean age was 59.6±7 (mean±SD) years in the intervention group and 62.4±6 years in the control group with a follow-up period of 4 years. Participants completed a neuropsychological test battery, consisting of 14 tests each year.[45]

In this study, selection bias is likely because participants voluntarily opted for university courses or no further education. It is not clear if investigators used appropriate methods to adjust for potential confounders (see supplementary file 5 for risk of bias ratings).

Overview of Reviews

All five included systematic reviews investigated the benefits of cognitive leisure activities in adults over the age of 45 years.[40-44] Four studies included any cognitive leisure activities in their analyses (e.g. reading books, doing crosswords, attending cultural events, knitting, painting), one study[43] specifically focused on the benefits of playing video games in older adults. The number of participants investigated in the reviews ranged from 913[43] to 24,554.[41]

We rated three of the included systematic reviews[40 42 43] as high and two studies[41 44] as medium risk of bias. Reasons for the high risk of bias ratings were lack of critical appraisal of included studies, single review of the literature, and insufficient literature searches (see supplementary file 5).

We graded the evidence for all meta-analysis outcomes with low certainty of evidence mostly because of high inconsistency and indirectness among studies (see supplementary file 7).

We present characteristics of included studies [40-44] in table 1 and table 2.

Reference	Study design	Aim	Sample Size	Population	Intervention	Measurements	Outcomes	Risk of bias
Lenhan et al., 2016[39]	Prospective cohort study, Tasmanian Healthy Brain Project (2011-2016)	To investigate changes in cognitive reserve in healthy older adults participating over four years in university-level education.	459 (359 in the Intervention group, 100 control group)	50-79 years, healthy older adults	Minimum of 12 months of part-time or full-time university study Follow-up: 4 years	Prior Cognitive reserve and current cognitive reserve were calculated for each participant.	55,7% in the control group vs. 92,5% in the university education group showed a significant increase of cognitive reserve	Medium
Thow et al., 2018[38]		To determine if the observed increase in cognitive reserve among older adults attending university is associated with a change in cognitive function over time.				Episodic memory, working memory, executive function, and language processing performances were assessed annually over 4 years.	Statistically significant improvement of language processing capacity. No significant improvement of episodic memory, working memory, executive function.	Medium

Table 1: Study Characteristics of included primary studies

Reference	Aim	Search Strategy	N of included studies	Study design	Total number of participants	Population	Outcomes	Risk of bias
Di Marco et al., 2014[40]	To provide a comprehensive summary of modifiable lifestyle factors (dietary habits, leisure activities, social network et cetera.) associated with the risk of late-onset incident dementia.	NR to 2013 PubMed, Ovid MEDLINE, PsycINFO, In-Process and other non-indexed citations Search terms provided English language publications	6 (cognitive leisure activities)	Longitudinal observational cohort-studies	NR	≥65 years, adults without dementia at baseline	No quantitative analysis Cognitive leisure activities might be associated with **reduced incidence of all-cause dementia**	High
Opdebeeck et al., 2016[41]	To assess the relationship between cognitive reserve (educational level, occupational status and engagement in cognitively stimulating activities) and cognition in multiple domains.	NR to 2014 PubMed, PsycInfo, ScienceDirect, CINHAL Search terms provided	31 (cognitive stimulating activities)	31 Cross-sectional studies	24561	≥60 years (at least 80% of study participants)	SMD 0.26 (95% CI 0.21-0.32) Participating in cognitive leisure activities is associated with **improved cognitive functions** (including memory, working memory, executive function, visuospatial ability, and language)	High
Sajeev et al., 2016[42]	To assess if engaging in late-life cognitive activities is able to delay or prevent dementia.	NR to June 2014 PubMed and EMBASE	12 (cognitive stimulating activities)	10 prospective cohort studies; 2 nested case-control studies	13939 (dementia: 1663 AD: 565)	≥45 years	No quantitative analysis	Medium

		No search terms provided					Late-life cognitive activity might be associated with **lower AD and/or all-cause dementia incidence**	
Toril et al., 2014[43]	To investigate the extent to which cognitive training with video games enhances cognitive functions in healthy older adults.	1986-2013 MEDLINE, PsycInfo and Google Scholar Search terms provided English language publications	20 (video game training)	18 controlled studies 2 uncontrolled studies	913 (474 trained, 439 healthy controls)	50 - 86 years, healthy older adults	SMD 0.37 (95% CI 0.26 – 0.48) Video game training is associated with **improved cognitive functions** in older adults (including memory, attention, reaction time, cognitive function, executive functions)	High
Yates et al., 2016[44]	To assess the impact of cognitively stimulating leisure activities on cognition and risk of dementia in later life.	2004 – 2014 PsychInfo, MEDLINE, CINAHL, EMBASE and the Web of Science Search terms provided	19 (cognitive leisure activities)	17 Cohort studies 2 Case control studies	32546	≥ 46 years, cognitively healthy adults (i.e. no diagnosis of impairment or dementia)	**All-cause dementia incidence:** RR 0.61 (95%CI 0.42 – 0.90), k=3, RE HR 0.58 (95%CI 0.46 – 0.74), k=2, RE OR 0.78 (95%CI 0.67 – 0.90), k=2, FE **Cognitive impairment incidence:** OR 0.69 (95%CI 0.56 – 0.85), k=5, RE HR 0.85 (95% CI 0.71 – 1.02), k=3, RE, n.s.	Medium

NR = Not reported, AD = Alzheimer's-type dementia, k = studies that assessed cognitive activities only, n= number of participants, RE = random-effects model, FE = fixed effects model, n.s. = not significant

Table 2: Study Characteristics of included systematic reviews

Outcomes

Key question 1a: Continuing education

Two interim analyses of the Tasmanian Healthy Brain Project focused on language processing[38] and cognitive reserve[39] after 4 years of follow-up. To date, no results on the incidence of mild cognitive impairment or Alzheimer's-type dementia are available yet. Both studies reported beneficial effects of continuing education. Thow and colleagues[38] showed that attending university courses over a period of 12 months statistically significantly ($p<0.05$) improved the language processing capacity in the intervention group compared to the control group. No statistically significant differences were detected for episodic memory, working memory, and executive function between groups. In all analyses, authors accounted for age and prior cognitive reserve (education, pre-existing intellectual capacity, life-experience).

Lenehan and coworkers[39] demonstrated by conducting growth mixture modeling that the cognitive reserve statistically significantly increased in 92.5% of participants in the intervention group (n=359) compared to 55.7% of participants in the control group (n=100). Investigators created a proxy measure of "current cognitive reserve" to capture dynamic changes in cognitive reserve over time, including intellectual capacity and academic ability.[46]

Key question 1b: Cognitive leisure activities

Overall, the five included systematic reviews reported consistently that participation in cognitive stimulating leisure activities can reduce the risk of developing mild cognitive impairment or Alzheimer's-type dementia and improves cognitive functioning of healthy older adults.

Two systematic reviews[40 42] investigated the impact of cognitive leisure activities on the incidence of Alzheimer's-type dementia. Di Marco and colleagues included six, Sajeev and colleagues 12 primary studies on cognitive leisure activities in their systematic reviews. Both systematic reviews concluded that leisure activities protect against dementia. Due to different categorization of cognitive leisure activities and a high heterogeneity between studies, quantitative analyses were not possible in the two reviews. The effect estimates of included studies ranged from hazard ratios [HR]

of 0.39 (95% CI: 0.21 - 0.71)[47] to HR of 0.93 (95% CI: 0.88 – 0.98)[48] showing statistically significantly reduced risks of Alzheimer's-type dementia when carrying out leisure activities. Sajeev et al.[42] performed an extensive bias analysis indicating that it is unlikely that the observed positive effects of cognitively stimulating activities on dementia incidence are exclusively explained by unmeasured confounders or reverse causation.

One review[44] assessed both incidence of mild cognitive impairment and Alzheimer's-type dementia and cognitive test performance. The authors conducted five meta-analyses based on groups for outcomes and reported effect estimates (risk ratio [RR], odds ratio [OR], and hazard ratio [HR]). Four out of five meta-analyses revealed statistically significant results showing that cognitive leisure activities were associated with a reduction of dementia incidence (RR = 0.61, 95% CI: 0.42-0.90; HR = 0.58, 95% CI: 0.46-0.74, OR = 0.78, 95% CI: 0.67 – 0.90) and a reduction of cognitive impairment incidence (OR = 0.69, 95% CI: 0.56 – 0.85). However, one meta-analysis, combining three cohort studies did not reach statistical significance (HR = 0.85, 95% CI: 0.71-1.02) for reduction of cognitive impairment. A narrative analysis of primary studies assessing cognitive test performance showed a statistically significant improvement of memory, speed of processing, language, and executive functioning and overall later life cognition.

Two other included studies[41 43], both rated as high risk of bias, focused on cognitive test performance. Opdebeeck et al.[41] reported a benefit in overall cognitive abilities for the group involving in cognitive leisure activities (standardized mean difference [SMD] of 0.26 (95% confidence interval [CI]: 0.21-0.32). The cognitive domains included memory, working memory, executive function, visuospatial ability, and language. According to the review by Toril et al. [43], playing video games enhanced several cognitive functions. They observed a SMD of 0.37 (95% CI 0.26 – 0.48) for global cognitive function (combining results for memory, attention, reaction time and executive functions), showing a benefit for the intervention group.

Key question 2: Harms

We found no evidence regarding harms of continuing education or cognitive leisure activities.

Key question 3: Subgroups

Toril and colleagues[43] performed several subgroup analyses. The study revealed that the age of the participants and the number of video game training sessions significantly changed the effect size. Older participants (between 71 and 80 years) seemed to benefit more from computer training than younger participants (60 to 70 years). For the improvement of cognitive test performance, shorter training sessions (1-6 weeks) seemed to show an advantage over longer training interventions (7-12 weeks). By contrast, for incidence of Alzheimer's-type dementia, DiMarco et al.[40] and Sajeev et al.[42] infer from their data that greater participation in cognitive leisure activities over a longer period of time contributes positively to the protective effect.

Key question 4: Optimal age

No study specifically discussed the optimal age to start with continuing education activities or cognitive leisure activities to prevent mild cognitive impairment or dementia.

DISCUSSION

The evidence assessing the impact of continuing education on the risk of MCI or Alzheimer-type dementia is limited. The only eligible primary study (Tasmanian Healthy Brain project) [45] is still ongoing but preliminary findings after four years of follow-up demonstrated that the dynamic nature of cognitive reserve permits improvements through education even at an advanced age. Nevertheless, these early findings have to be viewed cautiously. In addition, selection bias could potentially distort results of the Tasmanian Healthy Brain project because participants voluntarily opted for university courses or no further education. The available publications did not explain sufficiently how baseline differences such as comorbid diseases were taken into consideration during the analyses.

Because of the limited direct evidence, we focused on cognitive leisure activities as proxies for formal continuing education. Overall, the available evidence consistently indicates beneficial effects of cognitive leisure activities by improving the cognitive function of older adults and reducing the incidence of MCI and Alzheimer's-type dementia. These findings could be explained by the neuroplasticity of the human brain, which refers to the ability of the brain to adapt to every new stimulus by forming dendritic connections, creating morphological changes and increasing cognitive reserve.[49-51] Neuroplasticity is an intrinsic property of the human brain that allows us to learn and adapt to environmental changes. Depending on the stimuli, the changes can be positive or negative.[49-51] The concept of neuroplasticity is interrelated with the concept of cognitive reserve which refers to morphological changes that support cognitive functioning.[51]

The magnitudes of beneficial effects, however, varied across systematic reviews and confidence intervals encompassed effect sizes that would not be clinically relevant. Consequently, we rated the certainty of evidence as low or very low which means that future studies are likely to have a substantial impact on these findings.

To the best of our knowledge, our study was the first assessing the impact of continuing education on MCI and Alzheimer's-type dementia. It is also the first overview of systematic reviews presenting an up-to-date summary of currently available research in the field of cognitive leisure

activities and dementia. Nevertheless, our work has several limitations. First, in the overview of systematic reviews we had to rely on the quality of included systematic reviews which often had methodological shortcomings (e.g. no risk of bias assessment, no dual screening etc.). Second, most of the included studies were observational studies, which are prone to selection bias because participants self-select the group. Risk factors for MCI or dementia in participants selecting leisure activities or further education might be systematically different from participants in the control groups. For example, people who eventually suffer from preclinical dementia stages might be more likely to avoid cognitive leisure activities, which would lead to reverse causation. Third, many primary studies within the reviews used self-reported questionnaires that could be challenging for people who start having cognitive deficits. Finally, the variation of leisure activity categorization across studies made meta-analysis difficult and sometimes impossible. For example, "visiting a library" was classified as a cognitive activity by one author but as a physical activity by another. Some studies assessed current participation in activities, others participation at younger ages. Additionally, some studies assessed the frequency of participation, others the time devoted to activities and some the total number of leisure activities. Consequently, due to these limitations, the comparability of results among studies was limited. A standardization of measures and methods would be necessary to help synthesize evidence in the future and make more reliable recommendations.

Implication for future research, policy and practice

Based on preliminary results of a long-term cohort study and indirect evidence from studies on leisure activities, continuing education might be a promising option to help prevent dementia. A recent study suggests that modifiable risk factors (low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression) might be responsible for about a third of Alzheimer's-type dementia cases.[52] Hence, considering our results, a campaign promoting to "actively use the brain by participating in the wide range of continuing education" could possibly be added to the list of preventive options and could have an impact on the reduction of Alzheimer's-type dementia cases. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and

Disability (FINGER)[53], a randomized controlled trial, with a multi-domain approach (diet, exercise, cognitive training, vascular risk monitoring) supports the hypothesis that simultaneous changes in several risk factors can lead to a protective effect on cognition.

Further research is needed to address the evidence gap regarding continuing education and the extent to which it acts as a protective factor. A study similar to the Tasmanian Healthy Brain Project[39], but conducted as a randomized controlled trial, would be ideal because it would adequately handle known and unknown confounders. Computers and Internet could play a more significant role in future prevention trials. Older adults could, for instance, be randomized to attend online courses and communicate with professors and other students in virtual classrooms. This approach could save time, money, and increase the potential participant pool.

Conclusion

Although no firm conclusions about the effects of continuing education to prevent MCI and dementia can be drawn, data from preliminary and indirect evidence indicate that continuing education could potentially have important preventive effects. Physicians and policymakers should promote a healthy lifestyle, which also includes being cognitively active throughout late life.

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Author Contributions: All authors made substantial contribution to the conception and design of this study. GG, NM, MK, CG and SA developed the concept of the study. As an information specialist, IK developed the search strategy. GW, FKA, NM and BT conducted the literature review, abstracted data and graded the strength of evidence. NM wrote the first draft of the manuscript; all authors reviewed the manuscript and provided comments. All authors have given approval for this version to be published.

Figure Legends:

Figure 1: Analytic framework for continuing education to prevent mild cognitive impairment and Alzheimer's-type dementia

Figure 2: Flow diagram of systematic review of continuing education for the prevention of mild cognitive impairment and Alzheimer's-type dementia

Figure 3: Flow diagram of overview of systematic reviews of cognitive leisure activities for the prevention of mild cognitive impairment and Alzheimer's-type dementia

List of abbreviations

AD = Alzheimer Disease
aMCI = Amnestic Mild Cognitive Impairment
AMSTAR = Assessing the Methodological Quality of Systematic Reviews
CEDEFOP = European Centre for the Development of Vocational Training
CENTRAL = Cochrane Central Register of Controlled Trials
DSM = Diagnostic and Statistical Manual of Mental Disorders
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HR = Hazard Ratio
ICD = International Classification of Diseases
MCI = Mild Cognitive Impairment
MMSE = Mini-Mental State Examination
OECD = Organisation for Economic Co-operation and Development
OR = Odds Ratio
PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-I = Risk of Bias in non-randomized studies – of interventions
RR = Relative Risk
SD = Standard Deviation
SMD = Standardized mean difference
UNESCO = United Nations Educational, Scientific and Cultural Organization
WHO = World Health Organisation

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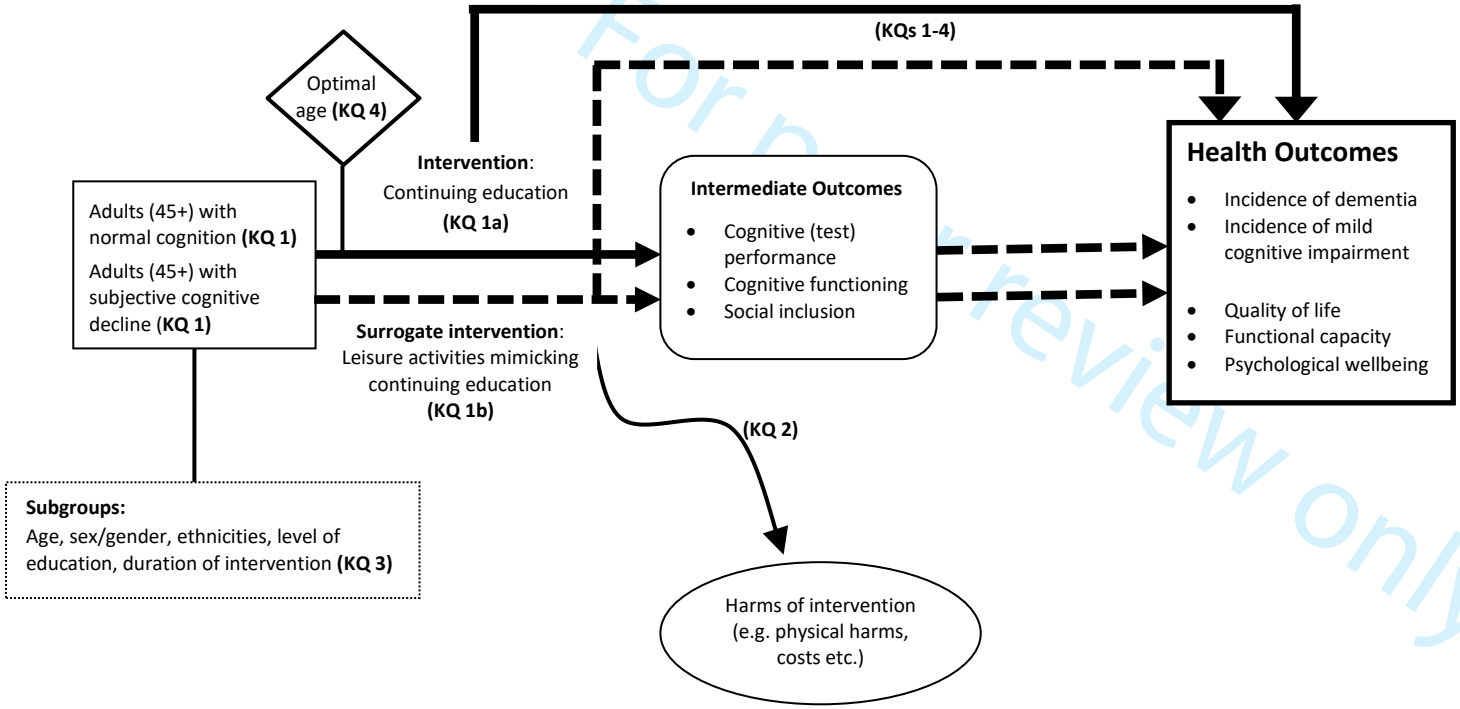

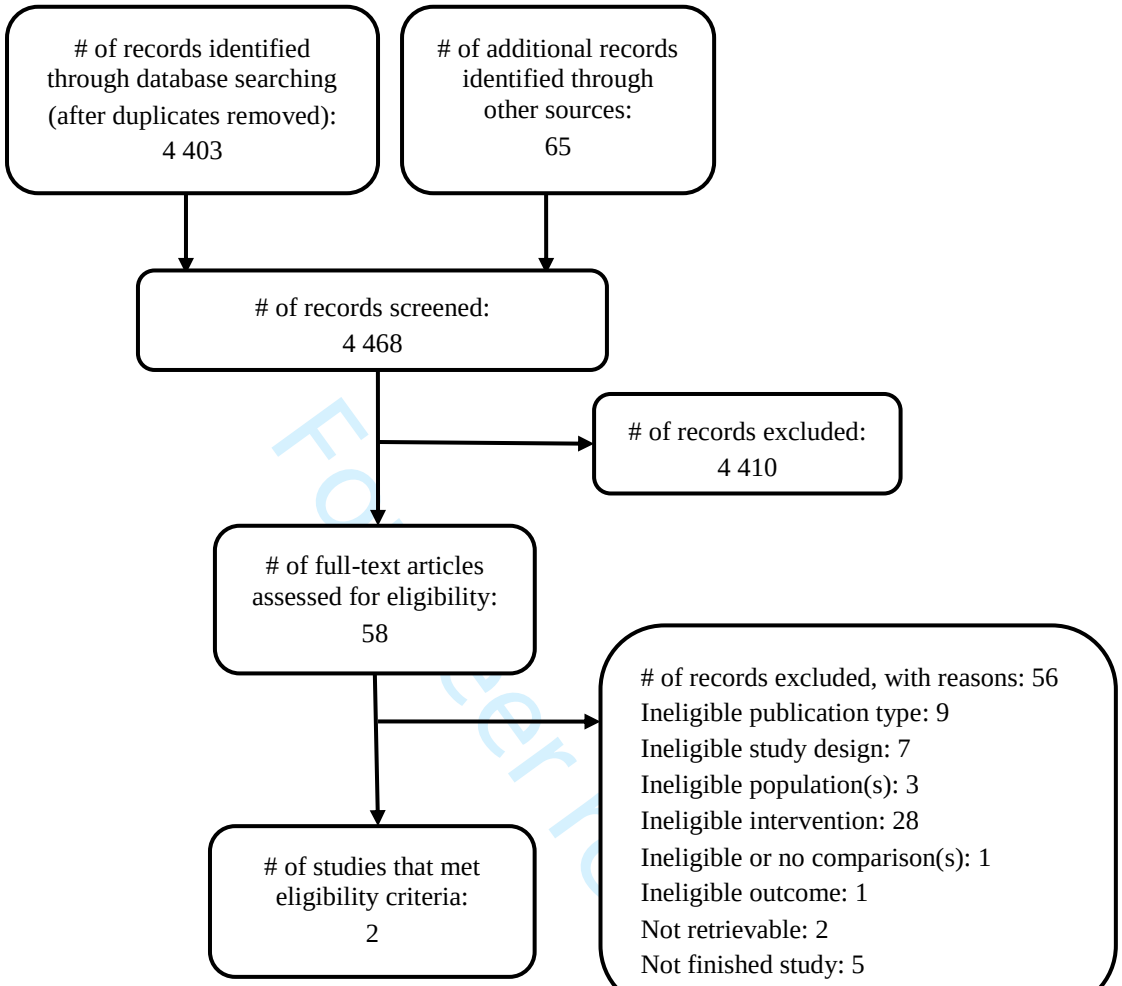

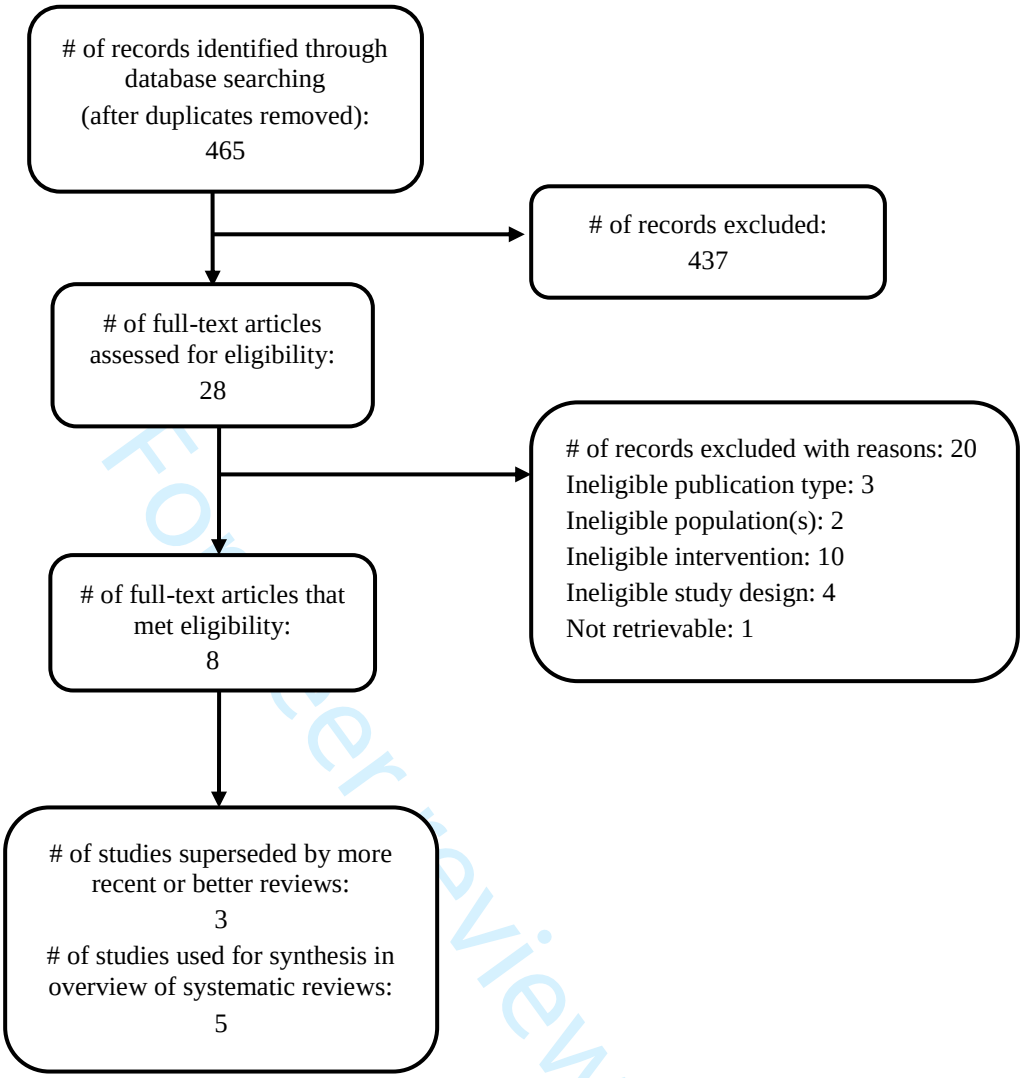

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 (line 1-3)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4 (line 40-67)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-7 (line 127-132)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7 (line 133-144)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 7 (line 149-151)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8-9 (line 171-196)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9-10 (line 197-214)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 3 and 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10 (line 215-218)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10 (line 219-226)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10 (line 222-226)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10-11 (line 227-233)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 11 (line 234-240)

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 11 (line 234-240)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11 (line 238-243) Figure 2 and figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-12 (line 255-278) Table 1 and table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13-14 Table 1 and table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-17 (line 288-351) Table 1 and table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12 (line 264-266; line 273-278) Supplementary file 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 18

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21 (line 423-425)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary File 2: Inclusion and exclusion criteria

	Criteria	
Category	**Inclusion**	**Exclusion**
Population	- Adults (45 years or older) without a clinical diagnosis of cognitive impairment; this includes people with subjective cognitive impairment	- People younger than 45 years - People with a clinical diagnosis of impaired cognition (e.g., MMSE < 24) -Populations comprised exclusively of patients with primary diseases with an increased risk for dementia such as Parkinson disease, HIV infection, multiple sclerosis, stroke, post traumatic brain injuries, infectious diseases, psychiatric conditions (e.g. alcohol abuse, drug abuse, major depressive disorder)
Subgroups	- Age - Sex/gender - Race/ethnicity - Level of education - Duration of intervention	
Geography	No limit	No limit
Date of search	Searches will go back until 1990	
Settings	Community-dwelling adults	Institutionalized people, e.g., people in nursing homes
Interventions	**For systematic review** - all cognitive activities that are provided by formal and non-formal educational institutions - classes/courses/trainings that are based on individual interests and that are attended voluntarily **For overview of systematic reviews** Leisure activities that are cognitively stimulating and mimic the content of continuing education but in an informal setting.	Formal (vocational) education and training; physical activities, topics and courses that are related to any special job position and/or occupation
Control Interventions	No continuing education	Any educational activities, physical activities
Outcomes	**Health Outcomes** - Incidence of dementia - Incidence of MCI - Psychological wellbeing - Functional capacity - Quality of life - Other relevant health outcomes **Intermediate Outcomes** - Cognitive functioning - Cognitive (test) performance - Social inclusion	
Timing	Minimum duration of the intervention: 3 months Minimum follow up time: 1 year	
Publication language	No language restrictions	
Study design	**For systematic reviews** - RCTs - Nonrandomized controlled trials - Prospective controlled cohort studies - Retrospective controlled cohort studies - Case-control studies - Nonrandomized studies must have a minimum sample size of 300 or more participants **For overview of systematic reviews** -systematic reviews and meta-analyses	- Case series - Case reports - Cross over trials - Nonsystematic reviews - Studies without a control group - Nonrandomized studies with fewer than 300 participants

Supplementary file 3: Search Strategies of Systematic Review, by database

Medline (via PubMed):10 July 2017

Medline

Search	Query	Hits
1	Dementia/ or exp Alzheimer Disease/	117464
2	Cognitive Dysfunction/	5918
3	Cognition/	81481
4	(dementia or alzheimer*).ti,ab.	174908
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	166793
6	or/1-5	370522
7	Primary Prevention/	16883
8	prevent*.ti,ab.	1207345
9	(protect* or reduc* or delay* or improv*).ti.	710454
10	or/7-9	1858549
11	6 and 10	39070
12	Dementia/pc or exp Alzheimer Disease/pc or Cognitive Dysfunction/pc [Prevention & Control]	4039
13	11 or 12	41057
14	exp Education, Continuing/	60977
15	((continuing or adult) adj2 (education or training)).af.	80639
16	(lifelong learning or life-long learning).af.	2396
17	education/ or exp curriculum/ or exp education, distance/ or exp education, nonprofessional/ or exp educational measurement/ or exp international educational exchange/ or mentoring/ or exp schools/ or exp teaching/	500562
18	Learning/	56308
19	Students/	47445
20	exp Educational Status/	47641
21	(learn* or class or classes or course? or educat* or school* or train* or seminar* or tutor*).ti.	569072
22	education.fs. not exp Health Personnel/ed	200448
23	(cognitiv* adj2 (stimulat* or activit*)).ti.	742
24	or/14-23	1075912
25	13 and 24	3357
26	exp Dementia/dt [Drug Therapy]	17955
27	25 not 26	3243
28	exp animals/ not exp humans/	4438320
29	27 not 28	2497
30	exp age groups/ not (exp aged/ or middle aged/)	3709828
31	29 not 30	1838
32	limit 31 to yr="1990 -Current"	1805
33	remove duplicates from 32	1695

Medline (via PubMed): updated 5 April 2018

Search	Query	Results
1	Dementia/ or exp Alzheimer Disease/	118649
2	Cognitive Dysfunction/	7920
3	Cognition/	82659
4	(dementia or alzheimer*).ti,ab.	178991
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	171636
6	or/1-5	378202
7	Primary Prevention/	16649
8	prevent*.ti,ab.	1222908
9	(protect* or reduc* or delay* or improv* or increas* or decreas*).ti.	1008130
10	or/7-9	2152629
11	6 and 10	46477
12	Dementia/pc or exp Alzheimer Disease/pc or Cognitive Dysfunction/pc or Cognition Disorders/pc [Prevention & Control]	6391
13	Cognitive Reserve/	388
14	cognitive reserve.ti,ab.	949
15	or/11-14	50722
16	exp Education, Continuing/	58777
17	((continuing or adult) adj2 (education or training)).af.	77985
18	(lifelong learning or life-long learning).af.	2438
19	education/ or exp curriculum/ or exp education, distance/ or exp education, nonprofessional/ or exp educational measurement/ or exp international educational exchange/ or mentoring/ or exp schools/ or exp teaching/	561833
20	Learning/	57102
21	Students/	48337
22	exp Educational Status/	47241
23	(learn* or class or classes or course? or educat* or school* or train* or seminar* or tutor*).ti.	571948
24	education.fs. not exp Health Personnel/ed	199668
25	(cognitiv* adj2 (stimulat* or activit*)).ti.	773
26	(late-life adj2 (activity or activities or learn* or school* or educat* or training)).ti,ab.	93
27	or/16-26	1135186
28	15 and 27	4360
29	exp Dementia/dt [Drug Therapy]	18096
30	28 not 29	4227
31	exp animals/ not exp humans/	4439627
32	30 not 31	3347
33	exp age groups/ not (exp aged/ or middle aged/)	3685655
34	32 not 33	2546
35	(201707* or 201708* or 201709* or 20171* or 2018*).ed.	749049
36	("2017/07*" or "2017/08*" or "2017/09*" or "2017/1*" or 2018*).dt.	942206
37	35 or 36	1540516
38	34 and 37	364
39	limit 34 to yr="2017 -Current"	348
40	38 or 39	435

Cochrane Library (10 July 2017)

Cochrane Library

Search	Query	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4053
#2	[mh ^"Cognitive Dysfunction"]	0
#3	[mh ^Cognition]	6276
#4	(dementia or alzheimer*):ti,ab,kw	11882
#5	((cognit* or memory or mental) near/3 (impair* or decline* or deficit* or reduc* or function*)):ti,ab	16173
#6	{or #1-#5}	27711
#7	[mh ^"Primary Prevention"]	1008
#8	prevent*:ti,ab,kw	107750
#9	(protect* or reduc* or delay* or improv*):ti	77161
#10	{or #7-#9}	175365
#11	#6 and #10	4432
#12	[mh Dementia/pc] or [mh ^"Cognitive Dysfunction"/pc]	208
#13	#11 or #12	4532
#14	[mh "Education, Continuing"]	1168
#15	((continuing or adult) near/2 (education or training)):ti,ab,kw	2819
#16	("lifelong learning" or "life-long learning"):ti,ab,kw	19
#17	[mh ^education] or [mh curriculum] or [mh "education, distance"] or [mh "education, nonprofessional"] or [mh "educational measurement"] or [mh "international educational exchange"] or [mh ^mentoring] or [mh schools] or [mh teaching]	21839
#18	[mh ^Learning]	1809
#19	[mh ^Students]	2041
#20	[mh "Educational Status"]	1348
#21	(learn* or class or classes or course or courses or educat* or school* or train* or seminar* or tutor*):ti	45060
#22	(cognitiv* near/2 (stimulat* or activit*)):ti	212
#23	(learning or ((education or training) near/2 (nonprofessional or non-professional or distance)) or teaching):kw	12784
#24	{or #14-#23}	67085
#25	#13 and #24	784
#26	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	104635
#27	#25 not #26	691
#28	#27 Publication Year from 1990 to 2017	691

Cochrane Library (updated 9 April 2018)

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4263
#2	[mh ^"Cognitive Dysfunction"]	450
#3	[mh ^Cognition]	6675
#4	(dementia or alzheimer*):ti,ab,kw	13099
#5	((cognit* or memory or mental) near/3 (impair* or decline* or deficit* or reduc* or function*)):ti,ab	18089
#6	{or #1-#5}	30564
#7	[mh ^"Primary Prevention"]	1065
#8	prevent*:ti,ab,kw	115159
#9	(protect* or reduc* or delay* or improv* or increas* or decreas*):ti	102653
#10	{or #7-#9}	205354
#11	#6 and #10	5434
#12	[mh Dementia/pc] or [mh ^"Cognitive Dysfunction"/pc] or [mh ^"Cognition Disorders"/pc]	603
#13	[mh ^"Cognitive Reserve"]	8
#14	cognitive reserve:ti,ab,kw	51
#15	{or #11-#14}	5791
#16	[mh "Education, Continuing"]	1209
#17	((continuing or adult) near/2 (education or training)):ti,ab,kw	3051
#18	("lifelong learning" or "life-long learning"):ti,ab,kw	21
#19	[mh ^education] or [mh curriculum] or [mh "education, distance"] or [mh "education, nonprofessional"] or [mh "educational measurement"] or [mh "international educational exchange"] or [mh ^mentoring] or [mh schools] or [mh teaching]	26602
#20	[mh ^Learning]	1962
#21	[mh ^Students]	2250
#22	[mh "Educational Status"]	1407
#23	(learn* or class or classes or course or courses or educat* or school* or train* or seminar* or tutor*):ti	48313
#24	(cognitiv* near/2 (stimulat* or activit*)):ti	246
#25	(learning or ((education or training) near/2 (nonprofessional or non-professional or distance)) or teaching):kw	14622
#26	(late-life near/2 (activity or activities or learn* or school* or educat* or training)):ti,ab,kw	8
#27	{or #16-#26}	75572
#28	#15 and #27	1055
#29	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
#30	#28 not #29	937
#31	#30 Publication Year from 2017 to 2018	106

Embase (10 July 2017)

Embase

Search	Query	Hits
#1	'dementia'/de	97110
#2	'alzheimer disease'/exp	156558
#3	'mild cognitive impairment'/exp	17067
#4	dementia:ti,ab OR alzheimer*:ti,ab	226442
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	221649
#6	#1 OR #2 OR #3 OR #4 OR #5	432689
#7	'primary prevention'/exp	33540
#8	'preventive medicine'/exp	25875
#9	prevent*:ti,ab	1469112
#10	protect*:ti OR reduc*:ti OR delay*:ti OR improv*:ti	850362
#11	#7 OR #8 OR #9 OR #10	2260166
#12	#6 AND #11	49357
#13	'dementia'/dm_pc	1833
#14	'mild cognitive impairment'/exp/dm_pc	90
#15	'alzheimer disease'/exp/dm_pc	4342
#16	#12 OR #13 OR #14 OR #15	52112
#17	'continuing education'/exp OR 'continuing education provider'/exp	29360
#18	((continuing OR adult) NEAR/2 (education OR training)):ti,ab	24617
#19	lifelong learning':ti,ab OR 'life-long learning':ti,ab	1695
#20	'education'/de OR 'adult education'/exp OR 'lifelong learning'/exp OR 'mentoring'/exp OR 'masters education'/exp OR 'postdoctoral education'/exp OR 'postgraduate education'/exp OR 'community college'/exp OR 'university'/exp	466817
#21	learn*:ti OR class:ti OR classes:ti OR course*:ti OR educat*:ti OR school*:ti OR train*:ti OR seminar*:ti OR tutor*:ti	633869
#22	(cognitiv* NEAR/2 (stimulat* OR activit*)):ti	930
#23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	1006895
#24	#16 AND #23	3837
#25	'animal'/exp NOT 'human'/exp	4833576
#26	#24 NOT #25	2924
#27	'groups by age'/exp NOT ('middle aged'/exp OR 'aged'/exp)	5653684
#28	#26 NOT #27	2223
#29	#28 AND [1990-2017]/py	2199
#30	'medication therapy management'/exp OR 'dementia'/exp/dm_dt OR 'pharmaceutical vehicles and additives'/exp	1386295
#31	#29 NOT #30	2022
#32	#31 NOT 'conference abstract'/it	996

Embase (updated 9 April 2018)

No.	Query	Hits
#1	'dementia'/exp	308108
#2	'alzheimer disease'/exp	167836
#3	'mild cognitive impairment'/exp	19554
#4	dementia:ti,ab OR alzheimer*:ti,ab	245698
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	244483
#6	#1 OR #2 OR #3 OR #4 OR #5	519886
#7	'primary prevention'/exp	35604
#8	'preventive medicine'/exp	26670
#9	prevent*:ti,ab	1576370
#10	protect*:ti OR reduc*:ti OR delay*:ti OR improv*:ti OR increas*:ti OR decreas*:ti	1272239
#11	#7 OR #8 OR #9 OR #10	2758722
#12	#6 AND #11	66376
#13	'dementia'/dm_pc	1929
#14	'mild cognitive impairment'/exp/dm_pc	101
#15	'alzheimer disease'/exp/dm_pc	4515
#16	'cognitive reserve'/exp	1346
#17	'cognitive reserve':ti,ab	1463
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	70716
#19	'continuing education'/exp OR 'continuing education provider'/exp	30115
#20	((continuing OR adult) NEAR/2 (education OR training)):ti,ab	25787
#21	'lifelong learning':ti,ab OR 'life-long learning':ti,ab	1820
#22	'education'/de OR 'adult education'/exp OR 'lifelong learning'/exp OR 'mentoring'/exp OR 'masters education'/exp OR 'postdoctoral education'/exp OR 'postgraduate education'/exp OR 'community college'/exp OR 'university'/exp	492706
#23	learn*:ti OR class:ti OR classes:ti OR course*:ti OR educat*:ti OR school*:ti OR train*:ti OR seminar*:ti OR tutor*:ti	669572
#24	(cognitiv* NEAR/2 (stimulat* OR activit*)):ti	1040
#25	('late life' NEAR/2 (activity OR activities OR learn* OR school* OR educat* OR training)):ti,ab	131
#26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1064036
#27	#18 AND #26	5231
#28	'animal'/exp NOT 'human'/exp	5020589
#29	#27 NOT #28	4140
#30	'groups by age'/exp NOT ('middle aged'/exp OR 'aged'/exp)	6115551
#31	#29 NOT #30	3114
#32	'medication therapy management'/exp OR 'dementia'/exp/dm_dt OR 'pharmaceutical vehicles and additives'/exp	1465869
#33	#31 NOT #32	2862
#34	#33 NOT 'conference abstract'/it	1380
#35	#34 AND [1-7-2017]/sd NOT [9-4-2018]/sd	131
#36	#34 AND [2017-2018]/py	174
#37	#35 OR #36	189

CINHAL (10 July 2017)

Search	Query	Limiters/Expanders	Hits
S1	(MH "Dementia") OR (MH "Alzheimer's Disease")	Search modes - Find all my search terms	37751
S2	dementia OR alzheimer*	Search modes - Find all my search terms	46604
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	29346
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	67725
S5	(MH "Preventive Health Care")	Search modes - Find all my search terms	1075
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	170718
S7	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	124328
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	290518
S9	S4 AND S8	Search modes - Find all my search terms	6261
S10	(MH "Dementia/PC") OR (MH "Alzheimer's Disease/PC")	Search modes - Find all my search terms	2009
S11	S9 OR S10	Search modes - Find all my search terms	7692
S12	(MH "Education, Continuing") OR (MH "Continuing Education Providers") OR (MH "Education, Diploma Programs") OR (MH "Education, Continuing (Credit)") OR (MH "Education, Masters") OR (MH "Education, Post-Doctoral")	Search modes - Find all my search terms	87064
S13	(MH "Learning") OR (MH "Lifelong Learning")	Search modes - Find all my search terms	10771
S14	(MH "Education, Nonprofessional") OR (MH "Adult Education") OR (MH "Education, Non-Traditional+")	Search modes - Find all my search terms	7406
S15	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*) OR TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	180228

S16	"lifelong learning" OR "life-long learning" OR ((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	106290
S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	27,763
S18	S11 AND S17	Search modes - Find all my search terms	667
S19	MH "Animal Studies"	Search modes - Find all my search terms	39763
S20	S18 NOT S19	Search modes - Find all my search terms	618
S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	55371
S22	S20 NOT S21	Search modes - Find all my search terms	552
S23	S22	Limiters - Published Date: 19900101-20171231	557

CINHAL (8 April 2018)

Search	Query	Limiters/Expanders	Results
S1	(MH "Dementia") OR (MH "Alzheimer's Disease")	Search modes - Find all my search terms	40,224
S2	dementia OR alzheimer*	Search modes - Find all my search terms	50,090
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	32,856
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	73,809
S5	(MH "Preventive Health Care")	Search modes - Find all my search terms	11,313
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	186,284
S7	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	134,37
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	315,336
S9	S4 AND S8	Search modes - Find all my search terms	7,002
S10	(MH "Dementia/PC") OR (MH "Alzheimer's Disease/PC")	Search modes - Find all my search terms	2,127
S11	S9 OR S10	Search modes - Find all my search terms	8,479
S12	(MH "Education, Continuing") OR (MH "Continuing Education Providers") OR (MH "Education, Diploma Programs") OR (MH "Education, Continuing (Credit)") OR (MH "Education, Masters") OR (MH "Education, Post-Doctoral")	Search modes - Find all my search terms	89,104
S13	(MH "Learning") OR (MH "Lifelong Learning")	Search modes - Find all my search terms	11,971
S14	(MH "Education, Nonprofessional") OR (MH "Adult Education") OR (MH "Education, Non-Traditional+")	Search modes - Find all my search terms	7,799
S15	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*) OR TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	191,967
S16	"lifelong learning" OR "life-long learning" OR ((continuing OR adult) N2 (education OR training)) OR ("late life" N1 (activity OR activities OR learn* OR school* OR educat* OR training))	Search modes - Find all my search terms	109,49

S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	290,595
S18	S11 AND S17	Search modes - Find all my search terms	753
S19	MH "Animal Studies"	Search modes - Find all my search terms	43,810
S20	S18 NOT S19	Search modes - Find all my search terms	691
S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	595,044
S22	S20 NOT S21	Search modes - Find all my search terms	617
S23	S22	Limiters - Published Date: 20170101-	78
S24	S22 AND EM 20170701-	Search modes - Find all my search terms	66
S25	S23 OR S24	Search modes - Find all my search terms	95

ERIC (10 July 2017)

Search	Query	Limiters/Expanders	Hits
S1	DE "Dementia" OR DE "Alzheimers Disease"	Search modes - Find all my search terms	1036
S2	DE "Cognitive Ability"	Search modes - Find all my search terms	8133
S3	dementia OR alzheimer*	Search modes - Find all my search terms	1286
S4	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	6424
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	14489
S6	(DE "Early Intervention" OR DE "Prevention") OR (DE "Preventive Medicine")	Search modes - Find all my search terms	22132
S7	TI prevent* OR AB prevent*	Search modes - Find all my search terms	33142
S8	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	30866
S9	S6 OR S7 OR S8	Search modes - Find all my search terms	71745
S10	S5 AND S9	Search modes - Find all my search terms	828
S11	DE "Adult Education" OR DE "Adult Basic Education" OR DE "Continuing Education" OR DE "Migrant Adult Education" OR DE "Preretirement Education" OR DE "Public School Adult Education" OR DE "Veterans Education"	Search modes - Find all my search terms	56528
S12	DE "Adult Learning" OR DE "Adult Programs" OR DE "Adult Reading Programs" OR DE "High School Equivalency Programs" OR DE "Evening Programs" OR DE "Part Time Students" OR DE "Distance Education" OR DE "Extension Education" OR DE "External Degree Programs" OR DE "Rural Extension" OR DE "Urban Extension"	Search modes - Find all my search terms	35681
S13	(DE "Adult Students") OR (DE "Evening Students")	Search modes - Find all my search terms	7787
S14	((DE "Nonschool Educational Programs") OR (DE "Community Education")) OR (DE "Postsecondary Education" OR DE "Higher Education")	Search modes - Find all my search terms	431319

S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8046
S16	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	555016
S17	TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	94
S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	76187
S19	"lifelong learning" or "life-long learning"	Search modes - Find all my search terms	10135
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	Search modes - Find all my search terms	851728
S21	S10 AND S20	Search modes - Find all my search terms	286
S22	S21	Limiters - Date Published: 19900101-20171231	234

ERIC (8 April 2018)

Search	Query	Limiters/Expanders	Results
S1	DE "Dementia" OR DE "Alzheimers Disease"	Search modes - Find all my search terms	1,075
S2	DE "Cognitive Ability"	Search modes - Find all my search terms	8,553
S3	dementia OR alzheimer*	Search modes - Find all my search terms	1,332
S4	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	6,684
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	15,155
S6	(DE "Early Intervention" OR DE "Prevention") OR (DE "Preventive Medicine")	Search modes - Find all my search terms	22,911
S7	TI prevent* OR AB prevent*	Search modes - Find all my search terms	34,284
S8	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	32,348
S9	S6 OR S7 OR S8	Search modes - Find all my search terms	74,665
S10	S5 AND S9	Search modes - Find all my search terms	873
S11	DE "Adult Education" OR DE "Adult Basic Education" OR DE "Continuing Education" OR DE "Migrant Adult Education" OR DE "Preretirement Education" OR DE "Public School Adult Education" OR DE "Veterans Education"	Search modes - Find all my search terms	57,669
S12	DE "Adult Learning" OR DE "Adult Programs" OR DE "Adult Reading Programs" OR DE "High School Equivalency Programs" OR DE "Evening Programs" OR DE "Part Time Students" OR DE "Distance Education" OR DE "Extension Education" OR DE "External Degree Programs" OR DE "Rural Extension" OR DE "Urban Extension"	Search modes - Find all my search terms	36,853
S13	(DE "Adult Students") OR (DE "Evening Students")	Search modes - Find all my search terms	8,01
S14	((DE "Nonschool Educational Programs") OR (DE "Community Education")) OR (DE "Postsecondary Education" OR DE "Higher Education")	Search modes - Find all my search terms	452,212
S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8,311
S16	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	579,695

S17	TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	102
S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	77,861
S19	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	17
S20	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	10,521
S21	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Find all my search terms	887,984
S22	S10 AND S21	Search modes - Find all my search terms	309
S23	S22	Limiters - Date Published: 20170101-	16
S24	S22 AND EM 20170701-	Search modes - Find all my search terms	0
S25	S23 OR S24	Search modes - Find all my search terms	16

PsycINFO (11 July 2017)

Search	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	39,900
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	30,409
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	65,198
S5	DE "Prevention" OR DE "Preventive Medicine" OR DE "Primary Mental Health Prevention"	Search modes - Find all my search terms	30,316
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	186,041
S7	TI protect* OR reduc* OR delay* OR improv*	Search modes - Find all my search terms	743,335
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	869,214
S9	S4 AND S8	Search modes - Find all my search terms	21,587
S10	DE "Adult Education" OR DE "Continuing Education"	Search modes - Find all my search terms	4,126
S11	TI (learning OR education OR educational OR training)	Search modes - Find all my search terms	259,848
S12	TI cognitiv* N1 (stimulat* OR activit*)	Search modes - Find all my search terms	751
S13	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	2,995
S14	(continuing OR adult) N2 (education OR training)	Search modes - Find all my search terms	15,241
S15	S9 AND S11	Search modes - Find all my search terms	826
S16	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,626,731
S17	S15 NOT S16	Search modes - Find all my search terms	683
S18	(DE "Health Education") OR (DE "Drug Therapy") OR (DE "Animals") OR DE "Animal Models" OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	454,796
S19	S17 NOT S18	Search modes - Find all my search terms	414
S20	S17 NOT S18	Limiters - Published Date: 19900101-20171231	403

PsycINFO (9 April 2018)

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	41,992
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	32,064
S4	dementia OR alzheimer*	Search modes - Find all my search terms	99,018
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	146,484
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	210,638
S7	DE "Prevention" OR DE "Preventive Medicine" OR DE "Primary Mental Health Prevention"	Search modes - Find all my search terms	31,621
S8	TI prevent* OR AB prevent*	Search modes - Find all my search terms	195,469
S9	TI protect* OR reduc* OR delay* OR improv*	Search modes - Find all my search terms	783,317
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	914,878
S11	S6 AND S10	Search modes - Find all my search terms	71,575
S12	DE "Cognitive Reserve"	Search modes - Find all my search terms	353
S13	"Cognitive Reserve"	Search modes - Find all my search terms	985
S14	S11 OR S12 OR S13	Search modes - Find all my search terms	72,193
S15	DE "Adult Education" OR DE "Continuing Education"	Search modes - Find all my search terms	4,2
S16	TI (learning OR education OR educational OR training)	Search modes - Find all my search terms	269,992
S17	TI cognitiv* N1 (stimulat* OR activit*)	Search modes - Find all my search terms	794
S18	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	3,169
S19	(continuing OR adult) N2 (education OR training)	Search modes - Find all my search terms	15,885
S20	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	159
S21	S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Find all my search terms	281,675

S22	S14 AND S21	Search modes - Find all my search terms	4,549
S23	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,695,649
S24	S22 NOT S23	Search modes - Find all my search terms	3,295
S25	(DE "Health Education") OR (DE "Drug Therapy") OR (DE "Animals") OR DE "Animal Models" OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	465,312
S26	S24 NOT S25	Search modes - Find all my search terms	2,094
S27	S26	Limiters - Publication Year: 2017-	276
S28	S26 AND RD 201707-	Search modes - Find all my search terms	197
S29	S27 OR S28	Search modes - Find all my search terms	299

ClinicalTrials.gov (16 May 2017)

280 studies found for: (prevention OR reduction OR risk OR improvement) AND (dementia OR alzheimer OR "cognitive impairment" OR "cognitive decline") | healthy OR aged OR adult OR cognitive | education OR learning OR lesson OR educational OR class OR mental OR cognitive | Adult, Senior | Studies that accept healthy volunteers

ClinicalTrials.gov (9 April 2018)

58 Studies found for: (prevention OR reduction OR risk OR improvement) AND (dementia OR alzheimer OR "cognitive impairment" OR "cognitive decline") | healthy OR aged OR adult OR cognitive | education OR learning OR lesson OR educational OR class OR mental OR cognitive | Adult, Senior | Studies that accept healthy volunteers | First posted from 05/01/2017 to 04/09/2018

ICTRP (16 May 2017)

ICTRP		
Search 1	21 records for 20 trials found for:	dementia AND education* AND prevent* OR alzheimer AND education* AND prevent* OR cognitive impairment AND education* AND prevent*
Search 2	3 records for 3 trials found for:	dementia AND mental activ* AND prevent* OR alzheimer AND mental activ* AND prevent* OR cognitive impairment AND mental activ* AND prevent*
Search 3	3 records for 3 trials found for:	dementia AND cognitive stimulat* AND prevent* OR alzheimer AND cognitive stimulat* AND prevent* OR cognitive impairment AND cognitive stimulat* AND prevent*
Search 4	11 records for 11 trials found for:	dementia AND learning AND prevent* OR alzheimer AND learning AND prevent* OR cognitive impairment AND learning AND prevent*
Search 5	No results were found for:	dementia AND lesson* AND prevent* OR alzheimer AND lesson* AND prevent* OR cognitive impairment AND lesson* AND prevent*
Search 6	45 records for 45 trials found for:	dementia AND training AND prevent* OR alzheimer AND training AND prevent* OR cognitive impairment AND training AND prevent*
SUM	**82**	

ICTRP (9 April 2018)

Search 1	20	dementia AND education* AND prevent* OR alzheimer AND education* AND prevent* OR cognitive impairment AND education* AND prevent*
Search 2	3	dementia AND mental activ* AND prevent* OR alzheimer AND mental activ* AND prevent* OR cognitive impairment AND mental activ* AND prevent*
Search 3	5	dementia AND cognitive stimulat* AND prevent* OR alzheimer AND cognitive stimulat* AND prevent* OR cognitive impairment AND cognitive stimulat* AND prevent*
Search 4	27	dementia AND learning AND prevent* OR alzheimer AND learning AND prevent* OR cognitive impairment AND learning AND prevent*
Search 5	1	dementia AND lesson* AND prevent* OR alzheimer AND lesson* AND prevent* OR cognitive impairment AND lesson* AND prevent*
Search 6	64	dementia AND training AND prevent* OR alzheimer AND training AND prevent* OR cognitive impairment AND training AND prevent*
SUM	120	

ALOIS (15 May 2017)

ALOIS		
Study Aim:	Cognitive Enhancement (healthy); Primary Prevention	
Intervention type:	Non-pharmacological	
Intervention:	Contains any word	learning education educational

18 Studies found

ALOIS (9 April 2018)

Not searched website down

DART-Europe (16 May 2017)

search	reults
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimualtion") AND (prevent* OR improve*)	43

DART-Europe (8 April 2018)

search	reults
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimualtion") AND (prevent* OR improve*)	56
YEAR: 2017	4

Supplementary file 4: Search Strategies of Overview of Systematic Reviews, by database

Medline (via PubMed): 10 July 2017

#	Suchen	Ergebnisse
1	Dementia/ or exp Alzheimer Disease/	117573
2	Cognitive Dysfunction/	5969
3	Cognition/	81563
4	(dementia or alzheimer*).ti,ab.	175194
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	167110
6	or/1-5	371089
7	exp Leisure Activities/	209051
8	leisure.ti,ab.	13073
9	(hobby or hobbies).ti,ab.	1465
10	free time.ti,ab.	1405
11	Recreation.ti,ab.	4826
12	(in-door or out-door or indoor or outdoor).ti.	8929
13	(garden* or horticultur*).ti.	3216
14	(play* or game? or gaming).ti.	46562
15	(creativ* or painting or drawing or reading).ti.	24387
16	(voluntary or volunteer* or extracurricular).ti.	32266
17	or/7-16	321695
18	6 and 17	9189
19	exp age groups/ not (exp aged/ or middle aged/)	3712487
20	18 not 19	6496
21	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	118333
22	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.	15710
23	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.	145368
24	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	117882
25	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.	171997

26	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.	167686
27	21 or 22 or 23 or 24 or 25 or 26	412039
28	27 not (case report/ or letter.pt.)	401602
29	20 and 28	243
30	remove duplicates from 29	229

Medline (via PubMed): 4 April 2018

#	Searches	Results
1	Dementia/ or exp Alzheimer Disease/	118622
2	Cognitive Dysfunction/	7904
3	Cognition/	82628
4	Cognitive Reserve/	388
5	(dementia or alzheimer*).ti,ab.	179042
6	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	171766
7	or/1-6	378437
8	exp Leisure Activities/	207917
9	leisure.ti,ab.	13201
10	(hobby or hobbies).ti,ab.	1472
11	free time.ti,ab.	1429
12	Recreation.ti,ab.	4900
13	(in-door or out-door or indoor or outdoor).ti.	9232
14	(garden* or horticultur*).ti.	3312
15	(play* or game? or gaming).ti.	47658
16	(creativ* or painting or drawing or reading).ti.	24235
17	(voluntary or volunteer* or extracurricular).ti.	32218
18	(cognitiv* adj2 (activity or activities)).ti.	521
19	or/8-18	322366
20	7 and 19	9826
21	exp age groups/ not (exp aged/ or middle aged/)	3685197
22	20 not 21	6996
23	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	126873
24	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.	15689
25	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.	151505
26	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	125835
27	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.	184250

28	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.	168915
29	23 or 24 or 25 or 26 or 27 or 28	425049
30	29 not (case report/ or letter.pt.)	414173
31	22 and 30	283
32	("2017/07*" or "2017/08*" or "2017/09*" or "2017/1*" or 2018*).dt.	947449
33	(201707* or 201708* or 201709* or 20171* or 2018*).ed.	745570
34	32 or 33	1543513
35	31 and 34	53
36	remove duplicates from 35	52

Embase: 17 Juli 2017

No.	Query	Results
#1	'alzheimer disease'/exp	158632
#2	'mild cognitive impairment'/exp	17483
#3	'dementia'/de	98402
#4	dementia:ti,ab OR alzheimer*:ti,ab	230453
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	226651
#6	#1 OR #2 OR #3 OR #4 OR #5	440912
#7	'recreation'/exp	57806
#8	leisure:ti,ab	16016
#9	hobby:ti,ab OR hobbies:ti,ab	2028
#10	'free time':ti,ab	1939
#11	recreation:ti,ab	6442
#12	'in door':ti OR 'out door':ti OR indoor:ti OR outdoor:ti	11551
#13	garden*:ti OR horticultur*:ti	3581
#14	play*:ti OR game:ti OR games:ti OR gaming:ti	52543
#15	creativ*:ti OR painting:ti OR drawing:ti OR reading:ti	25887
#16	voluntary:ti OR volunteer*:ti OR extracurricular:ti	38793
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	196912
#18	#6 AND #17	5027
#19	'groups by age'/exp AND ('middle aged'/exp OR 'aged'/exp)	3258589
#20	#18 NOT #19	3277
#21	systematic review'/exp OR 'meta analysis'/exp	211886
#22	meta analys*':ti,ab OR metaanalys*:ti,ab OR 'meta synth*':ti,ab OR metasynth*:ti,ab OR ((systematic* OR quantitativ* OR methodologic*) NEAR/5 (review* OR overview* OR synthes*)):ti,ab	239389
#23	systematic:ti OR structured:ti OR evidence:ti OR trials:ti AND (review:ti OR overview:ti OR look:ti OR examination:ti OR update*:ti OR summary:ti)	98173
#24	#21 OR #22 OR #23	306796
#25	#24 NOT ('case report'/exp OR 'case study'/exp)	301911
#26	#20 AND #25	128

Embase: 4 April 2018

No.	Query	Results
#1	'alzheimer disease'/exp	167669
#2	'mild cognitive impairment'/exp OR 'dementia'/de	115768
#3	'cognitive reserve'/de	1341
#4	dementia:ti,ab OR alzheimer*:ti,ab	245434
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	244167
#6	#1 OR #2 OR #3 OR #4 OR #5	470026
#7	'recreation'/exp	61588
#8	leisure:ti,ab	16979
#9	hobby:ti,ab OR hobbies:ti,ab	2145
#10	'free time':ti,ab	2061
#11	recreation:ti,ab	6767
#12	'in door':ti OR 'out door':ti OR indoor:ti OR outdoor:ti	12183
#13	garden*:ti OR horticultur*:ti	3745
#14	play*:ti OR game:ti OR games:ti OR gaming:ti	55639
#15	creativ*:ti OR painting:ti OR drawing:ti OR reading:ti	26738
#16	voluntary:ti OR volunteer*:ti OR extracurricular:ti OR ((cognitiv* NEAR/2 (activity OR activities)):ti)	39956
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	207154
#18	#6 AND #17	5442
#19	'groups by age'/exp AND ('middle aged'/exp OR 'aged'/exp)	3451202
#20	#18 NOT #19	3533
#21	'systematic review'/exp OR 'meta analysis'/exp	239710
#22	'meta analys*':ti,ab OR metaanalys*:ti,ab OR 'meta synth*':ti,ab OR metasynth*:ti,ab OR (((systematic* OR quantitativ* OR methodologic*) NEAR/5 (review* OR overview* OR synthes*)):ti,ab)	267896
#23	(systematic:ti OR structured:ti OR evidence:ti OR trials:ti) AND (review:ti OR overview:ti OR look:ti OR examination:ti OR update*:ti OR summary:ti)	112383
#24	#21 OR #22 OR #23	342728
#25	#24 NOT ('case report'/exp OR 'case study'/exp)	337160
#26	#20 AND #25	145
#27	#26 AND [1-7-2017]/sd NOT [5-4-2018]/sd	26
#28	#26 AND [2017-2018]/py	30
#29	#27 OR #28	35

CINAHL (Ebsco): 17 July 2017

#	Query	Limiters/Expanders	Results
S1	(MH "Alzheimer's Disease") OR (MH "Dementia")	Search modes - Find all my search terms	38,358
S2	dementia OR alzheimer*	Search modes - Find all my search terms	47,332
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	30,037
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	68,971
S5	(MH "Leisure Activities+")	Search modes - Find all my search terms	36,998
S6	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	11,096
S7	TI in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular	Search modes - Find all my search terms	31,628
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	69,497
S9	S4 AND S8	Search modes - Find all my search terms	2,053
S10	MH "Animal Studies"	Search modes - Find all my search terms	41,599
S11	S9 NOT S10	Search modes - Find all my search terms	2,051
S12	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	564,745
S13	S11 NOT S12	Search modes - Find all my search terms	1,855
S14	(MH "Systematic Review") OR (MH "Meta Analysis")	Search modes - Find all my search terms	42,089
S15	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	31,338
S16	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Boolean/Phrase	55,272
S17	TI (systematic OR structured OR evidence OR trials) AND (review OR overview OR look OR examination OR update* OR summary)	Search modes - Boolean/Phrase	27,392
S18	S14 OR S15 OR S16 OR S17	Search modes - Find all my search terms	72,333
S19	S13 AND S18	Search modes - Find all my search terms	71

CINAHL (Ebsco): 4 April 2018

#	Query	Limiters/Expanders	Results
S1	(MH "Alzheimer's Disease") OR (MH "Dementia")	Search modes - Find all my search terms	40,163
S2	dementia OR alzheimer*	Search modes - Find all my search terms	50,045
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	32,819
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	73,730
S5	(MH "Leisure Activities+")	Search modes - Find all my search terms	39,894
S6	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	11,740
S7	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR oluntary OR volunteer* OR extracurricular) OR TI (cognitiv* W1 (activity OR activities))	Search modes - Find all my search terms	33,266
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	73,940
S9	S4 AND S8	Search modes - Find all my search terms	2,298
S10	MH "Animal Studies"	Search modes - Find all my search terms	43,752
S11	S9 NOT S10	Search modes - Find all my search terms	2,295
S12	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	594,058
S13	S11 NOT S12	Search modes - Find all my search terms	2,079
S14	(MH "Systematic Review") OR (MH "Meta Analysis")	Search modes - Find all my search terms	50,503
S15	meta-analys* OR meta analys* OR metaanalys* OR	Search modes - Boolean/Phrase	34,556

	meta synth* OR meta-synth* OR metasynth*		
S16	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Boolean/Phrase	63,373
S17	TI (systematic OR structured OR evidence OR trials) AND (review OR overview OR look OR examination OR update* OR summary)	Search modes - Boolean/Phrase	30,586
S18	S14 OR S15 OR S16 OR S17	Search modes - Find all my search terms	81,245
S19	S13 AND S18	Search modes - Find all my search terms	93
S20		Limiters - Published Date: 20170701- Search modes - Find all my search terms	156,794
S21	EM 20170701-	Search modes - Find all my search terms	208,855
S22	S20 OR S21	Search modes - Find all my search terms	253,372
S23	S22 AND S19	Search modes - Find all my search terms	27

PsycINFO (Ebsco): 18 July 2017

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	39,908
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	30,416
S4	dementia OR alzheimer*	Search modes - Find all my search terms	94,008
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	138,651
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	200,033
S7	(((((DE "Leisure Time") OR (DE "Hobbies")) AND (DE "Recreation" OR DE "Clubs (Social Organizations)" OR DE "Traveling" OR DE "Vacationing")) OR (DE "Gambling")) AND (DE "Games" OR DE "Chess" OR DE "Computer Games"))	Search modes - Find all my search terms	347
S8	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	37,212
S9	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular) OR SU (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)	Search modes - Find all my search terms	175,457
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	207,264
S11	S6 AND S10	Search modes - Find all my search terms	5,662
S12	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,627,211
S13	S11 NOT S12	Search modes - Find all my search terms	3,357
S14	(DE "Animals") OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	311,593
S15	S13 NOT S14	Search modes - Find all my search terms	3,212

S16	(DE "Drug Therapy")	Search modes - Find all my search terms	127,11
S17	S15 NOT S16	Search modes - Find all my search terms	3,161
S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,026
S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	27,695
S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	27,454
S21	TI (systematic OR structured OR evidence OR trials) AND TI (review OR overview OR look OR examination OR update* OR summary)	Search modes - Find all my search terms	16,949
S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	51,681
S23	S17 AND S22	Search modes - Find all my search terms	73

PsycINFO (Ebsco): 5 April 2018

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	41,959
S2	DE "Senile Dementia" OR DE "Cognitive Impairment"	Search modes - Find all my search terms	33,077
S3	DE "Cognitive Reserve"	Search modes - Find all my search terms	353
S4	dementia OR alzheimer*	Search modes - Find all my search terms	98,945
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	146,379
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	210,573
S7	(((((DE "Leisure Time") OR (DE "Hobbies")) AND (DE "Recreation" OR DE "Clubs (Social Organizations)" OR DE "Traveling" OR DE "Vacationing")) OR (DE "Gambling")) AND (DE "Games" OR DE "Chess" OR DE "Computer Games"))	Search modes - Find all my search terms	358
S8	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	39,017
S9	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular OR (cognitiv* W1 activit*)) OR SU (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular OR (cognitiv* W1 activit*))	Search modes - Find all my search terms	182,299
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	215,667
S11	S6 AND S10	Search modes - Find all my search terms	6,166
S12	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,695,146

S13	S11 NOT S12	Search modes - Find all my search terms	3,706
S14	(DE "Animals") OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	318,343
S15	S13 NOT S14	Search modes - Find all my search terms	3,539
S16	(DE "Drug Therapy")	Search modes - Find all my search terms	129,812
S17	S15 NOT S16	Search modes - Find all my search terms	3,481
S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,152
S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	30,127
S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	30,748
S21	TI (systematic OR structured OR evidence OR trials) AND TI (review OR overview OR look OR examination OR update* OR summary)	Search modes - Find all my search terms	19,166
S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	56,448
S23	S17 AND S22	Search modes - Find all my search terms	84
S24	RD 201707-	Search modes - Find all my search terms	148,956
S25	DT 201707-	Search modes - Find all my search terms	100,982
S26	S24 OR S25	Search modes - Find all my search terms	159,715
S27	S23 AND S26	Search modes - Find all my search terms	13

Epistemonikos 18. Juli 2017

Search	Results
(dementia OR alzheimer* OR cognitiv*) AND (leisure OR recreation OR "free time" OR hobby OR hobbies OR (title:(in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)))	273
Filter: Systematic Review	64

Epistemonikos 18. Juli 2017

Search	Results
(dementia OR alzheimer* OR cognitiv*) AND (leisure OR recreation OR "free time" OR hobby OR hobbies OR (title:(in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)))	368
Filter: Systematic Review	146
Added to database: 01-07-17 to 05-04-18	25

Cochrane Library: 18. Juli 2017

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4053
#2	[mh ^"Cognitive Dysfunction"]	181
#3	[mh ^Cognition]	6276
#4	(dementia or alzheimer*):ti,ab,kw	11879
#5	((cognit* or memory or mental) next (impair* or decline* or deficit* or reduc* or function*)):ti,ab,kw	12722
#6	{or #1-#5}	25014
#7	[mh "Leisure Activities"]	15395
#8	leisure:ti,ab,kw	1481
#9	(hobby or hobbies):ti,ab,kw	55
#10	"free time":ti,ab,kw	162
#11	Recreation:ti,ab,kw	615
#12	(in-door or out-door or indoor or outdoor):ti,kw	478
#13	(garden* or horticultur*):ti,kw	106
#14	(play* or game* or gaming):ti,kw	3280
#15	(creativ* or painting or drawing or reading):ti,kw	2913
#16	(voluntary or volunteer* or extracurricular):ti,kw	17942
#17	{or #7-#16}	39978
#18	#6 and #17	1551
#19	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	104634
#20	#18 not #19 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	38

Cochrane Library: 5. April 2018

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4263
#2	[mh ^"Cognitive Dysfunction"]	450
#3	[mh ^Cognition]	6675
#4	[mh ^"Cognitive Reserve"]	8
#5	(dementia or alzheimer*):ti,ab,kw	13099
#6	((cognit* or memory or mental) next (impair* or decline* or deficit* or reduc* or function*)):ti,ab,kw	14315
#7	{or #1-#6}	27581
#8	[mh "Leisure Activities"]	16504
#9	leisure:ti,ab,kw	1683
#10	(hobby or hobbies):ti,ab,kw	59
#11	free time:ti,ab,kw	169
#12	Recreation:ti,ab,kw	674
#13	(in-door or out-door or indoor or outdoor):ti,kw	541

#14	(garden* or horticultur*):ti,kw	125
#15	(play* or game* or gaming):ti,kw	3653
#16	(creativ* or painting or drawing or reading):ti,kw	3482
#17	(voluntary or volunteer* or extracurricular):ti,kw	20037
#18	(cognitiv* near/2 (activity or activities)):ti,kw	80
#19	{or #8-#18}	44252
#20	#7 and #19	1838
#21	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
#22	#20 not #21 Publication Year from 2017 to 2018, in Cochrane Reviews (Reviews and Protocols) and Technology Assessments	1

Supplementary file 5: Risk of Bias of included studies

Systematic reviews

Author, Year	RISK OF BIAS	Dual Screening and Extraction	Comprehensive literature search	Study quality assessed	'A priori' design	Grey literature included	List of studies	Study characteristics provided	Scientific quality used appropriately	Appropriate methods to combine findings	Publication bias	Conflict of interest included	Reason for High Risk of Bias Decision
Di Marco et al., 2014 [41]	High	NR	Yes	No	Yes	No	No	No	NA	Yes	No	No	No information on screening methods or dual extraction No risk of bias assessment
Opdebeeck et al., 2016 [42]	High	Yes	Yes	No	Yes	Yes	No	Yes	NA	Yes	No	No	No risk of bias assessment No assessment of Publication bias
Sajeev et al., 2016 [43]	Medium	NR	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No information on dual screening or dual extraction
Toril et al., 2014 [44]	High	NR	Yes	No	Yes	No	No	Yes	NA	Yes	Yes	No	No information on screening methods or dual extraction No risk of bias assessment
Yates et al., 2016 [45]	Medium	NR	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No (too few studies)	Yes	No information on dual screening or dual extraction

NA = not applicable, NR = not reported

Supplementary file 6: List of excluded studies during full text screening

Systematic review:

Study	Title	Reason for Exclusion
Canadian Nursing Home, 2007	Studies confirm link between late-life cognitive activities and reduced risk of dementia	Not retrievable
Adam et al., 2013	Occupational activity and cognitive reserve: implications in terms of prevention of cognitive aging and Alzheimer's disease	Ineligible study design
GM: Midlife & Beyond, 2017	Study finds education does not protect against cognitive decline in later life	Ineligible study design
Dowd et al., 2003	Can mental and physical activities such as chess and gardening help in the prevention and treatment of Alzheimer's? Healthy aging through stimulation of the mind	Ineligible study design
Beydoun et al., 2014	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Ineligible study design
Gilland, 2007	Continuing education topic 4: dementia	Ineligible study design
Nursing Standard, 2010	Clinical digest. Cognitive stimulation delays dementia but later decline is faster	Ineligible publication type
Albert et al., 2007	Changing the trajectory of cognitive decline?	Ineligible publication type
Bak et al., 2016	Language lessons to help protect against dementia	Ineligible publication type
Bauer et al., 2002	RN news watch: clinical highlights. Mentally stimulating activities seem to cut Alzheimer's risk	Ineligible publication type
Burgener et al., 2009	Effectiveness of community-based, nonpharmacological interventions for early-stage dementia: conclusions and recommendations	Ineligible publication type
Gatz et al., 2005	Educating the brain to avoid dementia: can mental exercise prevent Alzheimer disease?	Ineligible publication type
Rosenberg et al., 2017	Influence of apoe, age, sex, education and baseline cognition on intervention effects on cognition in the finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)	Ineligible publication type
Summers et al., 2013	The Tasmanian Healthy Brain Project (THBP): a prospective longitudinal examination of the effect of university-level education in older adults in preventing age-related cognitive	Ineligible publication type
Wahlund et al., 2006	[Life-long mental exercise can prevent Alzheimer disease]	Ineligible publication type
ACTRN126120001 47886, 2012	The Body, Brain, Life Program â€“a prevention trial to reduce risk of Alzheimer's Disease	Ineligible intervention
Anon et al., 2008	The Study of Mental Activity and Regular Training for the Prevention of Cognitive Decline in at Risk Individuals: The SMART Trial Or The Study of Mental Activity and Regular	Ineligible intervention
Brenes et al., 2003	Cognitive training may improve targeted cognitive functions in older adults	Ineligible intervention
Fratiglioni et al., 2007	Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project	Ineligible intervention
Gatz et al., 2006	Lifestyle risk and delaying factors	Ineligible intervention
Hall et al., 2009	Cognitive activities delay onset of memory decline in persons who develop dementia	Ineligible intervention
Harmanci et al., 2003	Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey	Ineligible intervention
Harmanci et al., 2003	Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey	Ineligible intervention
Kwok et al., 2011	Effectiveness of coordination exercise in improving cognitive function in older adults: a prospective study	Ineligible intervention
Le Carret et al., 2003	The effect of education on cognitive performances and its implication for the constitution of the cognitive reserve	Ineligible intervention
Merom et al., 2016	Cognitive benefits of social dancing and walking in old age: The dancing mind randomized controlled trial	Ineligible intervention
Roberts et al., 2015	Risk and protective factors for cognitive impairment in persons aged 85 years and older	Ineligible intervention
Sandro et al., 2008	Risk-reducing effect of education in Alzheimer's disease	Ineligible intervention
Sattler et al., 2012	Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease	Ineligible intervention
Schultz et al., 2015	Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease	Ineligible intervention
Soubelet et al., 2011	Engaging in cultural activities compensates for educational differences in cognitive abilities	Ineligible intervention

Standford University, 2012	Activities for Cognitive Enhancement of Seniors	Ineligible intervention
Then et al., 2016	Education as protector against dementia, but what exactly do we mean by education?	Ineligible intervention
University Hospital 2016	Long-term Effects of Interventional Strategies to Prevent Cognitive Decline in Elderly	Ineligible intervention
VanDijk et al., 2008	No protective effects of education during normal cognitive aging: results from the 6-year follow-up of the Maastricht Aging Study	Ineligible intervention
Vemuri et al., 2014	Association of lifetime intellectual enrichment with cognitive decline in the older population	Ineligible intervention
Wang et al., 2002	Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project	Ineligible intervention
Yaffe et al., 2009	Predictors of maintaining cognitive function in older adults: the Health ABC study	Ineligible intervention
Kliegel et al., 2004	Life-long intellectual activities mediate the predictive effect of early education on cognitive impairment in centenarians: A retrospective study	Ineligible populations
Jonaitis et al., 2013	Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease	Ineligible populations
Friedland et al., 2001	Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members	No information about the intervention
National University,	Choral Singing For the Prevention of Dementia	not finished study
Marquez et al., 2017	Regular Latin Dancing and Health Education may Improve Cognition of Late Middle-Aged and Older Latinos	Ineligible comparison;
University Hospital 2018	Prospective Population Based Cohort Study on Cognitive and Cardiovascular Aging (MonaLisaPredor)	not finished study;
Janssen Research Development 2018	Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research: Prospective Readiness Cohort Study	not finished study
ACTRN126170008 58392 2017	Ageing and Folk Dances from the Basque Country: Functional and neuropsychological changes. A controlled trial.	Ineligible intervention
Biasutti et al., 2018	Assessing a cognitive music training for older participants: a randomised controlled trial	Ineligible population
Centre de Recherche del'Institut Universitaire de Geriatriede. 2018	Impact of a Cognitive Intervention Enriched With Leisure Activities in Persons With Subjective Cognitive Decline	Not finished study
Chan et al., 2016	Training Older Adults to Use Tablet Computers: Does It Enhance Cognitive Function?	Ineligible study design
Ihle et al., 2017	The relation of education and cognitive activity to mini-mental state in old age: The role of functional fitness status	Ineligible intervention
Krell-Roesch et al., 2017	Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE epsilon4 Genotype	Ineligible intervention
NCT02919748, 2016	Choral Singing For the Prevention of Dementia	Not finished study
Ramos et al., 2017	Does learning a language in the elderly enhance switching ability?	Ineligible outcome
Wang et al., 2017	Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study	Ineligible intervention
Zanesco et al., 2018	Mental training of attention through intensive meditation: Longitudinal behavioral and electrophysiological investigations of visual sustained attention and response inhibition	Not retreivable
Zhu et al., 2017	Leisure activities, education, and cognitive impairment in Chinese older adults: A population-based longitudinal study	Ineligible intervention
2017	Study suggests late-life activities reduce the risk of mild cognitive impairment	Ineligible study design

Overview of Systematic Reviews

Study	Title	Reason for Exclusion
Bernhardt et al., 2002	[The effect of psychosocial factors on risk of dementia]	Ineligible intervention
Bleakley et al., 2015	Gaming for health: a systematic review of the physical and cognitive effects of interactive computer games in older adults	Ineligible intervention
Conti et al., 2009	The potential role of leisure in the prevention of dementia	Not retreivable
Fratiglioni et al., 2004	An active and socially integrated lifestyle in late life might protect against dementia	Ineligible study design
Karkou et al., 2017	Dance movement therapy for dementia	Ineligible population
Lee et al., 2019	Systematic review of health behavioral risks and cognitive health in older adults	Ineligible intervention
Liapis et al., 2017	Meaningful use of computers has a potential therapeutic and preventative role in dementia care: A systematic review	Ineligible intervention
Munn et al., 2010	Review summaries: evidence for nursing practice. Cognitive leisure activities and their role in preventing dementia: a systematic review	Ineligible publication type
Opdebeeck et al., 2014	Cognitive reserve and cognitive function: A meta-analysis	Ineligible publication type
Stephen et al., 2017	Physical Activity and Alzheimer's Disease: A Systematic Review	Ineligible intervention
Stern et al., 2010	Cognitive leisure activities and their role in preventing dementia: a systematic review	Study superseeded by more recent study
Stern et al., 2009	Cognitive leisure activities and their role in preventing dementia: a systematic review	Ineligible publication type
Wang et al., 2012	Leisure activities, cognition and dementia	Study superseeded by more recent study
Wayne et al., 2014	Effect of tai chi on cognitive performance in older adults: systematic review and meta-analysis	Ineligible intervention
Zheng et al., 2015	Tai Chi and the Protection of Cognitive Ability: A Systematic Review of Prospective Studies in Healthy Adults	Ineligible intervention
Fallahpour et al., 2016	Leisure-activity participation to prevent later-life cognitive decline: a systematic review	Study superseeded by more recent study (search only till 2011)
Bediou et al., 2018	Meta-Analysis of Action Video Game Impact on Perceptual, Attentional, and Cognitive Skills	Ineligible population
Howes et al., 2017	Gaming for Health: Systematic Review and Meta-analysis of the Physical and Cognitive Effects of Active Computer Gaming in Older Adults	Inelgiible intervention
Klimova et al., 2017	Cognitive decline in normal aging and its prevention: a review on non-pharmacological lifestyle strategies	Ineligible intervention
Schneider et al., 2018	Potential Cognitive Benefits From Playing Music Among Cognitively Intact Older Adults: A Scoping Review	Ineligible study design
Solloway et al., 2016	An evidence map of the effect of Tai Chi on health outcomes	Ineligible study design
Wouters et al., 2013	A meta-analysis of the cognitive and motivational effects of serious games	Ineligible study design
Zhang et al., 2016	Physical and Cognitive Impacts of Digital Games on Older Adults: A Meta-Analytic Review	Ineligible intervention

GRADE of Recommendations:

Cognitive leisure activities compared to no cognitive leisure activities for the prevention of dementia (OPDEBEEK et al.)

Patient or population: over 60 years, non-demented adults at baseline

Intervention: cognitive leisure activities

Comparison: no cognitive leisure activities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no cognitive leisure activities	**Risk with cognitive leisure activities**				
Overall cognitive functioning	The mean overall cognitive functioning was **0** SD	The mean overall cognitive functioning in the intervention group was 0,26 SD higher (0,21 higher to 0,31 higher)	-	(31 observational studies)	⨁◯◯◯ VERY LOW [a,b]	

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

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

Explanations

a. I^2 = 94%, b. Interventions vary between studies

Video Games compared to no Video Games for the prevention of dementia (TORIL et al.)

Patient or population: 50-86 years, healthy older adults

Intervention: Video Games

Comparison: no Video Games

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no Video Games	Risk with Video Games				
Cognitive Function	-	-	-	913 (20 observational studies)	⨁◯◯◯ VERY LOW [a]	

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

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

Explanations

a. Mixing various different interventions and study designs

Cognitive leisure activities compared to no cognitive leisure activities for healthy older adults (YATES et al.)

Patient or population: over 46 years, healthy older adults, **Intervention**: cognitive leisure activities, **Comparison**: no cognitive leisure activities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no cognitive leisure activities	Risk with cognitive leisure activities				
Incidence of AD	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 0.610** (0.418 to 0.900)	(3 observational studies)	⨁◯◯◯ VERY LOW [a,b]	
Incidence of AD	0 per 1.000	**NaN per 1.000** (NaN to NaN)	**HR 0.584** (0.462 to 0.739)	(2 observational studies)	⨁◯◯◯ VERY LOW [b]	
Incidence of AD	**Low**		**OR 0.775** (0.668 to 0.899)	0 cases 0 controls (2 observational studies)	⨁◯◯◯ VERY LOW [b,c]	
	0 per 1.000	**0 per 1.000** (0 to 0)				
Incidence of cognitive impairment	0 per 1.000	**0 per 1.000** (0 to 0)	**OR 0.685** (0.550 to 0.845)	(5 observational studies)	⨁◯◯◯ VERY LOW [b]	
Incidence of cognitive impairment	0 per 1.000	**NaN per 1.000** (NaN to NaN)	**HR 0.853** (0.711 to 1.022)	(3 observational studies)	⨁◯◯◯ VERY LOW [b,c]	

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

Explanations

a. moderate heterogeneity, x^2 test p=0.09, b. differences in interventions (definition of cognitive leisure activities varies across studies), c. high heterogeneity, x^2 test p=0.00, confidence intervals do not overlap

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 (line 1-3)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4 (line 40-67)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-7 (line 127-132)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7 (line 133-144)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 7 (line 149-151)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8-9 (line 171-196)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9-10 (line 197-214)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 3 and 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10 (line 215-218)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10 (line 219-226)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10 (line 222-226)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10-11 (line 227-233)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 11 (line 234-240)

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 11 (line 234-240)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11 (line 238-243) Figure 2 and figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-12 (line 255-278) Table 1 and table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13-14 Table 1 and table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-17 (line 288-351) Table 1 and table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12 (line 264-266; line 273-278) Supplementary file 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 18

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21 (line 423-425)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Continuing Education for the Prevention of Mild Cognitive Impairment and Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic Reviews.

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Continuing Education for the Prevention of Mild Cognitive Impairment and Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic Reviews.

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ABSTRACT

Objective: To summarize evidence on the preventive effects of continuing education on mild cognitive impairment and Alzheimer's-type dementia in adults 45 years or older.

Design: Systematic review and overview of systematic reviews.

Data sources: We systematically searched MEDLINE, PsycINFO, EMBASE, CENTRAL, CINAHL and Scopus for published studies and gray literature databases for unpublished studies from January 1990 to April 2018.

Methods: To assess evidence directly addressing our objectives, we conducted a systematic review. Because we were aware of a dearth of direct evidence, we also performed an overview of systematic reviews on leisure activities that mimic formal continuing education. We a priori established inclusion and exclusion criteria. Two authors independently assessed inclusion and exclusion on abstract and full-text level, rated risk of bias, and determined the certainty of evidence using GRADE. We resolved all discrepancies by consensus. We synthesized the available evidence narratively.

Results: Our searches identified 4933 citations. For the systematic review, only two publications on the same prospective cohort study (Tasmanian Healthy Brain Project) met inclusion criteria; for the overview of reviews we included five systematic reviews. Based on 459 participants, preliminary data of the ongoing cohort study indicated that cognitive reserve statistically significantly increased in persons attending university classes compared to the control group (92.5% vs. 55.7%, $p<0.01$). Likewise, language processing capacities statistically significantly improved ($p<0.01$). Episodic memory, working memory, and executive function did not differ significantly between groups. Systematic reviews consistently reported a positive association between participation in cognitively stimulating leisure activities and reduced incidence of dementia and improved cognitive test performance.

Conclusion: Available results demonstrate that cognitive reserve increases through continuing education and show a positive association of cognitive leisure activities with both improved cognitive function and lower dementia incidence.

Systematic review registration: PROSPERO CRD42017063944

Strengths and Limitations of this study:

- This is the first systematic review assessing the benefits and harms of continuing education on the prevention of mild cognitive impairment or Alzheimer's type dementia.
- This is the first overview of systematic reviews presenting an up-to-date summary of currently available research in the field of cognitive leisure activities and dementia.
- The certainty of evidence is low, indicating that future studies might have a substantial impact on results of our review.
- Measurements and types of cognitive leisure activities differed widely across studies and quantitative analysis were often not possible.
- The majority of included systematic reviews have serious methodological shortcomings.

INTRODUCTION

In 2012, the World Health Organization (WHO) named the prevention and control of neurocognitive disorders such as mild cognitive impairment or Alzheimer's-type dementia a global public health priority.[1] Alzheimer's-type dementia is the most common form of dementia.[1] In 2018, 50 million people worldwide lived with Alzheimer's disease or another closely related form of dementia.[2] As a consequence of the rapidly aging world population, the prevalence of dementia is projected to rise up to 152 million people in 2050.[2]

The progressive loss of independent functioning of people with Alzheimer's-type dementia, leads to an enormous social and economic burden. In 2018, the U.S. economic burden associated with Alzheimer's type dementia was estimated to be 277 billion U.S. Dollars.[3] The total global costs for dementia were about a trillion US dollar in 2018.[2]

The Diagnostic and Statistical Manual (DSM-5) characterizes Alzheimer's disease as a significant decline of intellectual abilities in one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual motor function, social cognition) outside the context of delirium.[4]

Any dementia diagnosis, however, is frequently preceded by a long period of subclinical neuropathological disorder with subjective cognitive disorder and mild cognitive disorder as a transition phase before diagnostic criteria for dementia are fulfilled.[5] If cognitive decline progresses to a degree that a person's capability of carrying out everyday activities is significantly affected, this state is called major neurocognitive disorder.[4 5]

The risk of developing neurocognitive disorders increases substantially with age. The prevalence of Alzheimer's type dementia is 3.5% in persons aged 75 or older and 46.3% in those 95 years or older.[6] It is estimated that 15 to 20 percent of people age 65 or older are living with mild cognitive impairment.[3] Other risk factors than age contributing to the development of dementia are not yet thoroughly understood. In recent years, epidemiological studies have linked the development of dementia with risk factors such as low educational level, unhealthy diet, decreased physical

activity, and smoking.[7 8] In addition, potential predictors of dementia are chronic medical conditions such as cardiovascular diseases, diabetes, obesity, cancers, depression, thyroid disorder, or genetic factors.[9] Some studies, however, found a protective association of cognitively stimulating activities, such as learning a new language in middle age, with a slower cognitive decline during late life.[10-14] Such results underpin the "cognitive reserve hypothesis".[15-17] According to this theory, through every activity that stimulates the brain, the cognitive reserve gets boosted and the resistance towards any dementia-related brain pathology increases.[18] In animal trials, an enriched environment was associated with increased cortical thickness.[19] Epidemiological research on humans has shown that education[20] and probably also other forms of intellectual stimulation, during the whole lifespan, are associated with a lower risk to develop dementia.[21 22] A larger cognitive reserve acquired by continuing education activities, thus, might protect against cognitive decline.[18 23]

Continuing education activities are structured learning activities offered by educational institutes. These activities are designed to help individuals satisfy learning needs and interests after compulsory schooling, to enrich knowledge, to develop and improve abilities and skills, and to foster personality, social competences, families, networks, health, and professional life. Continuing education is voluntary, based on topics and courses that are not directly connected to any special job position or vocational training.[24-29] Cognitive leisure activities (e.g., learning a new language) often mimic continuing education activities but are not taking place within the framework of an educational institution.

Rationale

To date, the preventive effect of continuing education on cognitive impairment and Alzheimer's-type dementia has not been assessed in an objective and systematic way. The aim of our review was to summarize the evidence investigating the preventive effects of continuing education on the development of cognitive impairment and Alzheimer's-type dementia.

Our systematic review addressed the following questions:

Key question 1a: In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment, does continuing education lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type dementia compared with no continuing education?

Key question 1b: (In case no evidence on continuing education is available or the evidence is sparse): In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment, do cognitive leisure activities lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type dementia compared with no cognitive leisure activities?

Key question 2: What are potential harms of continuing education?

Key question 3: Do benefits and harms differ by subgroups based on age, sex/gender, race or ethnicities, level of education, or duration of intervention?

Key question 4: What is the optimal age to start continuing education to prevent mild cognitive impairment or dementia?

METHODS

Design

Throughout this manuscript we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[30] (see supplementary file 1). The protocol of this systematic review was registered in PROSPERO (International Prospective Register of Systematic Reviews) (Registration number CRD42017063944) and published previously.[31] Figure 1 depicts the analytic framework that guided our systematic review.

[Figure 1 about here]

For this systematic review, we define continuing education as structured learning activities and programs provided by formal and non-formal educational institutions for persons beyond the age of compulsory schooling (in most countries 16 years and older).[24-29]

We addressed our research questions with two different methodological approaches:

1) We performed a systematic review of primary studies to assess the preventive effects and potential harms of continuing education provided by formal and non-formal institutions (key questions 1a, 2, 3, and 4).

2) We conducted an overview of systematic reviews to determine the preventive effects and potential harms of related leisure activities (e.g. playing cards, reading books, etc., key question 1b).

We chose this two-step approach because studies in the field of continuing education and dementia are very rare. Certain leisure activities, however, are able to mimic continuing education regarding content (e.g. learning a new language privately versus learning a new language as an organized educational activity). Leisure activities are not our primary focus of interest but can be considered as proxy interventions for continuing education in some circumstances.

Study selection

Eligibility criteria for the systematic review

The population of interest were adults 45 years or older, without a clinical diagnosis of cognitive impairment at the time of study recruitment, which included people with subjective cognitive impairment. Eligible interventions comprised of all cognitive activities that are provided by formal and non-formal educational institutions. These activities include classes, courses, and trainings that are based on individual interests and that are attended voluntarily. We included randomized controlled trials, nonrandomized controlled trials, prospective controlled cohort studies, retrospective controlled cohort studies, and case-control studies. All nonrandomized studies needed to have a minimum sample size of 300 or more participants.

Eligible studies had a minimum follow up time of 1 year and a minimum duration of intervention of 3 months. We excluded studies that investigated formal (vocational) education (e.g. School or College), physical activities, and all job-related courses and trainings.

Outcomes of interest included patient-relevant health outcomes such as incidence of dementia, incidence of MCI, psychological wellbeing, functional capacity, quality of life, and other relevant health outcomes; in addition, we included intermediate outcomes such as cognitive functioning, cognitive (test) performance, or social inclusion. For the purpose of our study, mild cognitive impairment refers to "amnestic" mild cognitive impairment (aMCI), meaning that memory loss is the predominant symptom.[32]

Eligibility criteria for the overview of systematic reviews

Eligibility criteria for population and outcomes for the overview of systematic reviews were the same as for the systematic review. Eligible interventions were leisure activities that are cognitively stimulating and mimic the content of continuing education but in an informal setting. Just as in the systematic review, we excluded physical activities. Eligible study designs were exclusively systematic reviews and meta-analyses. We excluded reviews with searches conducted before 2013.

Further details about our inclusion and exclusion criteria can be found in our protocol[31] and in the supplementary file 2.

Search strategy

We systematically searched Ovid MEDLINE, Cochrane Library, Embase, PsycINFO, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ALOIS (the Cochrane Dementia and Cognitive Improvement Group Specialized Register), and ERIC (Education Resources Information Center) from January 1990 to April 2018 to identify relevant publications (see supplementary file 3 for the search strategy). For the overview of reviews, we searched Epistemonikos from inception to April 2018 in addition to the above mentioned databases (see supplementary file 4).

An experienced information specialist developed an appropriate search strategy using a combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the search to human-only studies without applying any language limitations. The electronic Ovid Medline search strategy was peer-reviewed by another information specialist following the PRESS (peer

review of the electronic search strategy) statement.[33] For the systematic review, we searched for gray literature in ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, web pages of relevant organizations, and a dissertation database ("Digital Access to Research Theses", DART-Europe). Additionally, in an attempt to avoid retrieval bias, we manually searched the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed. We imported all citations into an electronic database (EndNote X.8) and deleted duplicates.

Study selection

Two review authors independently screened abstracts and relevant full text articles for eligibility, using Covidence Software.[34] They resolved disagreements by discussion or by consultation with a third author.

Data abstraction

We designed, pilot-tested, and used a data abstraction form to gather pertinent information from each article. One author extracted relevant data from each study that met our inclusion criteria. A second author of the team cross-checked data abstractions for completeness and accuracy. We extracted study information (author, publication year, years covered by searches, location/setting, number of included studies and included study designs), sample size, study characteristics (population, interventions, and comparators), outcome measurements, and results. For systematic reviews we abstracted summary estimates of meta-analyses whenever available.

Risk of bias assessment

Two investigators independently assessed the risk of bias of included studies. They resolved any disagreements by consensus or by consulting a third team member. For eligible non-randomized studies we used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool.[35] For the assessment of eligible systematic reviews, we used the AMSTAR (Assessing the Methodological

Quality of Systematic Reviews) tool.[36] Detailed risk of bias ratings of included articles are given in supplementary file 5.

Data synthesis and statistical analysis

We narratively summarized evidence from included studies. If available, we present effect estimates of systematic reviews. For the incidence of dementia we present hazard ratios (HR), odds ratios (OR), and risk ratios (RR). For the assessment of cognitive test performance we use standardized mean differences because scales for measurements differed in the individual studies. A standardized mean difference of 0 indicates that both groups had the same cognitive test performance.

Certainty of evidence

We followed the recommendations of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group for rating the certainty of evidence for each outcome.[37]

Patient involvement

No patients were involved in the development of this research paper.

RESULTS

Our search identified in total 4933 citations after exclusion of duplicates. Based on title and abstract review, we considered 58 primary studies and 28 systematic reviews for full-text review. After scrutinising the full-text articles, we included two publications of one primary study[38 39] and five systematic reviews.[40-44] Figure 2 and figure 3 depict the study selection process. Supplementary file 6 provides a list of excluded studies at full-text level.

[Figure 2 and figure 3 about here]

Study characteristics

Systematic Review

We included two publications[38 39] that present interim findings of the same medium risk of bias prospective cohort study, namely the Tasmanian Healthy Brain Project that plans to follow participants for 10-20 years.[45] The two publications analysed different aspects of cognitive functioning of the same 459 participants who did or did not engage in a 12 month, part-time or full-time university-level education. Participants' mean age was 59.6±7 (mean±SD) years in the intervention group and 62.4±6 years in the control group with a follow-up period of 4 years. Participants completed a neuropsychological test battery, consisting of 14 tests each year.[45]

In this study, selection bias is likely because participants voluntarily opted for university courses or no further education. It is not clear if investigators used appropriate methods to adjust for potential confounders (see supplementary file 5 for risk of bias ratings).

Overview of Reviews

All five included systematic reviews investigated the benefits of cognitive leisure activities in adults over the age of 45 years.[40-44] Four studies included any cognitive leisure activities in their analyses (e.g. reading books, doing crosswords, attending cultural events, knitting, painting), one study[43] specifically focused on the benefits of playing video games in older adults. The number of participants investigated in the reviews ranged from 913[43] to 24,554.[41]

We rated three of the included systematic reviews[40 42 43] as high and two studies[41 44] as medium risk of bias. Reasons for the high risk of bias ratings were lack of critical appraisal of included studies, single review of the literature, and insufficient literature searches (see supplementary file 5).

We graded the evidence for all meta-analysis outcomes with low certainty of evidence mostly because of high inconsistency and indirectness among studies (see supplementary file 7).

We present characteristics of included studies [40-44] in table 1 and table 2.

Reference	Study design	Aim	Sample Size	Population	Intervention	Measurements	Outcomes	Risk of bias
Lenhan et al., 2016[39]	Prospective cohort study, Tasmanian Healthy Brain Project (2011-2016)	To investigate changes in cognitive reserve in healthy older adults participating over four years in university-level education.	459 (359 in the Intervention group, 100 control group)	50-79 years, healthy older adults	Minimum of 12 months of part-time or full-time university study Follow-up: 4 years	Prior Cognitive reserve and current cognitive reserve were calculated for each participant.	55,7% in the control group vs. 92,5% in the university education group showed a significant increase of cognitive reserve	Medium
Thow et al., 2018[38]		To determine if the observed increase in cognitive reserve among older adults attending university is associated with a change in cognitive function over time.				Episodic memory, working memory, executive function, and language processing performances were assessed annually over 4 years.	Statistically significant improvement of language processing capacity. No significant improvement of episodic memory, working memory, executive function.	Medium

Table 1: Study Characteristics of included primary studies

Reference	Aim	Search Strategy	N of included studies	Study design	Total number of participants	Population	Outcomes	Risk of bias
Di Marco et al., 2014[40]	To provide a comprehensive summary of modifiable lifestyle factors (dietary habits, leisure activities, social network et cetera.) associated with the risk of late-onset incident dementia.	NR to 2013 PubMed, Ovid MEDLINE, PsycINFO, In-Process and other non-indexed citations Search terms provided English language publications	6 (cognitive leisure activities)	Longitudinal observational cohort-studies	NR	≥65 years, adults without dementia at baseline	No quantitative analysis Cognitive leisure activities might be associated with **reduced incidence of all-cause dementia**	High
Opdebeeck et al., 2016[41]	To assess the relationship between cognitive reserve (educational level, occupational status and engagement in cognitively stimulating activities) and cognition in multiple domains.	NR to 2014 PubMed, PsycInfo, ScienceDirect, CINHAL Search terms provided	31 (cognitive stimulating activities)	31 Cross-sectional studies	24561	≥60 years (at least 80% of study participants)	SMD 0.26 (95% CI 0.21-0.32) Participating in cognitive leisure activities is associated with **improved cognitive functions** (including memory, working memory, executive function, visuospatial ability, and language)	High
Sajeev et al., 2016[42]	To assess if engaging in late-life cognitive activities is able to delay or prevent dementia.	NR to June 2014 PubMed and EMBASE	12 (cognitive stimulating activities)	10 prospective cohort studies; 2 nested case-control studies	13939 (dementia: 1663 AD: 565)	≥45 years	No quantitative analysis	Medium

		No search terms provided					Late-life cognitive activity might be associated with **lower AD and/or all-cause dementia incidence**	
Toril et al., 2014[43]	To investigate the extent to which cognitive training with video games enhances cognitive functions in healthy older adults.	1986-2013 MEDLINE, PsycInfo and Google Scholar Search terms provided English language publications	20 (video game training)	18 controlled studies 2 uncontrolled studies	913 (474 trained, 439 healthy controls)	50 - 86 years, healthy older adults	SMD 0.37 (95% CI 0.26 – 0.48) Video game training is associated with **improved cognitive functions** in older adults (including memory, attention, reaction time, cognitive function, executive functions)	High
Yates et al., 2016[44]	To assess the impact of cognitively stimulating leisure activities on cognition and risk of dementia in later life.	2004 – 2014 PsychInfo, MEDLINE, CINAHL, EMBASE and the Web of Science Search terms provided	19 (cognitive leisure activities)	17 Cohort studies 2 Case control studies	32546	≥ 46 years, cognitively healthy adults (i.e. no diagnosis of impairment or dementia)	**All-cause dementia incidence:** RR 0.61 (95%CI 0.42 – 0.90), k=3, RE HR 0.58 (95%CI 0.46 – 0.74), k=2, RE OR 0.78 (95%CI 0.67 – 0.90), k=2, FE **Cognitive impairment incidence:** OR 0.69 (95%CI 0.56 – 0.85), k=5, RE HR 0.85 (95% CI 0.71 – 1.02), k=3, RE, n.s.	Medium

NR = Not reported, AD = Alzheimer's-type dementia, k = studies that assessed cognitive activities only, n= number of participants, RE = random-effects model, FE = fixed effects model, n.s. = not significant

Table 2: Study Characteristics of included systematic reviews

Outcomes

Key question 1a: Continuing education

Two interim analyses of the Tasmanian Healthy Brain Project focused on language processing[38] and cognitive reserve[39] after 4 years of follow-up. To date, no results on the incidence of mild cognitive impairment or Alzheimer's-type dementia are available yet. Both studies reported beneficial effects of continuing education. Thow and colleagues[38] showed that attending university courses over a period of 12 months statistically significantly ($p<0.05$) improved the language processing capacity in the intervention group compared to the control group. No statistically significant differences were detected for episodic memory, working memory, and executive function between groups. In all analyses, authors accounted for age and prior cognitive reserve (education, pre-existing intellectual capacity, life-experience).

Lenehan and coworkers[39] demonstrated by conducting growth mixture modeling that the cognitive reserve statistically significantly increased in 92.5% of participants in the intervention group (n=359) compared to 55.7% of participants in the control group (n=100). Investigators created a proxy measure of "current cognitive reserve" to capture dynamic changes in cognitive reserve over time, including intellectual capacity and academic ability.[46]

Key question 1b: Cognitive leisure activities

Overall, the five included systematic reviews reported consistently that participation in cognitive stimulating leisure activities can reduce the risk of developing mild cognitive impairment or Alzheimer's-type dementia and improves cognitive functioning of healthy older adults.

Two systematic reviews[40 42] investigated the impact of cognitive leisure activities on the incidence of Alzheimer's-type dementia. Di Marco and colleagues included six, Sajeev and colleagues 12 primary studies on cognitive leisure activities in their systematic reviews. Both systematic reviews concluded that leisure activities protect against dementia. Due to different categorization of cognitive leisure activities and a high heterogeneity between studies, quantitative analyses were not possible in the two reviews. The effect estimates of included studies ranged from hazard ratios [HR]

of 0.39 (95% CI: 0.21 - 0.71)[47] to HR of 0.93 (95% CI: 0.88 – 0.98)[48] showing statistically significantly reduced risks of Alzheimer's-type dementia when carrying out leisure activities. Sajeev et al.[42] performed an extensive bias analysis indicating that it is unlikely that the observed positive effects of cognitively stimulating activities on dementia incidence are exclusively explained by unmeasured confounders or reverse causation.

One review[44] assessed both incidence of mild cognitive impairment and Alzheimer's-type dementia and cognitive test performance. The authors conducted five meta-analyses based on groups for outcomes and reported effect estimates (risk ratio [RR], odds ratio [OR], and hazard ratio [HR]). Four out of five meta-analyses revealed statistically significant results showing that cognitive leisure activities were associated with a reduction of dementia incidence (RR = 0.61, 95% CI: 0.42-0.90; HR = 0.58, 95% CI: 0.46-0.74, OR = 0.78, 95% CI: 0.67 – 0.90) and a reduction of cognitive impairment incidence (OR = 0.69, 95% CI: 0.56 – 0.85). However, one meta-analysis, combining three cohort studies did not reach statistical significance (HR = 0.85, 95% CI: 0.71-1.02) for reduction of cognitive impairment. A narrative analysis of primary studies assessing cognitive test performance showed a statistically significant improvement of memory, speed of processing, language, and executive functioning and overall later life cognition.

Two other included studies[41 43], both rated as high risk of bias, focused on cognitive test performance. Opdebeeck et al.[41] reported a benefit in overall cognitive abilities for the group involving in cognitive leisure activities (standardized mean difference [SMD] of 0.26 (95% confidence interval [CI]: 0.21-0.32). The cognitive domains included memory, working memory, executive function, visuospatial ability, and language. According to the review by Toril et al. [43], playing video games enhanced several cognitive functions. They observed a SMD of 0.37 (95% CI 0.26 – 0.48) for global cognitive function (combining results for memory, attention, reaction time and executive functions), showing a benefit for the intervention group.

Key question 2: Harms

We found no evidence regarding harms of continuing education or cognitive leisure activities.

Key question 3: Subgroups

Toril and colleagues[43] performed several subgroup analyses. The study revealed that the age of the participants and the number of video game training sessions significantly changed the effect size. Older participants (between 71 and 80 years) seemed to benefit more from computer training than younger participants (60 to 70 years). For the improvement of cognitive test performance, shorter training sessions (1-6 weeks) seemed to show an advantage over longer training interventions (7-12 weeks). By contrast, for incidence of Alzheimer's-type dementia, DiMarco et al.[40] and Sajeev et al.[42] infer from their data that greater participation in cognitive leisure activities over a longer period of time contributes positively to the protective effect.

Key question 4: Optimal age

No study specifically discussed the optimal age to start with continuing education activities or cognitive leisure activities to prevent mild cognitive impairment or dementia.

DISCUSSION

The evidence assessing the impact of continuing education on the risk of MCI or Alzheimer-type dementia is limited. The only eligible primary study (Tasmanian Healthy Brain project) [45] is still ongoing but preliminary findings after four years of follow-up demonstrated that the dynamic nature of cognitive reserve permits improvements through education even at an advanced age. Nevertheless, these early findings have to be viewed cautiously. In addition, selection bias could potentially distort results of the Tasmanian Healthy Brain project because participants voluntarily opted for university courses or no further education. The available publications did not explain sufficiently how baseline differences such as comorbid diseases were taken into consideration during the analyses.

Because of the limited direct evidence, we focused on cognitive leisure activities as proxies for formal continuing education. Overall, the available evidence consistently indicates beneficial effects of cognitive leisure activities by improving the cognitive function of older adults and reducing the incidence of MCI and Alzheimer's-type dementia. These findings could be explained by the neuroplasticity of the human brain, which refers to the ability of the brain to adapt to every new stimulus by forming dendritic connections, creating morphological changes and increasing cognitive reserve.[49-51] Neuroplasticity is an intrinsic property of the human brain that allows us to learn and adapt to environmental changes. Depending on the stimuli, the changes can be positive or negative.[49-51] The concept of neuroplasticity is interrelated with the concept of cognitive reserve which refers to morphological changes that support cognitive functioning.[51]

The magnitudes of beneficial effects, however, varied across systematic reviews and confidence intervals encompassed effect sizes that would not be clinically relevant. Consequently, we rated the certainty of evidence as low or very low which means that future studies are likely to have a substantial impact on these findings.

To the best of our knowledge, our study was the first assessing the impact of continuing education on MCI and Alzheimer's-type dementia. It is also the first overview of systematic reviews presenting an up-to-date summary of currently available research in the field of cognitive leisure

activities and dementia. Nevertheless, our work has several limitations. First, in the overview of systematic reviews we had to rely on the quality of included systematic reviews which often had methodological shortcomings (e.g. no risk of bias assessment, no dual screening etc.). Second, most of the included studies were observational studies, which are prone to selection bias because participants self-select the group. Risk factors for MCI or dementia in participants selecting leisure activities or further education might be systematically different from participants in the control groups. For example, people who eventually suffer from preclinical dementia stages might be more likely to avoid cognitive leisure activities, which would lead to reverse causation. Third, many primary studies within the reviews used self-reported questionnaires that could be challenging for people who start having cognitive deficits. Finally, the variation of leisure activity categorization across studies made meta-analysis difficult and sometimes impossible. For example, "visiting a library" was classified as a cognitive activity by one author but as a physical activity by another. Some studies assessed current participation in activities, others participation at younger ages. Additionally, some studies assessed the frequency of participation, others the time devoted to activities and some the total number of leisure activities. Consequently, due to these limitations, the comparability of results among studies was limited. A standardization of measures and methods would be necessary to help synthesize evidence in the future and make more reliable recommendations.

Implication for future research, policy and practice

Based on preliminary results of a long-term cohort study and indirect evidence from studies on leisure activities, continuing education might be a promising option to help prevent dementia. A recent study suggests that modifiable risk factors (low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression) might be responsible for about a third of Alzheimer's-type dementia cases.[52] Hence, considering our results, a campaign promoting to "actively use the brain by participating in the wide range of continuing education" could possibly be added to the list of preventive options and could have an impact on the reduction of Alzheimer's-type dementia cases. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and

Disability (FINGER)[53], a randomized controlled trial, with a multi-domain approach (diet, exercise, cognitive training, vascular risk monitoring) supports the hypothesis that simultaneous changes in several risk factors can lead to a protective effect on cognition.

Further research is needed to address the evidence gap regarding continuing education and the extent to which it acts as a protective factor. A study similar to the Tasmanian Healthy Brain Project[39], but conducted as a randomized controlled trial, would be ideal because it would adequately handle known and unknown confounders. Computers and Internet could play a more significant role in future prevention trials. Older adults could, for instance, be randomized to attend online courses and communicate with professors and other students in virtual classrooms. This approach could save time, money, and increase the potential participant pool.

Conclusion

Although no firm conclusions about the effects of continuing education to prevent MCI and dementia can be drawn, data from preliminary and indirect evidence indicate that continuing education could potentially have important preventive effects.

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Availability of data and materials: All extracted data are included in the manuscript. There are no additional datasets available.

Competing interests: All authors declare that they have no competing interest.

Author Contributions: All authors made substantial contribution to the conception and design of this study. GG, NM, MK, CG and SA developed the concept of the study. As an information specialist, IK developed the search strategy. GW, FKA, NM and BT conducted the literature review, abstracted data and graded the strength of evidence. NM wrote the first draft of the manuscript; all authors reviewed the manuscript and provided comments. All authors have given approval for this version to be published.

Figure Legends:

Figure 1: Analytic framework for continuing education to prevent mild cognitive impairment and Alzheimer's-type dementia

Figure 2: Flow diagram of systematic review of continuing education for the prevention of mild cognitive impairment and Alzheimer's-type dementia

Figure 3: Flow diagram of overview of systematic reviews of cognitive leisure activities for the prevention of mild cognitive impairment and Alzheimer's-type dementia

List of abbreviations

AD = Alzheimer Disease
aMCI = Amnestic Mild Cognitive Impairment
AMSTAR = Assessing the Methodological Quality of Systematic Reviews
CEDEFOP = European Centre for the Development of Vocational Training
CENTRAL = Cochrane Central Register of Controlled Trials
DSM = Diagnostic and Statistical Manual of Mental Disorders
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HR = Hazard Ratio
ICD = International Classification of Diseases
MCI = Mild Cognitive Impairment
MMSE = Mini-Mental State Examination
OECD = Organisation for Economic Co-operation and Development
OR = Odds Ratio
PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-I = Risk of Bias in non-randomized studies – of interventions
RR = Relative Risk
SD = Standard Deviation
SMD = Standardized mean difference
UNESCO = United Nations Educational, Scientific and Cultural Organization
WHO = World Health Organisation

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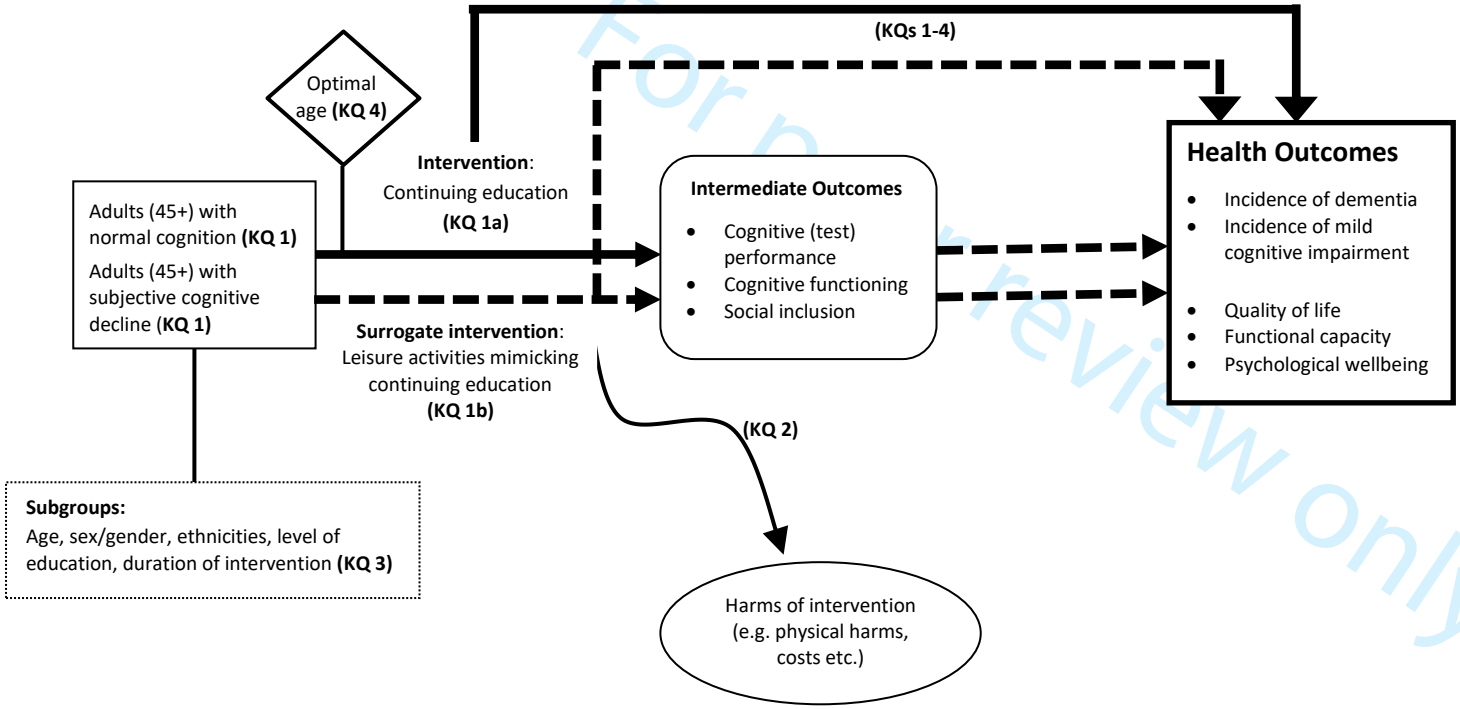

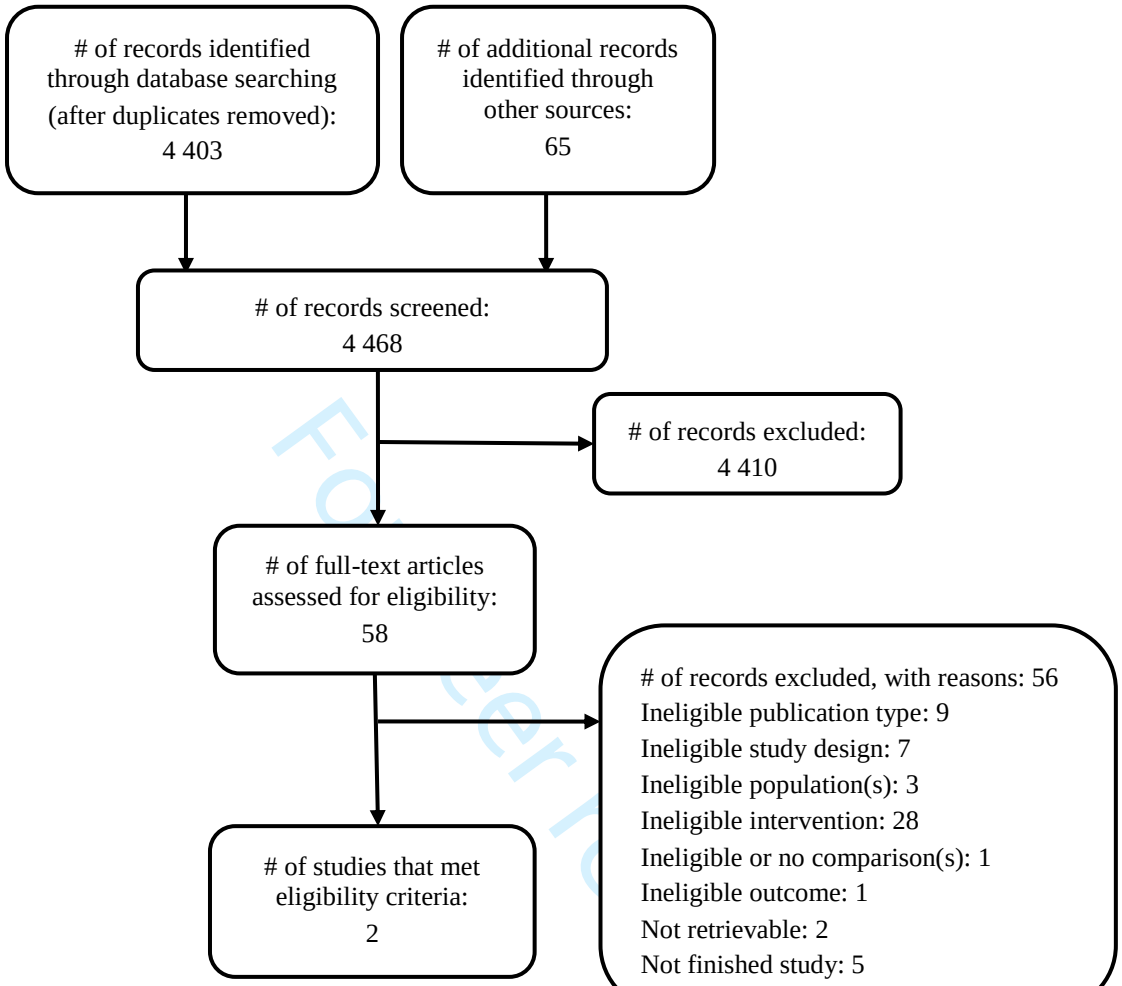

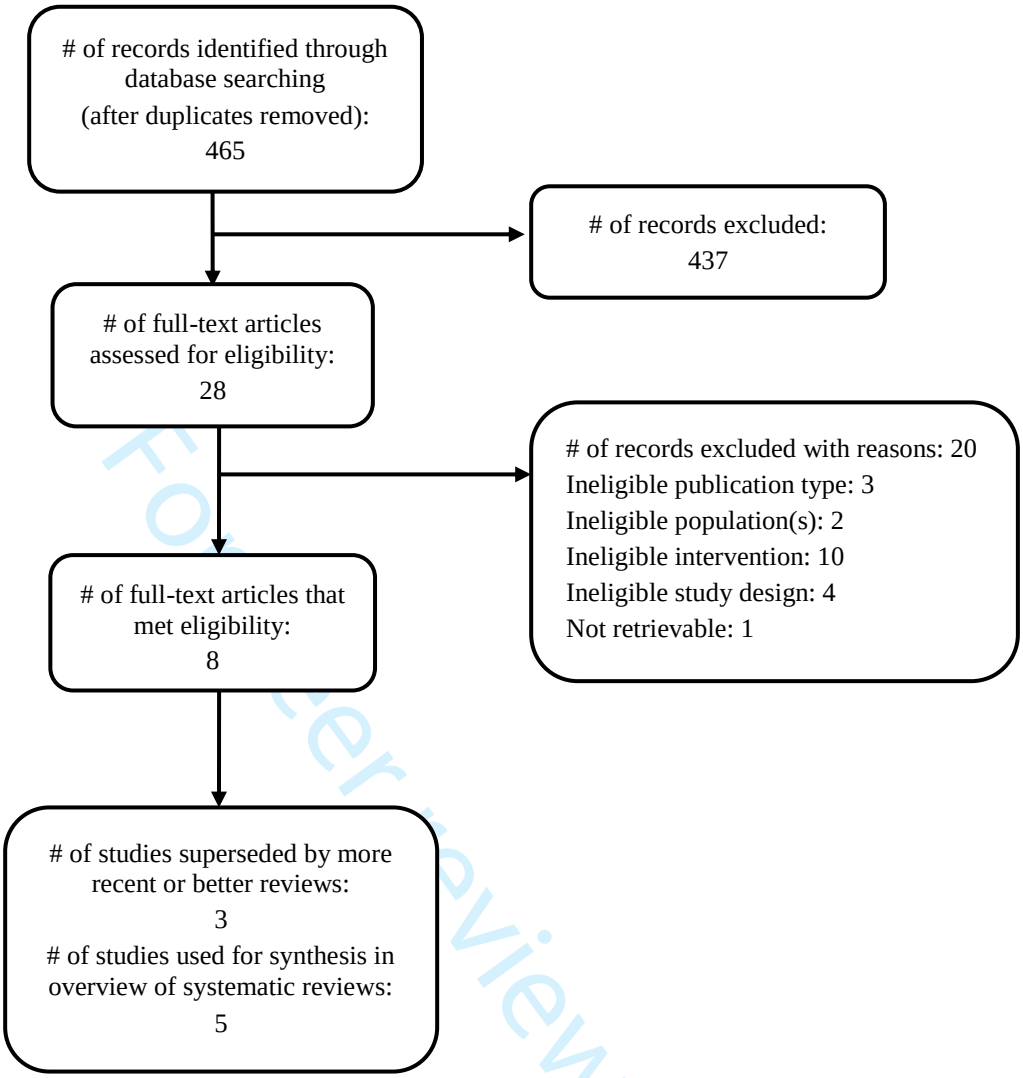

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 (line 1-3)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4 (line 40-67)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-7 (line 127-132)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7 (line 133-144)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 7 (line 149-151)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8-9 (line 171-196)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9-10 (line 197-214)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 3 and 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10 (line 215-218)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10 (line 219-226)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10 (line 222-226)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10-11 (line 227-233)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 11 (line 234-240)

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 11 (line 234-240)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11 (line 238-243) Figure 2 and figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-12 (line 255-278) Table 1 and table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13-14 Table 1 and table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-17 (line 288-351) Table 1 and table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12 (line 264-266; line 273-278) Supplementary file 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 18

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21 (line 423-425)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary File 2: Inclusion and exclusion criteria

	Criteria	
Category	**Inclusion**	**Exclusion**
Population	- Adults (45 years or older) without a clinical diagnosis of cognitive impairment; this includes people with subjective cognitive impairment	- People younger than 45 years - People with a clinical diagnosis of impaired cognition (e.g., MMSE < 24) -Populations comprised exclusively of patients with primary diseases with an increased risk for dementia such as Parkinson disease, HIV infection, multiple sclerosis, stroke, post traumatic brain injuries, infectious diseases, psychiatric conditions (e.g. alcohol abuse, drug abuse, major depressive disorder)
Subgroups	- Age - Sex/gender - Race/ethnicity - Level of education - Duration of intervention	
Geography	No limit	No limit
Date of search	Searches will go back until 1990	
Settings	Community-dwelling adults	Institutionalized people, e.g., people in nursing homes
Interventions	**For systematic review** - all cognitive activities that are provided by formal and non-formal educational institutions - classes/courses/trainings that are based on individual interests and that are attended voluntarily **For overview of systematic reviews** Leisure activities that are cognitively stimulating and mimic the content of continuing education but in an informal setting.	Formal (vocational) education and training; physical activities, topics and courses that are related to any special job position and/or occupation
Control Interventions	No continuing education	Any educational activities, physical activities
Outcomes	**Health Outcomes** - Incidence of dementia - Incidence of MCI - Psychological wellbeing - Functional capacity - Quality of life - Other relevant health outcomes **Intermediate Outcomes** - Cognitive functioning - Cognitive (test) performance - Social inclusion	
Timing	Minimum duration of the intervention: 3 months Minimum follow up time: 1 year	
Publication language	No language restrictions	
Study design	**For systematic reviews** - RCTs - Nonrandomized controlled trials - Prospective controlled cohort studies - Retrospective controlled cohort studies - Case-control studies - Nonrandomized studies must have a minimum sample size of 300 or more participants **For overview of systematic reviews** -systematic reviews and meta-analyses	- Case series - Case reports - Cross over trials - Nonsystematic reviews - Studies without a control group - Nonrandomized studies with fewer than 300 participants

Supplementary file 3: Search Strategies of Systematic Review, by database

Medline (via PubMed):10 July 2017

Medline

Search	Query	Hits
1	Dementia/ or exp Alzheimer Disease/	117464
2	Cognitive Dysfunction/	5918
3	Cognition/	81481
4	(dementia or alzheimer*).ti,ab.	174908
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	166793
6	or/1-5	370522
7	Primary Prevention/	16883
8	prevent*.ti,ab.	1207345
9	(protect* or reduc* or delay* or improv*).ti.	710454
10	or/7-9	1858549
11	6 and 10	39070
12	Dementia/pc or exp Alzheimer Disease/pc or Cognitive Dysfunction/pc [Prevention & Control]	4039
13	11 or 12	41057
14	exp Education, Continuing/	60977
15	((continuing or adult) adj2 (education or training)).af.	80639
16	(lifelong learning or life-long learning).af.	2396
17	education/ or exp curriculum/ or exp education, distance/ or exp education, nonprofessional/ or exp educational measurement/ or exp international educational exchange/ or mentoring/ or exp schools/ or exp teaching/	500562
18	Learning/	56308
19	Students/	47445
20	exp Educational Status/	47641
21	(learn* or class or classes or course? or educat* or school* or train* or seminar* or tutor*).ti.	569072
22	education.fs. not exp Health Personnel/ed	200448
23	(cognitiv* adj2 (stimulat* or activit*)).ti.	742
24	or/14-23	1075912
25	13 and 24	3357
26	exp Dementia/dt [Drug Therapy]	17955
27	25 not 26	3243
28	exp animals/ not exp humans/	4438320
29	27 not 28	2497
30	exp age groups/ not (exp aged/ or middle aged/)	3709828
31	29 not 30	1838
32	limit 31 to yr="1990 -Current"	1805
33	remove duplicates from 32	1695

Medline (via PubMed): updated 5 April 2018

Search	Query	Results
1	Dementia/ or exp Alzheimer Disease/	118649
2	Cognitive Dysfunction/	7920
3	Cognition/	82659
4	(dementia or alzheimer*).ti,ab.	178991
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	171636
6	or/1-5	378202
7	Primary Prevention/	16649
8	prevent*.ti,ab.	1222908
9	(protect* or reduc* or delay* or improv* or increas* or decreas*).ti.	1008130
10	or/7-9	2152629
11	6 and 10	46477
12	Dementia/pc or exp Alzheimer Disease/pc or Cognitive Dysfunction/pc or Cognition Disorders/pc [Prevention & Control]	6391
13	Cognitive Reserve/	388
14	cognitive reserve.ti,ab.	949
15	or/11-14	50722
16	exp Education, Continuing/	58777
17	((continuing or adult) adj2 (education or training)).af.	77985
18	(lifelong learning or life-long learning).af.	2438
19	education/ or exp curriculum/ or exp education, distance/ or exp education, nonprofessional/ or exp educational measurement/ or exp international educational exchange/ or mentoring/ or exp schools/ or exp teaching/	561833
20	Learning/	57102
21	Students/	48337
22	exp Educational Status/	47241
23	(learn* or class or classes or course? or educat* or school* or train* or seminar* or tutor*).ti.	571948
24	education.fs. not exp Health Personnel/ed	199668
25	(cognitiv* adj2 (stimulat* or activit*)).ti.	773
26	(late-life adj2 (activity or activities or learn* or school* or educat* or training)).ti,ab.	93
27	or/16-26	1135186
28	15 and 27	4360
29	exp Dementia/dt [Drug Therapy]	18096
30	28 not 29	4227
31	exp animals/ not exp humans/	4439627
32	30 not 31	3347
33	exp age groups/ not (exp aged/ or middle aged/)	3685655
34	32 not 33	2546
35	(201707* or 201708* or 201709* or 20171* or 2018*).ed.	749049
36	("2017/07*" or "2017/08*" or "2017/09*" or "2017/1*" or 2018*).dt.	942206
37	35 or 36	1540516
38	34 and 37	364
39	limit 34 to yr="2017 -Current"	348
40	38 or 39	435

Cochrane Library (10 July 2017)

Cochrane Library

Search	Query	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4053
#2	[mh ^"Cognitive Dysfunction"]	0
#3	[mh ^Cognition]	6276
#4	(dementia or alzheimer*):ti,ab,kw	11882
#5	((cognit* or memory or mental) near/3 (impair* or decline* or deficit* or reduc* or function*)):ti,ab	16173
#6	{or #1-#5}	27711
#7	[mh ^"Primary Prevention"]	1008
#8	prevent*:ti,ab,kw	107750
#9	(protect* or reduc* or delay* or improv*):ti	77161
#10	{or #7-#9}	175365
#11	#6 and #10	4432
#12	[mh Dementia/pc] or [mh ^"Cognitive Dysfunction"/pc]	208
#13	#11 or #12	4532
#14	[mh "Education, Continuing"]	1168
#15	((continuing or adult) near/2 (education or training)):ti,ab,kw	2819
#16	("lifelong learning" or "life-long learning"):ti,ab,kw	19
#17	[mh ^education] or [mh curriculum] or [mh "education, distance"] or [mh "education, nonprofessional"] or [mh "educational measurement"] or [mh "international educational exchange"] or [mh ^mentoring] or [mh schools] or [mh teaching]	21839
#18	[mh ^Learning]	1809
#19	[mh ^Students]	2041
#20	[mh "Educational Status"]	1348
#21	(learn* or class or classes or course or courses or educat* or school* or train* or seminar* or tutor*):ti	45060
#22	(cognitiv* near/2 (stimulat* or activit*)):ti	212
#23	(learning or ((education or training) near/2 (nonprofessional or non-professional or distance)) or teaching):kw	12784
#24	{or #14-#23}	67085
#25	#13 and #24	784
#26	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	104635
#27	#25 not #26	691
#28	#27 Publication Year from 1990 to 2017	691

Cochrane Library (updated 9 April 2018)

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4263
#2	[mh ^"Cognitive Dysfunction"]	450
#3	[mh ^Cognition]	6675
#4	(dementia or alzheimer*):ti,ab,kw	13099
#5	((cognit* or memory or mental) near/3 (impair* or decline* or deficit* or reduc* or function*)):ti,ab	18089
#6	{or #1-#5}	30564
#7	[mh ^"Primary Prevention"]	1065
#8	prevent*:ti,ab,kw	115159
#9	(protect* or reduc* or delay* or improv* or increas* or decreas*):ti	102653
#10	{or #7-#9}	205354
#11	#6 and #10	5434
#12	[mh Dementia/pc] or [mh ^"Cognitive Dysfunction"/pc] or [mh ^"Cognition Disorders"/pc]	603
#13	[mh ^"Cognitive Reserve"]	8
#14	cognitive reserve:ti,ab,kw	51
#15	{or #11-#14}	5791
#16	[mh "Education, Continuing"]	1209
#17	((continuing or adult) near/2 (education or training)):ti,ab,kw	3051
#18	("lifelong learning" or "life-long learning"):ti,ab,kw	21
#19	[mh ^education] or [mh curriculum] or [mh "education, distance"] or [mh "education, nonprofessional"] or [mh "educational measurement"] or [mh "international educational exchange"] or [mh ^mentoring] or [mh schools] or [mh teaching]	26602
#20	[mh ^Learning]	1962
#21	[mh ^Students]	2250
#22	[mh "Educational Status"]	1407
#23	(learn* or class or classes or course or courses or educat* or school* or train* or seminar* or tutor*):ti	48313
#24	(cognitiv* near/2 (stimulat* or activit*)):ti	246
#25	(learning or ((education or training) near/2 (nonprofessional or non-professional or distance)) or teaching):kw	14622
#26	(late-life near/2 (activity or activities or learn* or school* or educat* or training)):ti,ab,kw	8
#27	{or #16-#26}	75572
#28	#15 and #27	1055
#29	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
#30	#28 not #29	937
#31	#30 Publication Year from 2017 to 2018	106

Embase (10 July 2017)

Embase

Search	Query	Hits
#1	'dementia'/de	97110
#2	'alzheimer disease'/exp	156558
#3	'mild cognitive impairment'/exp	17067
#4	dementia:ti,ab OR alzheimer*:ti,ab	226442
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	221649
#6	#1 OR #2 OR #3 OR #4 OR #5	432689
#7	'primary prevention'/exp	33540
#8	'preventive medicine'/exp	25875
#9	prevent*:ti,ab	1469112
#10	protect*:ti OR reduc*:ti OR delay*:ti OR improv*:ti	850362
#11	#7 OR #8 OR #9 OR #10	2260166
#12	#6 AND #11	49357
#13	'dementia'/dm_pc	1833
#14	'mild cognitive impairment'/exp/dm_pc	90
#15	'alzheimer disease'/exp/dm_pc	4342
#16	#12 OR #13 OR #14 OR #15	52112
#17	'continuing education'/exp OR 'continuing education provider'/exp	29360
#18	((continuing OR adult) NEAR/2 (education OR training)):ti,ab	24617
#19	lifelong learning':ti,ab OR 'life-long learning':ti,ab	1695
#20	'education'/de OR 'adult education'/exp OR 'lifelong learning'/exp OR 'mentoring'/exp OR 'masters education'/exp OR 'postdoctoral education'/exp OR 'postgraduate education'/exp OR 'community college'/exp OR 'university'/exp	466817
#21	learn*:ti OR class:ti OR classes:ti OR course*:ti OR educat*:ti OR school*:ti OR train*:ti OR seminar*:ti OR tutor*:ti	633869
#22	(cognitiv* NEAR/2 (stimulat* OR activit*)):ti	930
#23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	1006895
#24	#16 AND #23	3837
#25	'animal'/exp NOT 'human'/exp	4833576
#26	#24 NOT #25	2924
#27	'groups by age'/exp NOT ('middle aged'/exp OR 'aged'/exp)	5653684
#28	#26 NOT #27	2223
#29	#28 AND [1990-2017]/py	2199
#30	'medication therapy management'/exp OR 'dementia'/exp/dm_dt OR 'pharmaceutical vehicles and additives'/exp	1386295
#31	#29 NOT #30	2022
#32	#31 NOT 'conference abstract'/it	996

Embase (updated 9 April 2018)

No.	Query	Hits
#1	'dementia'/exp	308108
#2	'alzheimer disease'/exp	167836
#3	'mild cognitive impairment'/exp	19554
#4	dementia:ti,ab OR alzheimer*:ti,ab	245698
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	244483
#6	#1 OR #2 OR #3 OR #4 OR #5	519886
#7	'primary prevention'/exp	35604
#8	'preventive medicine'/exp	26670
#9	prevent*:ti,ab	1576370
#10	protect*:ti OR reduc*:ti OR delay*:ti OR improv*:ti OR increas*:ti OR decreas*:ti	1272239
#11	#7 OR #8 OR #9 OR #10	2758722
#12	#6 AND #11	66376
#13	'dementia'/dm_pc	1929
#14	'mild cognitive impairment'/exp/dm_pc	101
#15	'alzheimer disease'/exp/dm_pc	4515
#16	'cognitive reserve'/exp	1346
#17	'cognitive reserve':ti,ab	1463
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17	70716
#19	'continuing education'/exp OR 'continuing education provider'/exp	30115
#20	((continuing OR adult) NEAR/2 (education OR training)):ti,ab	25787
#21	'lifelong learning':ti,ab OR 'life-long learning':ti,ab	1820
#22	'education'/de OR 'adult education'/exp OR 'lifelong learning'/exp OR 'mentoring'/exp OR 'masters education'/exp OR 'postdoctoral education'/exp OR 'postgraduate education'/exp OR 'community college'/exp OR 'university'/exp	492706
#23	learn*:ti OR class:ti OR classes:ti OR course*:ti OR educat*:ti OR school*:ti OR train*:ti OR seminar*:ti OR tutor*:ti	669572
#24	(cognitiv* NEAR/2 (stimulat* OR activit*)):ti	1040
#25	('late life' NEAR/2 (activity OR activities OR learn* OR school* OR educat* OR training)):ti,ab	131
#26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1064036
#27	#18 AND #26	5231
#28	'animal'/exp NOT 'human'/exp	5020589
#29	#27 NOT #28	4140
#30	'groups by age'/exp NOT ('middle aged'/exp OR 'aged'/exp)	6115551
#31	#29 NOT #30	3114
#32	'medication therapy management'/exp OR 'dementia'/exp/dm_dt OR 'pharmaceutical vehicles and additives'/exp	1465869
#33	#31 NOT #32	2862
#34	#33 NOT 'conference abstract'/it	1380
#35	#34 AND [1-7-2017]/sd NOT [9-4-2018]/sd	131
#36	#34 AND [2017-2018]/py	174
#37	#35 OR #36	189

CINHAL (10 July 2017)

Search	Query	Limiters/Expanders	Hits
S1	(MH "Dementia") OR (MH "Alzheimer's Disease")	Search modes - Find all my search terms	37751
S2	dementia OR alzheimer*	Search modes - Find all my search terms	46604
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	29346
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	67725
S5	(MH "Preventive Health Care")	Search modes - Find all my search terms	1075
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	170718
S7	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	124328
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	290518
S9	S4 AND S8	Search modes - Find all my search terms	6261
S10	(MH "Dementia/PC") OR (MH "Alzheimer's Disease/PC")	Search modes - Find all my search terms	2009
S11	S9 OR S10	Search modes - Find all my search terms	7692
S12	(MH "Education, Continuing") OR (MH "Continuing Education Providers") OR (MH "Education, Diploma Programs") OR (MH "Education, Continuing (Credit)") OR (MH "Education, Masters") OR (MH "Education, Post-Doctoral")	Search modes - Find all my search terms	87064
S13	(MH "Learning") OR (MH "Lifelong Learning")	Search modes - Find all my search terms	10771
S14	(MH "Education, Nonprofessional") OR (MH "Adult Education") OR (MH "Education, Non-Traditional+")	Search modes - Find all my search terms	7406
S15	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*) OR TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	180228

S16	"lifelong learning" OR "life-long learning" OR ((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	106290
S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	27,763
S18	S11 AND S17	Search modes - Find all my search terms	667
S19	MH "Animal Studies"	Search modes - Find all my search terms	39763
S20	S18 NOT S19	Search modes - Find all my search terms	618
S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	55371
S22	S20 NOT S21	Search modes - Find all my search terms	552
S23	S22	Limiters - Published Date: 19900101-20171231	557

CINHAL (8 April 2018)

Search	Query	Limiters/Expanders	Results
S1	(MH "Dementia") OR (MH "Alzheimer's Disease")	Search modes - Find all my search terms	40,224
S2	dementia OR alzheimer*	Search modes - Find all my search terms	50,090
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	32,856
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	73,809
S5	(MH "Preventive Health Care")	Search modes - Find all my search terms	11,313
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	186,284
S7	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	134,37
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	315,336
S9	S4 AND S8	Search modes - Find all my search terms	7,002
S10	(MH "Dementia/PC") OR (MH "Alzheimer's Disease/PC")	Search modes - Find all my search terms	2,127
S11	S9 OR S10	Search modes - Find all my search terms	8,479
S12	(MH "Education, Continuing") OR (MH "Continuing Education Providers") OR (MH "Education, Diploma Programs") OR (MH "Education, Continuing (Credit)") OR (MH "Education, Masters") OR (MH "Education, Post-Doctoral")	Search modes - Find all my search terms	89,104
S13	(MH "Learning") OR (MH "Lifelong Learning")	Search modes - Find all my search terms	11,971
S14	(MH "Education, Nonprofessional") OR (MH "Adult Education") OR (MH "Education, Non-Traditional+")	Search modes - Find all my search terms	7,799
S15	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*) OR TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	191,967
S16	"lifelong learning" OR "life-long learning" OR ((continuing OR adult) N2 (education OR training)) OR ("late life" N1 (activity OR activities OR learn* OR school* OR educat* OR training))	Search modes - Find all my search terms	109,49

S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	290,595
S18	S11 AND S17	Search modes - Find all my search terms	753
S19	MH "Animal Studies"	Search modes - Find all my search terms	43,810
S20	S18 NOT S19	Search modes - Find all my search terms	691
S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	595,044
S22	S20 NOT S21	Search modes - Find all my search terms	617
S23	S22	Limiters - Published Date: 20170101-	78
S24	S22 AND EM 20170701-	Search modes - Find all my search terms	66
S25	S23 OR S24	Search modes - Find all my search terms	95

ERIC (10 July 2017)

Search	Query	Limiters/Expanders	Hits
S1	DE "Dementia" OR DE "Alzheimers Disease"	Search modes - Find all my search terms	1036
S2	DE "Cognitive Ability"	Search modes - Find all my search terms	8133
S3	dementia OR alzheimer*	Search modes - Find all my search terms	1286
S4	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	6424
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	14489
S6	(DE "Early Intervention" OR DE "Prevention") OR (DE "Preventive Medicine")	Search modes - Find all my search terms	22132
S7	TI prevent* OR AB prevent*	Search modes - Find all my search terms	33142
S8	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	30866
S9	S6 OR S7 OR S8	Search modes - Find all my search terms	71745
S10	S5 AND S9	Search modes - Find all my search terms	828
S11	DE "Adult Education" OR DE "Adult Basic Education" OR DE "Continuing Education" OR DE "Migrant Adult Education" OR DE "Preretirement Education" OR DE "Public School Adult Education" OR DE "Veterans Education"	Search modes - Find all my search terms	56528
S12	DE "Adult Learning" OR DE "Adult Programs" OR DE "Adult Reading Programs" OR DE "High School Equivalency Programs" OR DE "Evening Programs" OR DE "Part Time Students" OR DE "Distance Education" OR DE "Extension Education" OR DE "External Degree Programs" OR DE "Rural Extension" OR DE "Urban Extension"	Search modes - Find all my search terms	35681
S13	(DE "Adult Students") OR (DE "Evening Students")	Search modes - Find all my search terms	7787
S14	((DE "Nonschool Educational Programs") OR (DE "Community Education")) OR (DE "Postsecondary Education" OR DE "Higher Education")	Search modes - Find all my search terms	431319

S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8046
S16	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	555016
S17	TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	94
S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	76187
S19	"lifelong learning" or "life-long learning"	Search modes - Find all my search terms	10135
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19	Search modes - Find all my search terms	851728
S21	S10 AND S20	Search modes - Find all my search terms	286
S22	S21	Limiters - Date Published: 19900101-20171231	234

ERIC (8 April 2018)

Search	Query	Limiters/Expanders	Results
S1	DE "Dementia" OR DE "Alzheimers Disease"	Search modes - Find all my search terms	1,075
S2	DE "Cognitive Ability"	Search modes - Find all my search terms	8,553
S3	dementia OR alzheimer*	Search modes - Find all my search terms	1,332
S4	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	6,684
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	15,155
S6	(DE "Early Intervention" OR DE "Prevention") OR (DE "Preventive Medicine")	Search modes - Find all my search terms	22,911
S7	TI prevent* OR AB prevent*	Search modes - Find all my search terms	34,284
S8	TI (protect* OR reduc* OR delay* OR improv*)	Search modes - Find all my search terms	32,348
S9	S6 OR S7 OR S8	Search modes - Find all my search terms	74,665
S10	S5 AND S9	Search modes - Find all my search terms	873
S11	DE "Adult Education" OR DE "Adult Basic Education" OR DE "Continuing Education" OR DE "Migrant Adult Education" OR DE "Preretirement Education" OR DE "Public School Adult Education" OR DE "Veterans Education"	Search modes - Find all my search terms	57,669
S12	DE "Adult Learning" OR DE "Adult Programs" OR DE "Adult Reading Programs" OR DE "High School Equivalency Programs" OR DE "Evening Programs" OR DE "Part Time Students" OR DE "Distance Education" OR DE "Extension Education" OR DE "External Degree Programs" OR DE "Rural Extension" OR DE "Urban Extension"	Search modes - Find all my search terms	36,853
S13	(DE "Adult Students") OR (DE "Evening Students")	Search modes - Find all my search terms	8,01
S14	((DE "Nonschool Educational Programs") OR (DE "Community Education")) OR (DE "Postsecondary Education" OR DE "Higher Education")	Search modes - Find all my search terms	452,212
S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8,311
S16	TI (learn* OR class OR classes OR course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	579,695

S17	TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	102
S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	77,861
S19	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	17
S20	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	10,521
S21	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Find all my search terms	887,984
S22	S10 AND S21	Search modes - Find all my search terms	309
S23	S22	Limiters - Date Published: 20170101-	16
S24	S22 AND EM 20170701-	Search modes - Find all my search terms	0
S25	S23 OR S24	Search modes - Find all my search terms	16

PsycINFO (11 July 2017)

Search	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	39,900
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	30,409
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	65,198
S5	DE "Prevention" OR DE "Preventive Medicine" OR DE "Primary Mental Health Prevention"	Search modes - Find all my search terms	30,316
S6	TI prevent* OR AB prevent*	Search modes - Find all my search terms	186,041
S7	TI protect* OR reduc* OR delay* OR improv*	Search modes - Find all my search terms	743,335
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	869,214
S9	S4 AND S8	Search modes - Find all my search terms	21,587
S10	DE "Adult Education" OR DE "Continuing Education"	Search modes - Find all my search terms	4,126
S11	TI (learning OR education OR educational OR training)	Search modes - Find all my search terms	259,848
S12	TI cognitiv* N1 (stimulat* OR activit*)	Search modes - Find all my search terms	751
S13	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	2,995
S14	(continuing OR adult) N2 (education OR training)	Search modes - Find all my search terms	15,241
S15	S9 AND S11	Search modes - Find all my search terms	826
S16	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,626,731
S17	S15 NOT S16	Search modes - Find all my search terms	683
S18	(DE "Health Education") OR (DE "Drug Therapy") OR (DE "Animals") OR DE "Animal Models" OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	454,796
S19	S17 NOT S18	Search modes - Find all my search terms	414
S20	S17 NOT S18	Limiters - Published Date: 19900101-20171231	403

PsycINFO (9 April 2018)

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	41,992
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	32,064
S4	dementia OR alzheimer*	Search modes - Find all my search terms	99,018
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	146,484
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	210,638
S7	DE "Prevention" OR DE "Preventive Medicine" OR DE "Primary Mental Health Prevention"	Search modes - Find all my search terms	31,621
S8	TI prevent* OR AB prevent*	Search modes - Find all my search terms	195,469
S9	TI protect* OR reduc* OR delay* OR improv*	Search modes - Find all my search terms	783,317
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	914,878
S11	S6 AND S10	Search modes - Find all my search terms	71,575
S12	DE "Cognitive Reserve"	Search modes - Find all my search terms	353
S13	"Cognitive Reserve"	Search modes - Find all my search terms	985
S14	S11 OR S12 OR S13	Search modes - Find all my search terms	72,193
S15	DE "Adult Education" OR DE "Continuing Education"	Search modes - Find all my search terms	4,2
S16	TI (learning OR education OR educational OR training)	Search modes - Find all my search terms	269,992
S17	TI cognitiv* N1 (stimulat* OR activit*)	Search modes - Find all my search terms	794
S18	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	3,169
S19	(continuing OR adult) N2 (education OR training)	Search modes - Find all my search terms	15,885
S20	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	159
S21	S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Find all my search terms	281,675

S22	S14 AND S21	Search modes - Find all my search terms	4,549
S23	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,695,649
S24	S22 NOT S23	Search modes - Find all my search terms	3,295
S25	(DE "Health Education") OR (DE "Drug Therapy") OR (DE "Animals") OR DE "Animal Models" OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	465,312
S26	S24 NOT S25	Search modes - Find all my search terms	2,094
S27	S26	Limiters - Publication Year: 2017-	276
S28	S26 AND RD 201707-	Search modes - Find all my search terms	197
S29	S27 OR S28	Search modes - Find all my search terms	299

ClinicalTrials.gov (16 May 2017)

280 studies found for: (prevention OR reduction OR risk OR improvement) AND (dementia OR alzheimer OR "cognitive impairment" OR "cognitive decline") | healthy OR aged OR adult OR cognitive | education OR learning OR lesson OR educational OR class OR mental OR cognitive | Adult, Senior | Studies that accept healthy volunteers

ClinicalTrials.gov (9 April 2018)

58 Studies found for: (prevention OR reduction OR risk OR improvement) AND (dementia OR alzheimer OR "cognitive impairment" OR "cognitive decline") | healthy OR aged OR adult OR cognitive | education OR learning OR lesson OR educational OR class OR mental OR cognitive | Adult, Senior | Studies that accept healthy volunteers | First posted from 05/01/2017 to 04/09/2018

ICTRP (16 May 2017)

ICTRP		
Search 1	21 records for 20 trials found for:	dementia AND education* AND prevent* OR alzheimer AND education* AND prevent* OR cognitive impairment AND education* AND prevent*
Search 2	3 records for 3 trials found for:	dementia AND mental activ* AND prevent* OR alzheimer AND mental activ* AND prevent* OR cognitive impairment AND mental activ* AND prevent*
Search 3	3 records for 3 trials found for:	dementia AND cognitive stimulat* AND prevent* OR alzheimer AND cognitive stimulat* AND prevent* OR cognitive impairment AND cognitive stimulat* AND prevent*
Search 4	11 records for 11 trials found for:	dementia AND learning AND prevent* OR alzheimer AND learning AND prevent* OR cognitive impairment AND learning AND prevent*
Search 5	No results were found for:	dementia AND lesson* AND prevent* OR alzheimer AND lesson* AND prevent* OR cognitive impairment AND lesson* AND prevent*
Search 6	45 records for 45 trials found for:	dementia AND training AND prevent* OR alzheimer AND training AND prevent* OR cognitive impairment AND training AND prevent*
SUM	**82**	

ICTRP (9 April 2018)

Search 1	20	dementia AND education* AND prevent* OR alzheimer AND education* AND prevent* OR cognitive impairment AND education* AND prevent*
Search 2	3	dementia AND mental activ* AND prevent* OR alzheimer AND mental activ* AND prevent* OR cognitive impairment AND mental activ* AND prevent*
Search 3	5	dementia AND cognitive stimulat* AND prevent* OR alzheimer AND cognitive stimulat* AND prevent* OR cognitive impairment AND cognitive stimulat* AND prevent*
Search 4	27	dementia AND learning AND prevent* OR alzheimer AND learning AND prevent* OR cognitive impairment AND learning AND prevent*
Search 5	1	dementia AND lesson* AND prevent* OR alzheimer AND lesson* AND prevent* OR cognitive impairment AND lesson* AND prevent*
Search 6	64	dementia AND training AND prevent* OR alzheimer AND training AND prevent* OR cognitive impairment AND training AND prevent*
SUM	120	

ALOIS (15 May 2017)

ALOIS		
Study Aim:	Cognitive Enhancement (healthy); Primary Prevention	
Intervention type:	Non-pharmacological	
Intervention:	Contains any word	learning education educational

18 Studies found

ALOIS (9 April 2018)

Not searched website down

DART-Europe (16 May 2017)

search	reults
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimualtion") AND (prevent* OR improve*)	43

DART-Europe (8 April 2018)

search	reults
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimualtion") AND (prevent* OR improve*)	56
YEAR: 2017	4

Supplementary file 4: Search Strategies of Overview of Systematic Reviews, by database

Medline (via PubMed): 10 July 2017

#	Suchen	Ergebnisse
1	Dementia/ or exp Alzheimer Disease/	117573
2	Cognitive Dysfunction/	5969
3	Cognition/	81563
4	(dementia or alzheimer*).ti,ab.	175194
5	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	167110
6	or/1-5	371089
7	exp Leisure Activities/	209051
8	leisure.ti,ab.	13073
9	(hobby or hobbies).ti,ab.	1465
10	free time.ti,ab.	1405
11	Recreation.ti,ab.	4826
12	(in-door or out-door or indoor or outdoor).ti.	8929
13	(garden* or horticultur*).ti.	3216
14	(play* or game? or gaming).ti.	46562
15	(creativ* or painting or drawing or reading).ti.	24387
16	(voluntary or volunteer* or extracurricular).ti.	32266
17	or/7-16	321695
18	6 and 17	9189
19	exp age groups/ not (exp aged/ or middle aged/)	3712487
20	18 not 19	6496
21	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	118333
22	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.	15710
23	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.	145368
24	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	117882
25	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.	171997

26	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.	167686
27	21 or 22 or 23 or 24 or 25 or 26	412039
28	27 not (case report/ or letter.pt.)	401602
29	20 and 28	243
30	remove duplicates from 29	229

Medline (via PubMed): 4 April 2018

#	Searches	Results
1	Dementia/ or exp Alzheimer Disease/	118622
2	Cognitive Dysfunction/	7904
3	Cognition/	82628
4	Cognitive Reserve/	388
5	(dementia or alzheimer*).ti,ab.	179042
6	((cognit* or memory or mental) adj3 (impair* or decline* or deficit* or reduc* or function*)).ti,ab.	171766
7	or/1-6	378437
8	exp Leisure Activities/	207917
9	leisure.ti,ab.	13201
10	(hobby or hobbies).ti,ab.	1472
11	free time.ti,ab.	1429
12	Recreation.ti,ab.	4900
13	(in-door or out-door or indoor or outdoor).ti.	9232
14	(garden* or horticultur*).ti.	3312
15	(play* or game? or gaming).ti.	47658
16	(creativ* or painting or drawing or reading).ti.	24235
17	(voluntary or volunteer* or extracurricular).ti.	32218
18	(cognitiv* adj2 (activity or activities)).ti.	521
19	or/8-18	322366
20	7 and 19	9826
21	exp age groups/ not (exp aged/ or middle aged/)	3685197
22	20 not 21	6996
23	(systematic or structured or evidence or trials).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)	126873
24	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X).is.	15689
25	meta-analysis.pt. or Network Meta-Analysis/ or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).tw,hw.	151505
26	review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)	125835
27	((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).tw,hw. or (quantitativ$ adj5 synthesis$).tw,hw.	184250

28	(integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.	168915
29	23 or 24 or 25 or 26 or 27 or 28	425049
30	29 not (case report/ or letter.pt.)	414173
31	22 and 30	283
32	("2017/07*" or "2017/08*" or "2017/09*" or "2017/1*" or 2018*).dt.	947449
33	(201707* or 201708* or 201709* or 20171* or 2018*).ed.	745570
34	32 or 33	1543513
35	31 and 34	53
36	remove duplicates from 35	52

Embase: 17 Juli 2017

No.	Query	Results
#1	'alzheimer disease'/exp	158632
#2	'mild cognitive impairment'/exp	17483
#3	'dementia'/de	98402
#4	dementia:ti,ab OR alzheimer*:ti,ab	230453
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	226651
#6	#1 OR #2 OR #3 OR #4 OR #5	440912
#7	'recreation'/exp	57806
#8	leisure:ti,ab	16016
#9	hobby:ti,ab OR hobbies:ti,ab	2028
#10	'free time':ti,ab	1939
#11	recreation:ti,ab	6442
#12	'in door':ti OR 'out door':ti OR indoor:ti OR outdoor:ti	11551
#13	garden*:ti OR horticultur*:ti	3581
#14	play*:ti OR game:ti OR games:ti OR gaming:ti	52543
#15	creativ*:ti OR painting:ti OR drawing:ti OR reading:ti	25887
#16	voluntary:ti OR volunteer*:ti OR extracurricular:ti	38793
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	196912
#18	#6 AND #17	5027
#19	'groups by age'/exp AND ('middle aged'/exp OR 'aged'/exp)	3258589
#20	#18 NOT #19	3277
#21	systematic review'/exp OR 'meta analysis'/exp	211886
#22	meta analys*':ti,ab OR metaanalys*:ti,ab OR 'meta synth*':ti,ab OR metasynth*:ti,ab OR ((systematic* OR quantitativ* OR methodologic*) NEAR/5 (review* OR overview* OR synthes*)):ti,ab	239389
#23	systematic:ti OR structured:ti OR evidence:ti OR trials:ti AND (review:ti OR overview:ti OR look:ti OR examination:ti OR update*:ti OR summary:ti)	98173
#24	#21 OR #22 OR #23	306796
#25	#24 NOT ('case report'/exp OR 'case study'/exp)	301911
#26	#20 AND #25	128

Embase: 4 April 2018

No.	Query	Results
#1	'alzheimer disease'/exp	167669
#2	'mild cognitive impairment'/exp OR 'dementia'/de	115768
#3	'cognitive reserve'/de	1341
#4	dementia:ti,ab OR alzheimer*:ti,ab	245434
#5	((cognit* OR memory OR mental) NEAR/3 (impair* OR decline* OR deficit* OR reduc* OR function*)):ti,ab	244167
#6	#1 OR #2 OR #3 OR #4 OR #5	470026
#7	'recreation'/exp	61588
#8	leisure:ti,ab	16979
#9	hobby:ti,ab OR hobbies:ti,ab	2145
#10	'free time':ti,ab	2061
#11	recreation:ti,ab	6767
#12	'in door':ti OR 'out door':ti OR indoor:ti OR outdoor:ti	12183
#13	garden*:ti OR horticultur*:ti	3745
#14	play*:ti OR game:ti OR games:ti OR gaming:ti	55639
#15	creativ*:ti OR painting:ti OR drawing:ti OR reading:ti	26738
#16	voluntary:ti OR volunteer*:ti OR extracurricular:ti OR ((cognitiv* NEAR/2 (activity OR activities)):ti)	39956
#17	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	207154
#18	#6 AND #17	5442
#19	'groups by age'/exp AND ('middle aged'/exp OR 'aged'/exp)	3451202
#20	#18 NOT #19	3533
#21	'systematic review'/exp OR 'meta analysis'/exp	239710
#22	'meta analys*':ti,ab OR metaanalys*:ti,ab OR 'meta synth*':ti,ab OR metasynth*:ti,ab OR (((systematic* OR quantitativ* OR methodologic*) NEAR/5 (review* OR overview* OR synthes*)):ti,ab)	267896
#23	(systematic:ti OR structured:ti OR evidence:ti OR trials:ti) AND (review:ti OR overview:ti OR look:ti OR examination:ti OR update*:ti OR summary:ti)	112383
#24	#21 OR #22 OR #23	342728
#25	#24 NOT ('case report'/exp OR 'case study'/exp)	337160
#26	#20 AND #25	145
#27	#26 AND [1-7-2017]/sd NOT [5-4-2018]/sd	26
#28	#26 AND [2017-2018]/py	30
#29	#27 OR #28	35

CINAHL (Ebsco): 17 July 2017

#	Query	Limiters/Expanders	Results
S1	(MH "Alzheimer's Disease") OR (MH "Dementia")	Search modes - Find all my search terms	38,358
S2	dementia OR alzheimer*	Search modes - Find all my search terms	47,332
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	30,037
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	68,971
S5	(MH "Leisure Activities+")	Search modes - Find all my search terms	36,998
S6	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	11,096
S7	TI in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular	Search modes - Find all my search terms	31,628
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	69,497
S9	S4 AND S8	Search modes - Find all my search terms	2,053
S10	MH "Animal Studies"	Search modes - Find all my search terms	41,599
S11	S9 NOT S10	Search modes - Find all my search terms	2,051
S12	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	564,745
S13	S11 NOT S12	Search modes - Find all my search terms	1,855
S14	(MH "Systematic Review") OR (MH "Meta Analysis")	Search modes - Find all my search terms	42,089
S15	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	31,338
S16	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Boolean/Phrase	55,272
S17	TI (systematic OR structured OR evidence OR trials) AND (review OR overview OR look OR examination OR update* OR summary)	Search modes - Boolean/Phrase	27,392
S18	S14 OR S15 OR S16 OR S17	Search modes - Find all my search terms	72,333
S19	S13 AND S18	Search modes - Find all my search terms	71

CINAHL (Ebsco): 4 April 2018

#	Query	Limiters/Expanders	Results
S1	(MH "Alzheimer's Disease") OR (MH "Dementia")	Search modes - Find all my search terms	40,163
S2	dementia OR alzheimer*	Search modes - Find all my search terms	50,045
S3	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	32,819
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	73,730
S5	(MH "Leisure Activities+")	Search modes - Find all my search terms	39,894
S6	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	11,740
S7	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR oluntary OR volunteer* OR extracurricular) OR TI (cognitiv* W1 (activity OR activities))	Search modes - Find all my search terms	33,266
S8	S5 OR S6 OR S7	Search modes - Find all my search terms	73,940
S9	S4 AND S8	Search modes - Find all my search terms	2,298
S10	MH "Animal Studies"	Search modes - Find all my search terms	43,752
S11	S9 NOT S10	Search modes - Find all my search terms	2,295
S12	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	594,058
S13	S11 NOT S12	Search modes - Find all my search terms	2,079
S14	(MH "Systematic Review") OR (MH "Meta Analysis")	Search modes - Find all my search terms	50,503
S15	meta-analys* OR meta analys* OR metaanalys* OR	Search modes - Boolean/Phrase	34,556

	meta synth* OR meta-synth* OR metasynth*		
S16	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Boolean/Phrase	63,373
S17	TI (systematic OR structured OR evidence OR trials) AND (review OR overview OR look OR examination OR update* OR summary)	Search modes - Boolean/Phrase	30,586
S18	S14 OR S15 OR S16 OR S17	Search modes - Find all my search terms	81,245
S19	S13 AND S18	Search modes - Find all my search terms	93
S20		Limiters - Published Date: 20170701- Search modes - Find all my search terms	156,794
S21	EM 20170701-	Search modes - Find all my search terms	208,855
S22	S20 OR S21	Search modes - Find all my search terms	253,372
S23	S22 AND S19	Search modes - Find all my search terms	27

PsycINFO (Ebsco): 18 July 2017

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	39,908
S2	DE "Senile Dementia"	Search modes - Find all my search terms	1,063
S3	DE "Cognitive Impairment"	Search modes - Find all my search terms	30,416
S4	dementia OR alzheimer*	Search modes - Find all my search terms	94,008
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	138,651
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	200,033
S7	(((((DE "Leisure Time") OR (DE "Hobbies")) AND (DE "Recreation" OR DE "Clubs (Social Organizations)" OR DE "Traveling" OR DE "Vacationing")) OR (DE "Gambling")) AND (DE "Games" OR DE "Chess" OR DE "Computer Games"))	Search modes - Find all my search terms	347
S8	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	37,212
S9	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular) OR SU (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)	Search modes - Find all my search terms	175,457
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	207,264
S11	S6 AND S10	Search modes - Find all my search terms	5,662
S12	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,627,211
S13	S11 NOT S12	Search modes - Find all my search terms	3,357
S14	(DE "Animals") OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	311,593
S15	S13 NOT S14	Search modes - Find all my search terms	3,212

S16	(DE "Drug Therapy")	Search modes - Find all my search terms	127,11
S17	S15 NOT S16	Search modes - Find all my search terms	3,161
S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,026
S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	27,695
S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	27,454
S21	TI (systematic OR structured OR evidence OR trials) AND TI (review OR overview OR look OR examination OR update* OR summary)	Search modes - Find all my search terms	16,949
S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	51,681
S23	S17 AND S22	Search modes - Find all my search terms	73

PsycINFO (Ebsco): 5 April 2018

#	Query	Limiters/Expanders	Results
S1	DE "Alzheimer's Disease"	Search modes - Find all my search terms	41,959
S2	DE "Senile Dementia" OR DE "Cognitive Impairment"	Search modes - Find all my search terms	33,077
S3	DE "Cognitive Reserve"	Search modes - Find all my search terms	353
S4	dementia OR alzheimer*	Search modes - Find all my search terms	98,945
S5	((cognit* OR memory OR mental) N3 (impair* OR decline* OR deficit* OR reduc* OR function*))	Search modes - Find all my search terms	146,379
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Find all my search terms	210,573
S7	(((((DE "Leisure Time") OR (DE "Hobbies")) AND (DE "Recreation" OR DE "Clubs (Social Organizations)" OR DE "Traveling" OR DE "Vacationing")) OR (DE "Gambling")) AND (DE "Games" OR DE "Chess" OR DE "Computer Games"))	Search modes - Find all my search terms	358
S8	leisure OR hobby OR hobbies OR "free time" OR Recreation	Search modes - Find all my search terms	39,017
S9	TI (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular OR (cognitiv* W1 activit*)) OR SU (in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular OR (cognitiv* W1 activit*))	Search modes - Find all my search terms	182,299
S10	S7 OR S8 OR S9	Search modes - Find all my search terms	215,667
S11	S6 AND S10	Search modes - Find all my search terms	6,166
S12	(ZG "adolescence (13-17 yrs)" or ZG "adulthood (18 yrs & older)" or ZG "childhood (birth-12 yrs)") not (ZG "aged (65 yrs & older)" or ZG "middle age (40-64 yrs)")	Search modes - Find all my search terms	1,695,146

S13	S11 NOT S12	Search modes - Find all my search terms	3,706
S14	(DE "Animals") OR TI (rat OR rats OR mouse OR mice OR dog OR dogs) OR SU (rat OR rats OR mouse OR mice OR dog OR dogs)	Search modes - Find all my search terms	318,343
S15	S13 NOT S14	Search modes - Find all my search terms	3,539
S16	(DE "Drug Therapy")	Search modes - Find all my search terms	129,812
S17	S15 NOT S16	Search modes - Find all my search terms	3,481
S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,152
S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	30,127
S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	30,748
S21	TI (systematic OR structured OR evidence OR trials) AND TI (review OR overview OR look OR examination OR update* OR summary)	Search modes - Find all my search terms	19,166
S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	56,448
S23	S17 AND S22	Search modes - Find all my search terms	84
S24	RD 201707-	Search modes - Find all my search terms	148,956
S25	DT 201707-	Search modes - Find all my search terms	100,982
S26	S24 OR S25	Search modes - Find all my search terms	159,715
S27	S23 AND S26	Search modes - Find all my search terms	13

Epistemonikos 18. Juli 2017

Search	Results
(dementia OR alzheimer* OR cognitiv*) AND (leisure OR recreation OR "free time" OR hobby OR hobbies OR (title:(in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)))	273
Filter: Systematic Review	64

Epistemonikos 18. Juli 2017

Search	Results
(dementia OR alzheimer* OR cognitiv*) AND (leisure OR recreation OR "free time" OR hobby OR hobbies OR (title:(in-door OR out-door OR indoor OR outdoor OR garden* OR horticultur* OR play* OR game OR games OR gaming OR creativ* OR painting OR drawing OR reading OR voluntary OR volunteer* OR extracurricular)))	368
Filter: Systematic Review	146
Added to database: 01-07-17 to 05-04-18	25

Cochrane Library: 18. Juli 2017

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4053
#2	[mh ^"Cognitive Dysfunction"]	181
#3	[mh ^Cognition]	6276
#4	(dementia or alzheimer*):ti,ab,kw	11879
#5	((cognit* or memory or mental) next (impair* or decline* or deficit* or reduc* or function*)):ti,ab,kw	12722
#6	{or #1-#5}	25014
#7	[mh "Leisure Activities"]	15395
#8	leisure:ti,ab,kw	1481
#9	(hobby or hobbies):ti,ab,kw	55
#10	"free time":ti,ab,kw	162
#11	Recreation:ti,ab,kw	615
#12	(in-door or out-door or indoor or outdoor):ti,kw	478
#13	(garden* or horticultur*):ti,kw	106
#14	(play* or game* or gaming):ti,kw	3280
#15	(creativ* or painting or drawing or reading):ti,kw	2913
#16	(voluntary or volunteer* or extracurricular):ti,kw	17942
#17	{or #7-#16}	39978
#18	#6 and #17	1551
#19	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	104634
#20	#18 not #19 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations	38

Cochrane Library: 5. April 2018

ID	Search	Hits
#1	[mh ^Dementia] or [mh "Alzheimer Disease"]	4263
#2	[mh ^"Cognitive Dysfunction"]	450
#3	[mh ^Cognition]	6675
#4	[mh ^"Cognitive Reserve"]	8
#5	(dementia or alzheimer*):ti,ab,kw	13099
#6	((cognit* or memory or mental) next (impair* or decline* or deficit* or reduc* or function*)):ti,ab,kw	14315
#7	{or #1-#6}	27581
#8	[mh "Leisure Activities"]	16504
#9	leisure:ti,ab,kw	1683
#10	(hobby or hobbies):ti,ab,kw	59
#11	free time:ti,ab,kw	169
#12	Recreation:ti,ab,kw	674
#13	(in-door or out-door or indoor or outdoor):ti,kw	541

#14	(garden* or horticultur*):ti,kw	125
#15	(play* or game* or gaming):ti,kw	3653
#16	(creativ* or painting or drawing or reading):ti,kw	3482
#17	(voluntary or volunteer* or extracurricular):ti,kw	20037
#18	(cognitiv* near/2 (activity or activities)):ti,kw	80
#19	{or #8-#18}	44252
#20	#7 and #19	1838
#21	[mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
#22	#20 not #21 Publication Year from 2017 to 2018, in Cochrane Reviews (Reviews and Protocols) and Technology Assessments	1

Supplementary file 5: Risk of Bias of included studies

Systematic reviews

Author, Year	RISK OF BIAS	Dual Screening and Extraction	Comprehensive literature search	Study quality assessed	'A priori' design	Grey literature included	List of studies	Study characteristics provided	Scientific quality used appropriately	Appropriate methods to combine findings	Publication bias	Conflict of interest included	Reason for High Risk of Bias Decision
Di Marco et al., 2014 [41]	High	NR	Yes	No	Yes	No	No	No	NA	Yes	No	No	No information on screening methods or dual extraction No risk of bias assessment
Opdebeeck et al., 2016 [42]	High	Yes	Yes	No	Yes	Yes	No	Yes	NA	Yes	No	No	No risk of bias assessment No assessment of Publication bias
Sajeev et al., 2016 [43]	Medium	NR	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No information on dual screening or dual extraction
Toril et al., 2014 [44]	High	NR	Yes	No	Yes	No	No	Yes	NA	Yes	Yes	No	No information on screening methods or dual extraction No risk of bias assessment
Yates et al., 2016 [45]	Medium	NR	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No (too few studies)	Yes	No information on dual screening or dual extraction

NA = not applicable, NR = not reported

Supplementary file 6: List of excluded studies during full text screening

Systematic review:

Study	Title	Reason for Exclusion
Canadian Nursing Home, 2007	Studies confirm link between late-life cognitive activities and reduced risk of dementia	Not retrievable
Adam et al., 2013	Occupational activity and cognitive reserve: implications in terms of prevention of cognitive aging and Alzheimer's disease	Ineligible study design
GM: Midlife & Beyond, 2017	Study finds education does not protect against cognitive decline in later life	Ineligible study design
Dowd et al., 2003	Can mental and physical activities such as chess and gardening help in the prevention and treatment of Alzheimer's? Healthy aging through stimulation of the mind	Ineligible study design
Beydoun et al., 2014	Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis	Ineligible study design
Gilland, 2007	Continuing education topic 4: dementia	Ineligible study design
Nursing Standard, 2010	Clinical digest. Cognitive stimulation delays dementia but later decline is faster	Ineligible publication type
Albert et al., 2007	Changing the trajectory of cognitive decline?	Ineligible publication type
Bak et al., 2016	Language lessons to help protect against dementia	Ineligible publication type
Bauer et al., 2002	RN news watch: clinical highlights. Mentally stimulating activities seem to cut Alzheimer's risk	Ineligible publication type
Burgener et al., 2009	Effectiveness of community-based, nonpharmacological interventions for early-stage dementia: conclusions and recommendations	Ineligible publication type
Gatz et al., 2005	Educating the brain to avoid dementia: can mental exercise prevent Alzheimer disease?	Ineligible publication type
Rosenberg et al., 2017	Influence of apoe, age, sex, education and baseline cognition on intervention effects on cognition in the finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)	Ineligible publication type
Summers et al., 2013	The Tasmanian Healthy Brain Project (THBP): a prospective longitudinal examination of the effect of university-level education in older adults in preventing age-related cognitive	Ineligible publication type
Wahlund et al., 2006	[Life-long mental exercise can prevent Alzheimer disease]	Ineligible publication type
ACTRN126120001 47886, 2012	The Body, Brain, Life Program â€“a prevention trial to reduce risk of Alzheimer's Disease	Ineligible intervention
Anon et al., 2008	The Study of Mental Activity and Regular Training for the Prevention of Cognitive Decline in at Risk Individuals: The SMART Trial Or The Study of Mental Activity and Regular	Ineligible intervention
Brenes et al., 2003	Cognitive training may improve targeted cognitive functions in older adults	Ineligible intervention
Fratiglioni et al., 2007	Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project	Ineligible intervention
Gatz et al., 2006	Lifestyle risk and delaying factors	Ineligible intervention
Hall et al., 2009	Cognitive activities delay onset of memory decline in persons who develop dementia	Ineligible intervention
Harmanci et al., 2003	Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey	Ineligible intervention
Harmanci et al., 2003	Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey	Ineligible intervention
Kwok et al., 2011	Effectiveness of coordination exercise in improving cognitive function in older adults: a prospective study	Ineligible intervention
Le Carret et al., 2003	The effect of education on cognitive performances and its implication for the constitution of the cognitive reserve	Ineligible intervention
Merom et al., 2016	Cognitive benefits of social dancing and walking in old age: The dancing mind randomized controlled trial	Ineligible intervention
Roberts et al., 2015	Risk and protective factors for cognitive impairment in persons aged 85 years and older	Ineligible intervention
Sandro et al., 2008	Risk-reducing effect of education in Alzheimer's disease	Ineligible intervention
Sattler et al., 2012	Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease	Ineligible intervention
Schultz et al., 2015	Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease	Ineligible intervention
Soubelet et al., 2011	Engaging in cultural activities compensates for educational differences in cognitive abilities	Ineligible intervention

Standford University, 2012	Activities for Cognitive Enhancement of Seniors	Ineligible intervention
Then et al., 2016	Education as protector against dementia, but what exactly do we mean by education?	Ineligible intervention
University Hospital 2016	Long-term Effects of Interventional Strategies to Prevent Cognitive Decline in Elderly	Ineligible intervention
VanDijk et al., 2008	No protective effects of education during normal cognitive aging: results from the 6-year follow-up of the Maastricht Aging Study	Ineligible intervention
Vemuri et al., 2014	Association of lifetime intellectual enrichment with cognitive decline in the older population	Ineligible intervention
Wang et al., 2002	Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project	Ineligible intervention
Yaffe et al., 2009	Predictors of maintaining cognitive function in older adults: the Health ABC study	Ineligible intervention
Kliegel et al., 2004	Life-long intellectual activities mediate the predictive effect of early education on cognitive impairment in centenarians: A retrospective study	Ineligible populations
Jonaitis et al., 2013	Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease	Ineligible populations
Friedland et al., 2001	Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members	No information about the intervention
National University,	Choral Singing For the Prevention of Dementia	not finished study
Marquez et al., 2017	Regular Latin Dancing and Health Education may Improve Cognition of Late Middle-Aged and Older Latinos	Ineligible comparison;
University Hospital 2018	Prospective Population Based Cohort Study on Cognitive and Cardiovascular Aging (MonaLisaPredor)	not finished study;
Janssen Research Development 2018	Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research: Prospective Readiness Cohort Study	not finished study
ACTRN126170008 58392 2017	Ageing and Folk Dances from the Basque Country: Functional and neuropsychological changes. A controlled trial.	Ineligible intervention
Biasutti et al., 2018	Assessing a cognitive music training for older participants: a randomised controlled trial	Ineligible population
Centre de Recherche del'Institut Universitaire de Geriatriede. 2018	Impact of a Cognitive Intervention Enriched With Leisure Activities in Persons With Subjective Cognitive Decline	Not finished study
Chan et al., 2016	Training Older Adults to Use Tablet Computers: Does It Enhance Cognitive Function?	Ineligible study design
Ihle et al., 2017	The relation of education and cognitive activity to mini-mental state in old age: The role of functional fitness status	Ineligible intervention
Krell-Roesch et al., 2017	Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the APOE epsilon4 Genotype	Ineligible intervention
NCT02919748, 2016	Choral Singing For the Prevention of Dementia	Not finished study
Ramos et al., 2017	Does learning a language in the elderly enhance switching ability?	Ineligible outcome
Wang et al., 2017	Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study	Ineligible intervention
Zanesco et al., 2018	Mental training of attention through intensive meditation: Longitudinal behavioral and electrophysiological investigations of visual sustained attention and response inhibition	Not retreivable
Zhu et al., 2017	Leisure activities, education, and cognitive impairment in Chinese older adults: A population-based longitudinal study	Ineligible intervention
2017	Study suggests late-life activities reduce the risk of mild cognitive impairment	Ineligible study design

Overview of Systematic Reviews

Study	Title	Reason for Exclusion
Bernhardt et al., 2002	[The effect of psychosocial factors on risk of dementia]	Ineligible intervention
Bleakley et al., 2015	Gaming for health: a systematic review of the physical and cognitive effects of interactive computer games in older adults	Ineligible intervention
Conti et al., 2009	The potential role of leisure in the prevention of dementia	Not retreivable
Fratiglioni et al., 2004	An active and socially integrated lifestyle in late life might protect against dementia	Ineligible study design
Karkou et al., 2017	Dance movement therapy for dementia	Ineligible population
Lee et al., 2019	Systematic review of health behavioral risks and cognitive health in older adults	Ineligible intervention
Liapis et al., 2017	Meaningful use of computers has a potential therapeutic and preventative role in dementia care: A systematic review	Ineligible intervention
Munn et al., 2010	Review summaries: evidence for nursing practice. Cognitive leisure activities and their role in preventing dementia: a systematic review	Ineligible publication type
Opdebeeck et al., 2014	Cognitive reserve and cognitive function: A meta-analysis	Ineligible publication type
Stephen et al., 2017	Physical Activity and Alzheimer's Disease: A Systematic Review	Ineligible intervention
Stern et al., 2010	Cognitive leisure activities and their role in preventing dementia: a systematic review	Study superseeded by more recent study
Stern et al., 2009	Cognitive leisure activities and their role in preventing dementia: a systematic review	Ineligible publication type
Wang et al., 2012	Leisure activities, cognition and dementia	Study superseeded by more recent study
Wayne et al., 2014	Effect of tai chi on cognitive performance in older adults: systematic review and meta-analysis	Ineligible intervention
Zheng et al., 2015	Tai Chi and the Protection of Cognitive Ability: A Systematic Review of Prospective Studies in Healthy Adults	Ineligible intervention
Fallahpour et al., 2016	Leisure-activity participation to prevent later-life cognitive decline: a systematic review	Study superseeded by more recent study (search only till 2011)
Bediou et al., 2018	Meta-Analysis of Action Video Game Impact on Perceptual, Attentional, and Cognitive Skills	Ineligible population
Howes et al., 2017	Gaming for Health: Systematic Review and Meta-analysis of the Physical and Cognitive Effects of Active Computer Gaming in Older Adults	Inelgiible intervention
Klimova et al., 2017	Cognitive decline in normal aging and its prevention: a review on non-pharmacological lifestyle strategies	Ineligible intervention
Schneider et al., 2018	Potential Cognitive Benefits From Playing Music Among Cognitively Intact Older Adults: A Scoping Review	Ineligible study design
Solloway et al., 2016	An evidence map of the effect of Tai Chi on health outcomes	Ineligible study design
Wouters et al., 2013	A meta-analysis of the cognitive and motivational effects of serious games	Ineligible study design
Zhang et al., 2016	Physical and Cognitive Impacts of Digital Games on Older Adults: A Meta-Analytic Review	Ineligible intervention

GRADE of Recommendations:

Cognitive leisure activities compared to no cognitive leisure activities for the prevention of dementia (OPDEBEEK et al.)

Patient or population: over 60 years, non-demented adults at baseline

Intervention: cognitive leisure activities

Comparison: no cognitive leisure activities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no cognitive leisure activities	**Risk with cognitive leisure activities**				
Overall cognitive functioning	The mean overall cognitive functioning was **0** SD	The mean overall cognitive functioning in the intervention group was 0,26 SD higher (0,21 higher to 0,31 higher)	-	(31 observational studies)	⨁◯◯◯ VERY LOW [a,b]	

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

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

Explanations

a. I^2 = 94%, b. Interventions vary between studies

Video Games compared to no Video Games for the prevention of dementia (TORIL et al.)

Patient or population: 50-86 years, healthy older adults

Intervention: Video Games

Comparison: no Video Games

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no Video Games	Risk with Video Games				
Cognitive Function	-	-	-	913 (20 observational studies)	⨁◯◯◯ VERY LOW [a]	

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

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

Explanations

a. Mixing various different interventions and study designs

Cognitive leisure activities compared to no cognitive leisure activities for healthy older adults (YATES et al.)

Patient or population: over 46 years, healthy older adults, **Intervention**: cognitive leisure activities, **Comparison**: no cognitive leisure activities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no cognitive leisure activities	Risk with cognitive leisure activities				
Incidence of AD	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 0.610** (0.418 to 0.900)	(3 observational studies)	⨁◯◯◯ VERY LOW [a,b]	
Incidence of AD	0 per 1.000	**NaN per 1.000** (NaN to NaN)	**HR 0.584** (0.462 to 0.739)	(2 observational studies)	⨁◯◯◯ VERY LOW [b]	
Incidence of AD	**Low**		**OR 0.775** (0.668 to 0.899)	0 cases 0 controls (2 observational studies)	⨁◯◯◯ VERY LOW [b,c]	
	0 per 1.000	**0 per 1.000** (0 to 0)				
Incidence of cognitive impairment	0 per 1.000	**0 per 1.000** (0 to 0)	**OR 0.685** (0.550 to 0.845)	(5 observational studies)	⨁◯◯◯ VERY LOW [b]	
Incidence of cognitive impairment	0 per 1.000	**NaN per 1.000** (NaN to NaN)	**HR 0.853** (0.711 to 1.022)	(3 observational studies)	⨁◯◯◯ VERY LOW [b,c]	

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

Explanations

a. moderate heterogeneity, x^2 test p=0.09, b. differences in interventions (definition of cognitive leisure activities varies across studies), c. high heterogeneity, x^2 test p=0.00, confidence intervals do not overlap

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 (line 1-3)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4 (line 40-67)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-7 (line 127-132)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7 (line 133-144)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 7 (line 149-151)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8-9 (line 171-196)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9-10 (line 197-214)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file 3 and 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10 (line 215-218)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10 (line 219-226)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10 (line 222-226)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10-11 (line 227-233)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 11 (line 234-240)

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 11 (line 234-240)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11 (line 238-243) Figure 2 and figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-12 (line 255-278) Table 1 and table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13-14 Table 1 and table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-17 (line 288-351) Table 1 and table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 12 (line 264-266; line 273-278) Supplementary file 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 18

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 21 (line 423-425)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.