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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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Manuscripts

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2 1 **Continuing Education for the Prevention of Mild Cognitive Impairment and**
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5 2 **Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic**
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8 3 **Reviews.**

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32 **ABSTRACT**

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

35 **Design:** Systematic review and overview of systematic reviews.

36 **Data sources:** We systematically searched MEDLINE, PsycINFO, EMBASE, CENTRAL, CINAHL and
37 Scopus for published studies and gray literature databases for unpublished studies from January
38 1990 to April 2018.

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

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

56 **Conclusion:** Available results demonstrate that cognitive reserve increases through continuing
57 education and show a positive association of cognitive leisure activities with both improved cognitive
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2 58 function and lower dementia incidence. Healthcare providers and policymakers should promote a
3
4 59 healthy lifestyle, which also includes being cognitively active throughout life.

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6 60 **Systematic review registration:** PROSPERO CRD42017063944
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13 63 **Strengths and Limitations of this study:**

- 14
15 64 • This is the first systematic review assessing the benefits and harms of continuing education
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17 65 on the prevention of mild cognitive impairment or Alzheimer's type dementia.
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19 66 • This is the first overview of systematic reviews presenting an up-to-date summary of
20
21 67 currently available research in the field of cognitive leisure activities and dementia.
22
23 68 • The certainty of evidence is low, indicating that future studies might have a substantial
24
25 69 impact on results of our review.
26
27 70 • Measurements and types of cognitive leisure activities differed widely across studies and
28
29 71 quantitative analysis were often not possible.
30
31 72 • The majority of included systematic reviews have serious methodological shortcomings.
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75 INTRODUCTION

76 In 2012, the World Health Organization (WHO) named the prevention and control of
77 neurocognitive disorders such as mild cognitive impairment or Alzheimer's-type dementia a global
78 public health priority.¹ Alzheimer's-type dementia is the most common form of dementing illnesses.¹
79 In 2015, 47.5 million people worldwide lived with Alzheimer's disease or another closely related
80 dementing illness.² As a consequence of the rapidly aging world population, the prevalence is
81 projected to rise up to 135.5 million patients in 2050.²

82 The progressive loss of independent functioning of patients with Alzheimer's-type dementia,
83 leads to an enormous social and economic burden. In 2017, the U.S. economic burden associated
84 with Alzheimer's type dementia was estimated to be 259 billion U.S. Dollars³ the total global costs for
85 dementia were 818 billion in 2015.⁴

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

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

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

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2 101 cardiovascular diseases, diabetes, obesity, cancers, depression, thyroid disorder, or genetic factors.¹⁰
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4 102 However, some studies found a protective association of cognitively stimulating activities, such as
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6 103 learning a new language in middle age, with a slower cognitive decline during late life.¹¹⁻¹⁵ Such
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8 104 results underpin the “cognitive reserve hypothesis”.¹⁶⁻¹⁸ According to this theory, through every
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10 105 activity that stimulates the brain, the cognitive reserve gets boosted and the resistance towards any
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12 106 dementia-related brain pathology increases.¹⁹ In animal trials, an enriched environment was
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14 107 associated with increased cortical thickness.²⁰ Epidemiological research on humans has shown that
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16 108 education²¹ and probably also other forms of intellectual stimulation, during the whole lifespan, is
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18 109 associated with a lower risk to develop dementia.^{22,23} A larger cognitive reserve acquired by
19
20 110 continuing education activities, thus, might protect against cognitive decline.^{19,24}
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25 111 For this systematic review, we define continuing education as structured learning activities
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27 112 and programs provided by formal and non-formal educational institutions for persons beyond the
28
29 113 age of compulsory schooling. These activities are designed to help individuals satisfy learning needs
30
31 114 and interests, to enrich knowledge, to develop and improve abilities and skills, and to foster
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33 115 personality, social competences, families, networks, health, and professional life. Continuing
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35 116 education is voluntary, and based on topics and courses that are not directly connected to any
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37 117 special job position or vocational training.²⁵⁻³⁰
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41 118 **Rationale**

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44 119 To date, the preventive effect of continuing education on cognitive impairment and Alzheimer’s-type
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46 120 dementia has not been assessed in an objective and systematic way. The aim of our review was to
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48 121 summarise the evidence investigating the preventive effects of continuing education on the
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50 122 development of cognitive impairment and Alzheimer’s-type dementia.
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53 123 Our systematic review addressed the following questions:
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2 124 **Key question 1a:** In adults 45 years of age or older with normal cognition or merely subjective
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4 125 cognitive impairment, does continuing education lead to a reduction in the risk of mild cognitive
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6 126 impairment or Alzheimer's-type dementia compared with no continuing education?
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9 127 **Key question 1b:** (In case no evidence on continuing education is available or the evidence is sparse):
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11 128 In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment,
12
13 129 do leisure activities lead to a reduction in the risk of mild cognitive impairment or Alzheimer's-type
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15 130 dementia compared with no continuing education?
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18 131 **Key question 2:** What are potential harms of continuing education?
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21 132 **Key question 3:** Do benefits and harms differ by subgroups based on age, sex/gender, race or
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23 133 ethnicities, level of education, or duration of intervention?
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26 134 **Key question 4:** What is the optimal age to start continuing education to prevent mild cognitive
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28 135 impairment or dementia?
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33 137 **METHODS**

36 138 **Design**

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38 139 Throughout this manuscript we followed the PRISMA (Preferred Reporting Items for
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40 140 Systematic Reviews and Meta-Analyses) statement³¹ (See supplementary file 1). The protocol of this
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42 141 systematic review was published³² and registered in PROSPERO (International Prospective Register of
43
44 142 Systematic Reviews) (Registration number CRD42017063944). Figure 1 depicts the analytic
45
46 143 framework that guided our systematic review.
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49 144 [Figure 1 about here]

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52 145 We addressed our research questions with two different methodological approaches:
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- 54 146 1) We performed a systematic review of primary studies to assess the preventive
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56 147 effects and potential harms of continuing education provided by formal and non-formal
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58 148 institutions (key questions 1a, 2, 3, and 4)
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2 149 2) We conducted an overview of systematic reviews to determine the preventive effects
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4 150 and potential harms of related leisure activities (e.g. playing cards, reading books, etc., key
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6 151 question 1b).

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8 152 We chose this two-step approach because studies in the field of continuing education and
9
10 153 dementia are very rare. Certain leisure activities, however, are able to mimic continuing education
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12 154 regarding content (e.g. learning a new language privately versus learning a new language as an
13
14 155 organized educational activity). Leisure activities are not our primary focus of interest but can be
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16 156 considered as surrogate interventions for continuing education in some circumstances.
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21 22 158 **Study selection**

23 24 159 **Eligibility criteria for the systematic review**

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26 160 The population of interest were adults 45 years or older, without a clinical diagnosis of
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28 161 cognitive impairment at the time of study recruitment, which included people with subjective
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30 162 cognitive impairment. Eligible interventions comprised of all cognitive activities that are provided by
31
32 163 formal and non-formal educational institutions. These activities include classes, courses, and
33
34 164 trainings that are based on individual interests and that are attended voluntarily. We included
35
36 165 randomized controlled trials, nonrandomized controlled trials, prospective controlled cohort studies,
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38 166 retrospective controlled cohort studies, and case-control studies. All nonrandomized studies needed
39
40 167 to have a minimum sample size of 300 or more participants.
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45 168 Eligible studies had a minimum follow up time of 1 year and a minimum duration of
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47 169 intervention of 3 months. We excluded studies that investigated formal (vocational) education (e.g.
48
49 170 School or College), physical activities, and all job-related courses and trainings.

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51 171 Outcomes of interest included patient-relevant health outcomes such as incidence of
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53 172 dementia, incidence of MCI, psychological wellbeing, functional capacity, quality of life, and other
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55 173 relevant health outcomes; in addition, we included intermediate outcomes such as cognitive
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57 174 functioning, cognitive (test) performance, or social inclusion. For the purpose of our study, mild
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2 175 cognitive impairment refers to “amnesic” mild cognitive impairment (aMCI), meaning that memory
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4 176 loss is the predominant symptom.³³
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7 177 **Eligibility criteria for the overview of systematic reviews**

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9 178 Eligibility criteria for population and outcomes for the overview of systematic reviews were
10
11 179 the same as for the systematic review. Eligible interventions were leisure activities that are
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13 180 cognitively stimulating and mimic the content of continuing education but in an informal setting. Just
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15 181 as in the systematic review, we excluded physical activities. Eligible study designs were exclusively
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17 182 systematic reviews and meta-analyses. We excluded reviews with searches conducted before 2013.
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20 183 Further details about our inclusion and exclusion criteria can be found in our protocol³² and
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22 184 in the supplementary file 2.
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26 185 **Search strategy**

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28 186 We systematically searched Ovid MEDLINE, Cochrane Library, Embase, PsycINFO, CINAHL
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30 187 (Cumulative Index to Nursing and Allied Health Literature), ALOIS (the Cochrane Dementia and
31
32 188 Cognitive Improvement Group Specialized Register), and ERIC (Education Resources Information
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34 189 Center) from January 1990 to April 2018 to identify relevant publications (see supplementary file 3
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36 190 for the search strategy). For the overview of reviews, we searched Epistemonikos from inception to
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38 191 April 2018 in addition to the above mentioned databases (see supplementary file 4).
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42 192 An experienced information specialist developed an appropriate search strategy using a
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44 193 combination of medical subject headings (MeSH[®]) and title and abstract keywords, limiting the
45
46 194 search to human-only studies without applying any language limitations. The electronic Ovid Medline
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48 195 search strategy was peer-reviewed by another information specialist following the PRESS (peer
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50 196 review of the electronic search strategy) statement.³⁴ For the systematic review, we searched for
51
52 197 gray literature in ClinicalTrials.gov, the World Health Organization’s International Clinical Trials
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54 198 Registry Platform, web pages of relevant organizations, and a dissertation database (“Digital Access
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56 199 to Research Theses”, [DART-Europe](#)). Additionally, in an attempt to avoid retrieval bias, we manually
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1
2 200 searched the reference lists of landmark studies and background articles on this topic to look for any
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4 201 relevant citations that our electronic searches might have missed. We imported all citations into an
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6 202 electronic database (EndNote X.8) and deleted duplicates.
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9 203 **Study selection**

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11 204 Two review authors independently screened abstracts and relevant full text articles for
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13 205 eligibility, using Covidence Software.³⁵ They resolved disagreements by discussion or by consultation
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15 206 with a third author.
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18 19 207 **Data abstraction**

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22 208 We designed, pilot-tested, and used a data abstraction form to gather pertinent information
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24 209 from each article. One author extracted relevant data from each study that met our inclusion criteria.
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26 210 A second author of the team cross-checked data abstractions for completeness and accuracy. We
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28 211 extracted study information (author, publication year, years covered by searches, location/setting,
29
30 212 number of included studies and included study designs), sample size, study characteristics
31
32 213 (population, interventions, and comparators), outcome measurements, and results. For systematic
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34 214 reviews we abstracted summary estimates of meta-analyses whenever available.
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38 215 **Risk of bias assessment**

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40 216 Two investigators independently assessed the risk of bias of included studies. They resolved
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42 217 any disagreements by consensus or by consulting a third team member. For eligible non-randomized
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44 218 studies we used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool.³⁶ For
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46 219 the assessment of eligible systematic reviews, we used the AMSTAR (Assessing the Methodological
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48 220 Quality of Systematic Reviews) tool.³⁷ Detailed risk of bias ratings of included articles are given in
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50 221 supplementary file 5.
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55 222 **Data synthesis and statistical analysis**

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57 223 We narratively summarized evidence from included studies. If available, we present effect
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59 224 estimates of systematic reviews. For the incidence of dementia we present hazard ratios (HR), odds
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2 225 ratios (OR), and risk ratios (RR). A value below 1 represents a lower risk for the intervention, a value
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4 226 greater than 1 indicates a lower risk for the control group; an estimate of 1 means no difference
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6 227 between intervention and control. For the assessment of cognitive test performance we use
7
8 228 standardized mean differences because scales for measurements differed in the individual studies. A
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10 229 standardized mean difference of 0 indicates that both groups had the same cognitive test
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13 230 performance.

16 231 **Certainty of evidence**

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18 232 We followed the recommendations of the GRADE (Grading of Recommendations
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20 233 Assessment, Development and Evaluation) working group for rating the certainty of evidence for
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22
23 234 each outcome.³⁸

26 235 **Patient involvement**

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28 236 No patients were involved in the development of this research paper.
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34 238 **RESULTS**

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36 239 Our search identified in total 4933 citations after exclusion of duplicates. Based on title and
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38 240 abstract review, we considered 58 primary studies and 28 systematic reviews for full-text review.
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40 241 After scrutinising the full-text articles, we included two primary studies^{39 40} and five systematic
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42 242 reviews.⁴¹⁻⁴⁵ Figure 2 and figure 3 depict the study selection process. Supplementary file 6 provides a
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44 243 list of excluded studies at full-text level.
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47 244 [Figure 2 and figure 3 about here]
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50 245 **Study characteristics**

52 246 **Systematic Review**

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54 247 We included two publications^{39 40} that present interim findings of the same medium risk of
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56 248 bias prospective cohort study, namely the Tasmanian Healthy Brain Project that plans to follow
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58 249 participants for 10-20 years.⁴⁶ The two publications analysed different aspects of cognitive
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2 250 functioning of the same 459 participants who did or did not engage in a 12 month, part-time or full-
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4 251 time university-level education. Participants' mean age was 59.6±7 (mean±SD) years in the
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6 252 intervention group and 62.4±6 years in the control group with a follow-up period of 4 years.
7
8 253 Participants completed a neuropsychological test battery, consisting of 14 tests each year.⁴⁶
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11 254 In this study, selection bias is likely because participants voluntarily opted for university
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13 255 courses or no further education. It is not clear if investigators used appropriate methods to adjust for
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15 256 potential confounders (See supplementary file 5 for risk of bias ratings).
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18 257 **Overview of Reviews**

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21 258 All five included systematic reviews investigated the benefits of cognitive leisure activities in
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23 259 adults over the age of 45 years.⁴¹⁻⁴⁵ Four studies included any cognitive leisure activities in their
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25 260 analyses (e.g. reading books, doing crosswords, attending cultural events, knitting, painting), one
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27 261 study⁴⁴ specifically focused on the benefits of playing video games in older adults. The number of
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29 262 participants investigated in the reviews ranged from 913⁴⁴ to 24,554.⁴²
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32 263 We rated three of the included systematic reviews^{41 43 44} as high and two studies^{42 45} as
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34 264 medium risk of bias. Reasons for the high risk of bias ratings were lack of critical appraisal of included
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36 265 studies, single review of the literature, and insufficient literature searches (See supplementary file 5).
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39 266 We graded the evidence for all meta-analysis outcomes with low certainty of evidence
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41 267 mostly because of high inconsistency and indirectness among studies (See supplementary file 7).
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43 268 We present characteristics of included studies ⁴¹⁻⁴⁵ in Table 1.
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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

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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
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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

For peer review only

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275 **Outcomes**

276 **Key question 1a: Continuing education**

277 Two interim analyses of the Tasmanian Healthy Brain Project focused on language
278 processing³⁹ and cognitive reserve⁴⁰ after 4 years of follow-up. To date, no results on the incidence of
279 mild cognitive impairment or Alzheimer's-type dementia are available yet. Both studies reported
280 beneficial effects of continuing education. Thow and colleagues³⁹ showed that attending university
281 courses over a period of 12 months statistically significantly ($p < 0.05$) improved language processing
282 capacity in the intervention group compared to the control group. No statistically significant
283 differences were detected for episodic memory, working memory, and executive function between
284 groups. In all analyses, authors accounted for age and prior cognitive reserve (education, pre-existing
285 intellectual capacity, life-experience).

286 Lenehan and coworkers⁴⁰ demonstrated by conducting growth mixture modeling that the
287 cognitive reserve statistically significantly increased in 92.5% of participants in the intervention group
288 ($n=359$) compared to 55.7% of participants in the control group ($n=100$). Investigators created a
289 proxy measure of "current cognitive reserve" to capture dynamic changes in cognitive reserve over
290 time, including intellectual capacity and academic ability.⁴⁷

291 **Key question 1b: Cognitive leisure activities**

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

295 Two systematic reviews^{41,43} investigated the impact of cognitive leisure activities on the
296 incidence of Alzheimer's-type dementia. Both studies concluded that leisure activities protect against
297 dementia. Due to different categorization of cognitive leisure activities and a high heterogeneity
298 between studies, quantitative analyses were not possible in the two reviews. The effect estimates of
299 included studies ranged from hazard ratios [HR] of 0.39 (95% CI: 0.21 - 0.71)⁴⁸ to HR of 0.93 (95% CI:
300 0.88 - 0.98)⁴⁹ showing a reduced risk of Alzheimer's-type dementia when carrying out leisure

1
2 301 activities. Sajeev et al.⁴³ performed an extensive bias analysis showing that it is unlikely that the
3
4 302 observed positive effects of cognitively stimulating activities on dementia incidence are exclusively
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6 303 explained by unmeasured confounders or reverse causation.
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9 304 One review⁴⁵ assessed both incidence of mild cognitive impairment and Alzheimer's-type
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11 305 dementia and cognitive test performance. The authors conducted five meta-analyses based on
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13 306 groups for outcomes and reported effect estimates (risk ratio [RR], odds ratio [OR], and hazard ratio
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15 307 [HR]). Four out of five meta-analyses revealed statistically significant results showing that cognitive
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17 308 leisure activities were associated with a reduction of dementia incidence (RR = 0.61, 95% CI: 0.42-
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19 309 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
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21 310 cognitive impairment incidence (OR = 0.69, 95% CI: 0.56 – 0.85, p=0.00). However, one meta-
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23 311 analysis, combining three cohort studies did not reach statistical significance (HR = 0.85, 95% CI: 0.71-
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25 312 1.02, p=0.08) for reduction of cognitive impairment. A narrative analysis of primary studies assessing
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27 313 cognitive test performance showed a statistically significant improvement of memory, speed of
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29 314 processing, language, and executive functioning and overall later life cognition.
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33 315 Two other included studies^{42 44}, both rated as high risk of bias, focused on cognitive test
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35 316 performance. Opdebeeck et al.⁴² reported a benefit in overall cognitive abilities for the group
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37 317 involving in cognitive leisure activities (standardized mean difference [SMD] of 0.26 (95% confidence
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39 318 interval [CI]: 0.21-0.32). The cognitive domains included memory, working memory, executive
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41 319 function, visuospatial ability, and language. According to the review by Toril et al. ⁴⁴, playing video
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43 320 games enhances several cognitive functions. They observed a SMD of 0.37 (95% CI 0.26 – 0.48) for
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45 321 global cognitive function (combining results for memory, attention, reaction time and executive
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47 322 functions), showing a benefit for the intervention group.
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50 51 323 **Key question 2: Harms**

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53 324 We found no evidence regarding harms of continuing education or cognitive leisure activities.
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56 57 325 **Key question 3: Subgroups**

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2 326 Toril and colleagues⁴⁴ performed several subgroup analyses. The study revealed that the age
3
4 327 of the participants and the number of video game training sessions significantly changed the effect
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6 328 size. Older participants (between 71 and 80 years) seemed to benefit more from computer training
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8 329 than younger participants (60 to 70 years). For the improvement of cognitive test performance,
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10 330 shorter training sessions (1-6 weeks) seemed to show an advantage over longer training
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12 331 interventions (7-12 weeks). By contrast, for incidence of Alzheimer's-type dementia, DiMarco et al.⁴¹
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14 332 and Sajeev et al.⁴³ infer from their data that greater participation in cognitive leisure activities over a
15
16 333 longer period of time contributes positively to the protective effect.
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20 334 **Key question 4: Optimal age**

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22 335 No study specifically discussed the optimal age to start with continuing education activities or
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24 336 cognitive leisure activities to prevent mild cognitive impairment or dementia.
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2 337 **DISCUSSION**

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4 338 The evidence assessing the impact of continuing education on the risk of MCI or Alzheimer-
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6 339 type dementia is limited. The only eligible primary study is still ongoing and reports findings on
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8 340 intermediate outcomes only after 4 years of follow-up. Cognitive leisure activities can be viewed as
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10 341 proxies for formal continuing education and provide the best available evidence on the prevention of
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12 342 MCI and Alzheimer's-type dementia. Overall, the available evidence consistently indicates beneficial
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14 343 effects of cognitive leisure activities by reducing incidence of MCI and Alzheimer's-type dementia and
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16 344 improving cognitive function of older adults. The certainty of evidence, however, is low which means
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18 345 that future studies are likely to have a substantial impact on these findings.

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21 346 The ongoing Tasmanian Healthy Brain project⁴⁶ was the only cohort study that met the
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23 347 eligibility criteria of our systematic review. So far, after 4 years of follow-up, this study has not
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25 348 yielded results about the impact of continuing education on the incidence of MCI or Alzheimer's-type
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27 349 dementia but reports promising findings on cognitive function. It demonstrated the dynamic nature
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29 350 of cognitive reserve that permits changes through education even at an advanced age. Previous
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31 351 studies revealed that individuals with high cognitive reserve were able to better cope with age-
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33 352 related brain damage^{17 50} and had a 46% lower risk to develop dementia.¹⁸ Nevertheless, these early
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35 353 findings of the Tasmanian Healthy Brain Project have to be viewed cautiously because selection bias
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37 354 could potentially distort results. Participants voluntarily opted for university courses or no further
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39 355 education. From the available publications, it wasn't explained sufficiently how baseline differences
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41 356 such as comorbid diseases were taken into consideration during the analyses.

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44 357 The five included systematic reviews investigating cognitive leisure activities demonstrated
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46 358 both a reduction of MCI and Alzheimer's-type dementia incidence^{41 43 45} and improvements in several
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48 359 cognitive domains.^{42 44 45} Four reviews assessed the involvement in leisure activities during the past
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50 360 12 months or a much longer period. The study of Toril⁴⁴, which assessed video game trainings,
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52 361 however had a much shorter follow-up time and showed significant improvements in cognitive
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54 362 functions, even after very short training sessions (1-6 weeks). These results could be explained by the
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56 363 neuroplasticity of the human brain, which refers to the ability of the brain to adapt to every new

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2 364 stimulus by forming dendritic connections, creating morphological changes and increasing cognitive
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4 365 reserve.⁵¹⁻⁵³
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6 366 As far as we know, our study was the first assessing the impact of continuing education on
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8 367 MCI and Alzheimer's-type dementia. It is also the first overview of systematic reviews presenting an
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10 368 up-to-date summary of currently available research in the field of cognitive leisure activities and
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12 369 dementia. It has several limitations, however. First of all, there is a lack of evidence in our systematic
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14 370 review, directly addressing our research question. Inferences from indirect evidence such as studies
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16 371 on leisure activities have to be viewed cautiously. Second, in the overview of systematic reviews we
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18 372 had to rely on the quality of included systematic reviews. Several methodological shortcomings were
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20 373 detected (e.g. no risk of bias assessment, no dual screening etc.) thus our confidence in the
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22 374 robustness of some findings is low. Third, most of the included studies were observational studies,
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24 375 which are prone to selection bias because participants self-select the group. Risk factors for MCI or
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26 376 dementia in participants selecting leisure activities or further education might be systematically
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28 377 different from participants in the control group. For example, people who eventually suffer from
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30 378 preclinical dementia stages might be more likely to avoid cognitive leisure activities, which would
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32 379 lead to reverse causation. Fourth, many primary studies within the reviews used self-reported
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34 380 questionnaires that could be challenging for people who start having cognitive deficits. Finally, the
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36 381 variation of leisure activity categorization across studies made meta-analysis difficult and sometimes
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38 382 impossible. For example, "visiting a library" was classified as a cognitive activity by one author but as
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40 383 a physical activity by another. Some studies assessed current participation in activities, others
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42 384 participation at younger ages. Additionally, some studies assessed the frequency of participation,
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44 385 others the time devoted to activities and some the total number of leisure activities. Consequently,
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46 386 due to these limitations, the comparability of results among studies was limited. A standardization of
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48 387 measures and methods would be necessary to help synthesize evidence in the future and make more
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50 388 reliable recommendations.
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58 389 **Implication for future research, policy and practice**
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2 390 Based on preliminary results of a long-term cohort study and indirect evidence from studies
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4 391 on leisure activities, continuing education might be a promising option to help prevent dementia. A
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6 392 recent study suggests that modifiable risk factors (low education, midlife hypertension, midlife
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8 393 obesity, diabetes, physical inactivity, smoking, and depression) might be responsible for about a third
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10 394 of Alzheimer's-type dementia cases.⁵⁴ Hence, considering our results, a campaign promoting to
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12 395 "actively use the brain by participating in the wide range of continuing education" could be added to
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14 396 the list of preventive options and could have an impact on the reduction of Alzheimer's-type
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16 397 dementia cases. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and
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18 398 Disability (FINGER)⁵⁵, randomized controlled trial, with a multi-domain approach (diet, exercise,
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20 399 cognitive training, vascular risk monitoring) supports the hypothesis that simultaneous changes in
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22 400 several risk factors can lead to a protective effect on cognition. In light of previously published
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24 401 studies, we agree that in order to prevent Alzheimer's-type dementia in the future, a multi-domain
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26 402 prevention approach seems to be the most promising solution.

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29 403 Further research is needed to address the evidence gap regarding continuing education and
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31 404 the extent to which it acts as a protective factor. A study similar to the Tasmanian Healthy Brain
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33 405 Project⁴⁰, but conducted as a randomized controlled trial, would be ideal because it would
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35 406 adequately handle known and unknown confounders. Computers and Internet could play a more
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37 407 significant role in future prevention trials. Instead of "sending your grandparents to university," older
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39 408 adults could, for instance, be randomized to attend online courses and communicate with professors
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41 409 and other students in virtual classrooms. This approach could save time, money, and increase the
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43 410 potential participant pool.

411 **Conclusion**

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

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12
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14
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16
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19
20 425 **Author Contributions:** All authors made substantial contribution to the conception and design of this
21
22 426 study. GG, NM, MK, CG and SA developed the concept of the study. As an information specialist, IK
23
24 427 developed the search strategy. GW, FKA, NM and BT conducted the literature review, abstracted
25
26 428 data and graded the strength of evidence. NM wrote the first draft of the manuscript; all authors
27
28 429 reviewed the manuscript and provided comments. All authors have given approval for this version to
29
30 430 be published.

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35 432 **Figure Legends:**

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38 433 **Figure 1:** Analytic framework for continuing education to prevent mild cognitive impairment and
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40 434 Alzheimer's-type dementia

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42 435 **Figure 2:** Flow diagram of systematic review of continuing education for the prevention of mild
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44 436 cognitive impairment and Alzheimer's-type dementia

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47 437 **Figure 3:** Flow diagram of overview of systematic reviews of cognitive leisure activities for the
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49 438 prevention of mild cognitive impairment and Alzheimer's-type dementia

1
2 439 **List of abbreviations**
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- 5 440 AD = Alzheimer Disease
6 441 aMCI = Amnesic Mild Cognitive Impairment
7 442 AMSTAR = Assessing the Methodological Quality of Systematic Reviews
8 443 CEDEFOP = European Centre for the Development of Vocational Training
9 444 CENTRAL = Cochrane Central Register of Controlled Trials
10 445 DSM = Diagnostic and Statistical Manual of Mental Disorders
11 446 GRADE = Grading of Recommendations Assessment, Development and Evaluation
12 447 HR = Harzard Ratio
13 448 ICD = International Classification of Diseases
14 449 MCI = Mild Cognitive Impairment
15 450 MMSE = Mini-Mental State Examination
16 451 OECD = Organisation for Economic Co-operation and Development
17 452 OR = Odds Ratio
18 453 PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
19 454 ROBINS-I = Risk of Bias in non-randomized studies – of interventions
20 455 RR = Relative Risk
21 456 SD = Standard Deviation
22 457 SMD = Standardized mean difference
23 458 UNESCO = United Nations Educational, Scientific and Cultural Organization
24 459 WHO = World Health Organisation
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26 487 [type-dementia-mild-cognitive-impairment-and-age-related-cognitive-decline.](https://www.nap.edu/catalog/21885/considerations-for-the-design-of-a-systematic-review-of-interventions-for-preventing-clinical-alzheimers-type-dementia-mild-cognitive-impairment-and-age-related-cognitive-decline)
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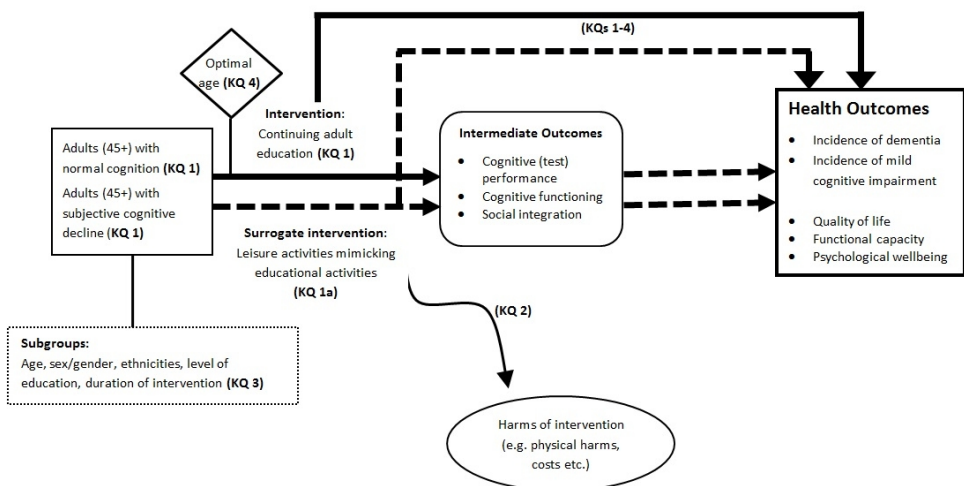
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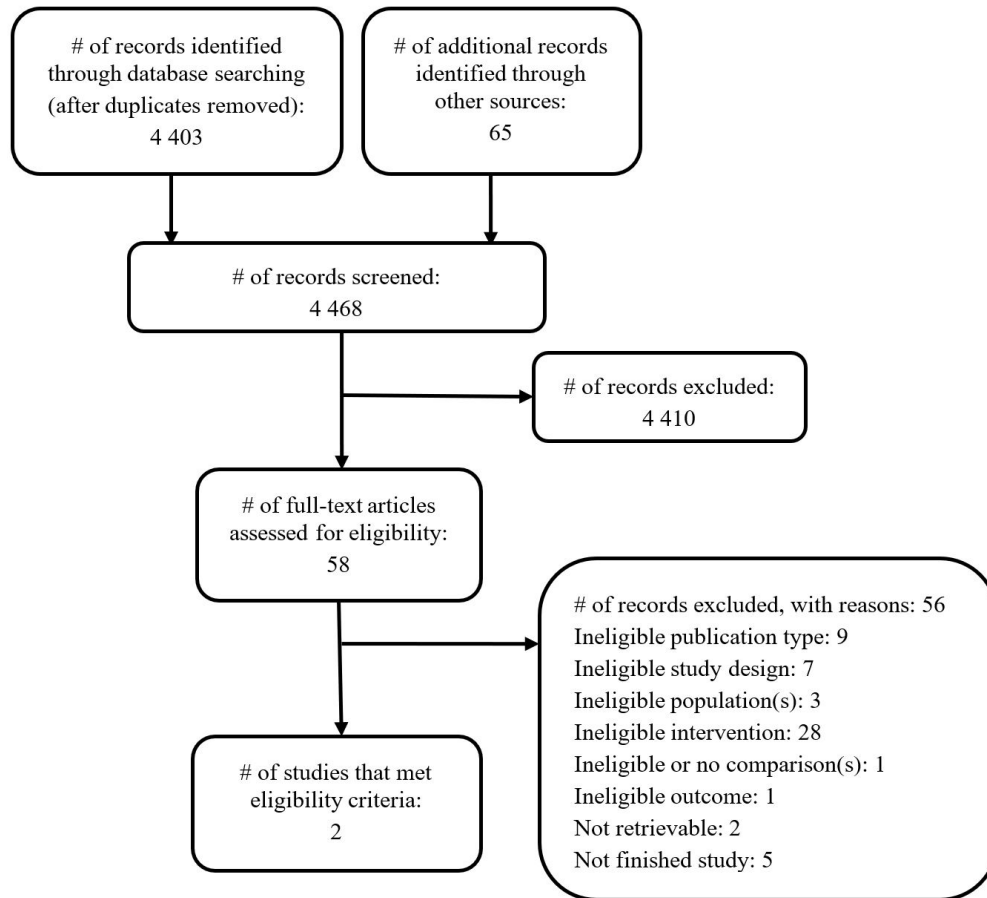
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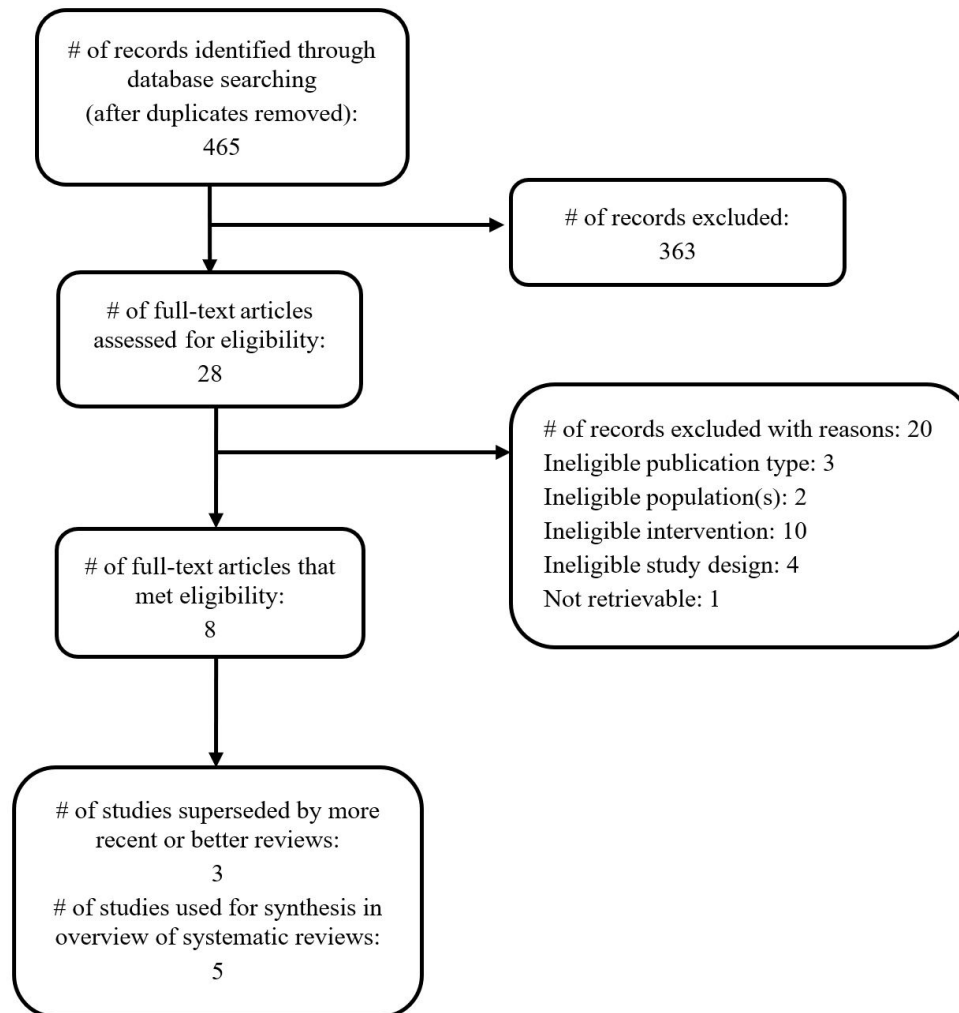
Analytic framework for continuing education to prevent mild cognitive impairment and Alzheimer's-type dementia

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)

Page 1 of 2

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

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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): e100097
doi:10.1371/journal.pmed100097

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

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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

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4		"lifelong learning" OR "life-long	
5		learning" OR ((continuing OR	
6		adult) N2 (education OR	
7		training))	Search modes - Find all my
8	S16		search terms 106290
9		S12 OR S13 OR S14 OR S15 OR	Search modes - Find all my
10	S17	S16	search terms 27,763
11			Search modes - Find all my
12	S18	S11 AND S17	search terms 667
13			Search modes - Find all my
14	S19	MH "Animal Studies"	search terms 39763
15			Search modes - Find all my
16	S20	S18 NOT S19	search terms 618
17			Search modes - Find all my
18		MH "Named Groups by Age+"	
19		NOT (MH "Middle Age" OR MH	Search modes - Find all my
20	S21	"Aged+")	search terms 55371
21			Search modes - Find all my
22	S22	S20 NOT S21	search terms 552
23			Limiters - Published Date:
24	S23	S22	19900101-20171231 557
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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

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3	S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	290,595
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5	S18	S11 AND S17	Search modes - Find all my search terms	753
6				
7	S19	MH "Animal Studies"	Search modes - Find all my search terms	43,810
8				
9	S20	S18 NOT S19	Search modes - Find all my search terms	691
10				
11	S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	595,044
12				
13	S22	S20 NOT S21	Search modes - Find all my search terms	617
14				
15	S23	S22	Limiters - Published Date: 20170101-	78
16				
17	S24	S22 AND EM 20170701-	Search modes - Find all my search terms	66
18				
19	S25	S23 OR S24	Search modes - Find all my search terms	95
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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

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4	S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8046
5				
6		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
7	S16			
8		TI (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	94
9	S17			
10		((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	76187
11	S18			
12		"lifelong learning" or "life-long learning"	Search modes - Find all my search terms	10135
13	S19			
14		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
15	S20			
16		S10 AND S20	Search modes - Find all my search terms	286
17	S21			
18		S21	Limiters - Date Published: 19900101-20171231	234
19	S22			
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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

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3	S17	T1 (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	102
4				
5	S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	77,861
6				
7	S19	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	17
8				
9	S20	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	10,521
10				
11	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
12				
13	S22	S10 AND S21	Search modes - Find all my search terms	309
14				
15	S23	S22	Limiters - Date Published: 20170101-	16
16				
17	S24	S22 AND EM 20170701-	Search modes - Find all my search terms	0
18				
19	S25	S23 OR S24	Search modes - Find all my search terms	16
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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
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Intervention type:	Non-pharmacological
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Intervention:	Contains any word	learning education educational
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18 Studies found

ALOIS (9 April 2018)

Not searched website down

DART-Europe (16 May 2017)

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

DART-Europe (8 April 2018)

search	results
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimulation") 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

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3	26	(integrative research review* or research integration).tw. or scoping	167686
4		review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as	
5		topic).hw.) or (evidence adj3 review*).ti,ab,kf.	
6			
7	27	21 or 22 or 23 or 24 or 25 or 26	412039
8	28	27 not (case report/ or letter.pt.)	401602
9	29	20 and 28	243
10	30	remove duplicates from 29	229
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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 metasynt*).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 metasynt*: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)	345120
		2
#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 metasynt*: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 metasynt*		
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

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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

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3	S16	(DE "Drug Therapy")	Search modes - Find all my search terms
4			127,11
5	S17	S15 NOT S16	Search modes - Find all my search terms
6			3,161
7	S18	DE "Meta Analysis"	Search modes - Find all my search terms
8			4,026
9	S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynt*	Search modes - Boolean/Phrase
10			27,695
11	S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms
12			27,454
13	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
14			16,949
15	S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms
16			51,681
17	S23	S17 AND S22	Search modes - Find all my search terms
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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

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3	S13	S11 NOT S12	Search modes - Find all my search terms
4			3,706
5	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
6			318,343
7	S15	S13 NOT S14	Search modes - Find all my search terms
8			3,539
9	S16	(DE "Drug Therapy")	Search modes - Find all my search terms
10			129,812
11	S17	S15 NOT S16	Search modes - Find all my search terms
12			3,481
13	S18	DE "Meta Analysis"	Search modes - Find all my search terms
14			4,152
15	S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase
16			30,127
17	S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms
18			30,748
19	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
20			19,166
21	S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms
22			56,448
23	S23	S17 AND S22	Search modes - Find all my search terms
24			84
25	S24	RD 201707-	Search modes - Find all my search terms
26			148,956
27	S25	DT 201707-	Search modes - Find all my search terms
28			100,982
29	S26	S24 OR S25	Search modes - Find all my search terms
30			159,715
31	S27	S23 AND S26	Search modes - Find all my search terms
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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

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3	#14 (garden* or horticultur*):ti,kw	125
4	#15 (play* or game* or gaming):ti,kw	3653
5	#16 (creativ* or painting or drawing or reading):ti,kw	3482
6	#17 (voluntary or volunteer* or extracurricular):ti,kw	20037
7	#18 (cognitiv* near/2 (activity or activities)):ti,kw	80
8	#19 {or #8-#18}	44252
9	#20 #7 and #19	1838
10	#21 [mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
11	#22 #20 not #21 Publication Year from 2017 to 2018, in Cochrane Reviews	1
12	(Reviews and Protocols) and Technology Assessments	
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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 "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

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4	Stanford University, 2012	Activities for Cognitive Enhancement of Seniors	Ineligible intervention
5	Then et al., 2016	Education as protector against dementia, but what exactly do we mean by education?	Ineligible intervention
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7	University Hospital 2016	Long-term Effects of Interventional Strategies to Prevent Cognitive Decline in Elderly	Ineligible intervention
8	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
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10	Vemuri et al., 2014	Association of lifetime intellectual enrichment with cognitive decline in the older population	Ineligible intervention
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12	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
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14	Yaffe et al., 2009	Predictors of maintaining cognitive function in older adults: the Health ABC study	Ineligible intervention
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16	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
17			
18	Jonaitis et al., 2013	Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease	Ineligible populations
19	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
20	National University,	Choral Singing For the Prevention of Dementia	not finished study
21			
22	Marquez et al., 2017	Regular Latin Dancing and Health Education may Improve Cognition of Late Middle-Aged and Older Latinos	Ineligible comparison;
23	University Hospital 2018	Prospective Population Based Cohort Study on Cognitive and Cardiovascular Aging (MonaLisaPredor)	not finished study;
24			
25	Janssen Research Development 2018	Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research: Prospective Readiness Cohort Study	not finished study
26	ACTRN126170008 58392 2017	Ageing and Folk Dances from the Basque Country: Functional and neuropsychological changes. A controlled trial.	Ineligible intervention
27	Biasutti et al., 2018	Assessing a cognitive music training for older participants: a randomised controlled trial	Ineligible population
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29	Centre de Recherche del'Institut Universitaire de Geriatrie, 2018	Impact of a Cognitive Intervention Enriched With Leisure Activities in Persons With Subjective Cognitive Decline	Not finished study
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31	Chan et al., 2016	Training Older Adults to Use Tablet Computers: Does It Enhance Cognitive Function?	Ineligible study design
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33	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
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35	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
36	NCT02919748, 2016	Choral Singing For the Prevention of Dementia	Not finished study
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38	Ramos et al., 2017	Does learning a language in the elderly enhance switching ability?	Ineligible outcome
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40	Wang et al., 2017	Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study	Ineligible intervention
41	ZanESCO et al., 2018	Mental training of attention through intensive meditation: Longitudinal behavioral and electrophysiological investigations of visual sustained attention and response inhibition	Not retrievable
42	Zhu et al., 2017	Leisure activities, education, and cognitive impairment in Chinese older adults: A population-based longitudinal study	Ineligible intervention
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44	2017	Study suggests late-life activities reduce the risk of mild cognitive impairment	Ineligible study design
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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 retrievable
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 superseded 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 superseded 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 superseded 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	Ineligible 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)	No 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. I² = 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)	No 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

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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)	No 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, x² test p=0.09, b. differences in interventions (definition of cognitive leisure activities varies across studies), c. high heterogeneity, x² 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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027719.R1
Article Type:	Research
Date Submitted by the Author:	28-Feb-2019
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Keywords:	Systematic review, Dementia < NEUROLOGY, mild cognitive impairment, PREVENTIVE MEDICINE, continuing education

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5 2 **Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic**
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8 3 **Reviews.**
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39 **ABSTRACT**

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

42 **Design:** Systematic review and overview of systematic reviews.

43 **Data sources:** We systematically searched MEDLINE, PsycINFO, EMBASE, CENTRAL, CINAHL and
44 Scopus for published studies and gray literature databases for unpublished studies from January
45 1990 to April 2018.

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

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

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

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

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2 64 function and lower dementia incidence. Healthcare providers and policymakers should promote a
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4 65 healthy lifestyle, which also includes being cognitively active throughout life.
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6 66 **Systematic review registration:** PROSPERO CRD42017063944
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13 69 **Strengths and Limitations of this study:**
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- 15 70 • This is the first systematic review assessing the benefits and harms of continuing education
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17 71 on the prevention of mild cognitive impairment or Alzheimer's type dementia.
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20 72 • This is the first overview of systematic reviews presenting an up-to-date summary of
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22 73 currently available research in the field of cognitive leisure activities and dementia.
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24 74 • The certainty of evidence is low, indicating that future studies might have a substantial
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26 75 impact on results of our review.
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29 76 • Measurements and types of cognitive leisure activities differed widely across studies and
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31 77 quantitative analysis were often not possible.
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33 78 • The majority of included systematic reviews have serious methodological shortcomings.
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81 INTRODUCTION

82 In 2012, the World Health Organization (WHO) named the prevention and control of
83 neurocognitive disorders such as mild cognitive impairment or Alzheimer's-type dementia a global
84 public health priority.¹ Alzheimer's-type dementia is the most common form of dementia.¹ In 2018,
85 50 million people worldwide lived with Alzheimer's disease or another closely related form of
86 dementia.² As a consequence of the rapidly aging world population, the prevalence of dementia is
87 projected to rise up to 152 million people in 2050.²

88 The progressive loss of independent functioning of people with Alzheimer's-type dementia,
89 leads to an enormous social and economic burden. In 2018, the U.S. economic burden associated
90 with Alzheimer's type dementia was estimated to be 277 billion U.S. Dollars.³ The total global costs
91 for dementia were about a trillion US dollar in 2018.²

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

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

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

1
2 107 activity, and smoking.^{7,8} In addition, potential predictors of dementia are chronic medical conditions
3
4 108 such as cardiovascular diseases, diabetes, obesity, cancers, depression, thyroid disorder, or genetic
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6 109 factors.⁹ Some studies, however, found a protective association of cognitively stimulating activities,
7
8 110 such as learning a new language in middle age, with a slower cognitive decline during late life.¹⁰⁻¹⁴
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10 111 Such results underpin the “cognitive reserve hypothesis”.¹⁵⁻¹⁷ According to this theory, through every
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12 112 activity that stimulates the brain, the cognitive reserve gets boosted and the resistance towards any
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14 113 dementia-related brain pathology increases.¹⁸ In animal trials, an enriched environment was
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16 114 associated with increased cortical thickness.¹⁹ Epidemiological research on humans has shown that
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18 115 education²⁰ and probably also other forms of intellectual stimulation, during the whole lifespan, are
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20 116 associated with a lower risk to develop dementia.^{21, 22} A larger cognitive reserve acquired by
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22 117 continuing education activities, thus, might protect against cognitive decline.^{18, 23}
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26 118 Continuing education activities are structured learning activities offered by educational
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28 119 institutes. These activities are designed to help individuals satisfy learning needs and interests after
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30 120 compulsory schooling, to enrich knowledge, to develop and improve abilities and skills, and to foster
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32 121 personality, social competences, families, networks, health, and professional life. Continuing
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34 122 education is voluntary, based on topics and courses that are not directly connected to any special job
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36 123 position or vocational training.²⁴⁻²⁹ Cognitive leisure activities (e.g., learning a new language) often
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38 124 mimic continuing education activities but are not taking place within the framework of an
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40 125 educational institution.
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44 126 **Rationale**

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47 127 To date, the preventive effect of continuing education on cognitive impairment and Alzheimer’s-type
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49 128 dementia has not been assessed in an objective and systematic way. The aim of our review was to
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51 129 summarize the evidence investigating the preventive effects of continuing education on the
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53 130 development of cognitive impairment and Alzheimer’s-type dementia.
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57 131 Our systematic review addressed the following questions:
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2 132 **Key question 1a:** In adults 45 years of age or older with normal cognition or merely subjective
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4 133 cognitive impairment, does continuing education lead to a reduction in the risk of mild cognitive
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6 134 impairment or Alzheimer's-type dementia compared with no continuing education?
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9 135 **Key question 1b:** (In case no evidence on continuing education is available or the evidence is sparse):
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11 136 In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment,
12
13 137 do cognitive leisure activities lead to a reduction in the risk of mild cognitive impairment or
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15 138 Alzheimer's-type dementia compared with no cognitive leisure activities?
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18 139 **Key question 2:** What are potential harms of continuing education?
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21 140 **Key question 3:** Do benefits and harms differ by subgroups based on age, sex/gender, race or
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23 141 ethnicities, level of education, or duration of intervention?
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26 142 **Key question 4:** What is the optimal age to start continuing education to prevent mild cognitive
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28 143 impairment or dementia?
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145 **METHODS**

146 **Design**

147 Throughout this manuscript we followed the PRISMA (Preferred Reporting Items for
148 Systematic Reviews and Meta-Analyses) statement³⁰ (see supplementary file 1). The protocol of this
149 systematic review was registered in PROSPERO (International Prospective Register of Systematic
150 Reviews) (Registration number CRD42017063944) and published previously.³¹ Figure 1 depicts the
151 analytic framework that guided our systematic review.

152 [Figure 1 about here]

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

156 We addressed our research questions with two different methodological approaches:

1
2 157 1) We performed a systematic review of primary studies to assess the preventive
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4 158 effects and potential harms of continuing education provided by formal and non-formal
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6 159 institutions (key questions 1a, 2, 3, and 4).
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8 160 2) We conducted an overview of systematic reviews to determine the preventive effects
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10 161 and potential harms of related leisure activities (e.g. playing cards, reading books, etc., key
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12 162 question 1b).
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15 163 We chose this two-step approach because studies in the field of continuing education and
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17 164 dementia are very rare. Certain leisure activities, however, are able to mimic continuing education
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19 165 regarding content (e.g. learning a new language privately versus learning a new language as an
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21 166 organized educational activity). Leisure activities are not our primary focus of interest but can be
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23 167 considered as proxy interventions for continuing education in some circumstances.
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28 29 169 **Study selection**

30 31 170 **Eligibility criteria for the systematic review**

32
33 171 The population of interest were adults 45 years or older, without a clinical diagnosis of
34
35 172 cognitive impairment at the time of study recruitment, which included people with subjective
36
37 173 cognitive impairment. Eligible interventions comprised of all cognitive activities that are provided by
38
39 174 formal and non-formal educational institutions. These activities include classes, courses, and
40
41 175 trainings that are based on individual interests and that are attended voluntarily. We included
42
43 176 randomized controlled trials, nonrandomized controlled trials, prospective controlled cohort studies,
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45 177 retrospective controlled cohort studies, and case-control studies. All nonrandomized studies needed
46
47 178 to have a minimum sample size of 300 or more participants.
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51 179 Eligible studies had a minimum follow up time of 1 year and a minimum duration of
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53 180 intervention of 3 months. We excluded studies that investigated formal (vocational) education (e.g.
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55 181 School or College), physical activities, and all job-related courses and trainings.
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2 182 Outcomes of interest included patient-relevant health outcomes such as incidence of
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4 183 dementia, incidence of MCI, psychological wellbeing, functional capacity, quality of life, and other
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6 184 relevant health outcomes; in addition, we included intermediate outcomes such as cognitive
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8 185 functioning, cognitive (test) performance, or social inclusion. For the purpose of our study, mild
9
10 186 cognitive impairment refers to “amnesic” mild cognitive impairment (aMCI), meaning that memory
11
12 187 loss is the predominant symptom.³²

16 188 **Eligibility criteria for the overview of systematic reviews**

18 189 Eligibility criteria for population and outcomes for the overview of systematic reviews were
19
20 190 the same as for the systematic review. Eligible interventions were leisure activities that are
21
22 191 cognitively stimulating and mimic the content of continuing education but in an informal setting. Just
23
24 192 as in the systematic review, we excluded physical activities. Eligible study designs were exclusively
25
26 193 systematic reviews and meta-analyses. We excluded reviews with searches conducted before 2013.

27
28 194 Further details about our inclusion and exclusion criteria can be found in our protocol³¹ and
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30 195 in the supplementary file 2.

35 196 **Search strategy**

36
37 197 We systematically searched Ovid MEDLINE, Cochrane Library, Embase, PsycINFO, CINAHL
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39 198 (Cumulative Index to Nursing and Allied Health Literature), ALOIS (the Cochrane Dementia and
40
41 199 Cognitive Improvement Group Specialized Register), and ERIC (Education Resources Information
42
43 200 Center) from January 1990 to April 2018 to identify relevant publications (see supplementary file 3
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45 201 for the search strategy). For the overview of reviews, we searched Epistemonikos from inception to
46
47 202 April 2018 in addition to the above mentioned databases (see supplementary file 4).

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51 203 An experienced information specialist developed an appropriate search strategy using a
52
53 204 combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the
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55 205 search to human-only studies without applying any language limitations. The electronic Ovid Medline
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57 206 search strategy was peer-reviewed by another information specialist following the PRESS (peer
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2 207 review of the electronic search strategy) statement.³³ For the systematic review, we searched for
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4 208 gray literature in ClinicalTrials.gov, the World Health Organization's International Clinical Trials
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6 209 Registry Platform, web pages of relevant organizations, and a dissertation database ("Digital Access
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8 210 to Research Theses", DART-Europe). Additionally, in an attempt to avoid retrieval bias, we manually
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10 211 searched the reference lists of landmark studies and background articles on this topic to look for any
11
12 212 relevant citations that our electronic searches might have missed. We imported all citations into an
13
14 213 electronic database (EndNote X.8) and deleted duplicates.

18 214 **Study selection**

20 215 Two review authors independently screened abstracts and relevant full text articles for
21
22 216 eligibility, using Covidence Software.³⁴ They resolved disagreements by discussion or by consultation
23
24 217 with a third author.

28 218 **Data abstraction**

31 219 We designed, pilot-tested, and used a data abstraction form to gather pertinent information
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33 220 from each article. One author extracted relevant data from each study that met our inclusion criteria.
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35 221 A second author of the team cross-checked data abstractions for completeness and accuracy. We
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37 222 extracted study information (author, publication year, years covered by searches, location/setting,
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39 223 number of included studies and included study designs), sample size, study characteristics
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41 224 (population, interventions, and comparators), outcome measurements, and results. For systematic
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43 225 reviews we abstracted summary estimates of meta-analyses whenever available.
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47 226 **Risk of bias assessment**

49 227 Two investigators independently assessed the risk of bias of included studies. They resolved
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51 228 any disagreements by consensus or by consulting a third team member. For eligible non-randomized
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53 229 studies we used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool.³⁵ For
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55 230 the assessment of eligible systematic reviews, we used the AMSTAR (Assessing the Methodological
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231 Quality of Systematic Reviews) tool.³⁶ Detailed risk of bias ratings of included articles are given in
232 supplementary file 5.

233 **Data synthesis and statistical analysis**

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

240 **Certainty of evidence**

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

244 **Patient involvement**

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

247 **RESULTS**

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

253 [Figure 2 and figure 3 about here]

254 **Study characteristics**

255 **Systematic Review**

1
2 256 We included two publications^{38 39} that present interim findings of the same medium risk of
3
4 257 bias prospective cohort study, namely the Tasmanian Healthy Brain Project that plans to follow
5
6 258 participants for 10-20 years.⁴⁵ The two publications analysed different aspects of cognitive
7
8 259 functioning of the same 459 participants who did or did not engage in a 12 month, part-time or full-
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10 260 time university-level education. Participants' mean age was 59.6±7 (mean±SD) years in the
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12 261 intervention group and 62.4±6 years in the control group with a follow-up period of 4 years.
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14 262 Participants completed a neuropsychological test battery, consisting of 14 tests each year.⁴⁵
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17 263 In this study, selection bias is likely because participants voluntarily opted for university
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19 264 courses or no further education. It is not clear if investigators used appropriate methods to adjust for
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21 265 potential confounders (see supplementary file 5 for risk of bias ratings).
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25 266 **Overview of Reviews**

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27 267 All five included systematic reviews investigated the benefits of cognitive leisure activities in
28
29 268 adults over the age of 45 years.⁴⁰⁻⁴⁴ Four studies included any cognitive leisure activities in their
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31 269 analyses (e.g. reading books, doing crosswords, attending cultural events, knitting, painting), one
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33 270 study⁴³ specifically focused on the benefits of playing video games in older adults. The number of
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35 271 participants investigated in the reviews ranged from 913⁴³ to 24,554.⁴¹
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38 272 We rated three of the included systematic reviews^{40 42 43} as high and two studies^{41 44} as
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40 273 medium risk of bias. Reasons for the high risk of bias ratings were lack of critical appraisal of included
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42 274 studies, single review of the literature, and insufficient literature searches (see supplementary file 5).
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45 275 We graded the evidence for all meta-analysis outcomes with low certainty of evidence
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47 276 mostly because of high inconsistency and indirectness among studies (see supplementary file 7).
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50 277 We present characteristics of included studies⁴⁰⁻⁴⁴ in table 1 and table 2.
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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, CINHALL 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

287 **Outcomes**

288 **Key question 1a: Continuing education**

289 Two interim analyses of the Tasmanian Healthy Brain Project focused on language
290 processing³⁸ and cognitive reserve³⁹ after 4 years of follow-up. To date, no results on the incidence of
291 mild cognitive impairment or Alzheimer's-type dementia are available yet. Both studies reported
292 beneficial effects of continuing education. Thow and colleagues³⁸ showed that attending university
293 courses over a period of 12 months statistically significantly ($p<0.05$) improved the language
294 processing capacity in the intervention group compared to the control group. No statistically
295 significant differences were detected for episodic memory, working memory, and executive function
296 between groups. In all analyses, authors accounted for age and prior cognitive reserve (education,
297 pre-existing intellectual capacity, life-experience).

298 Lenehan and coworkers³⁹ demonstrated by conducting growth mixture modeling that the
299 cognitive reserve statistically significantly increased in 92.5% of participants in the intervention group
300 ($n=359$) compared to 55.7% of participants in the control group ($n=100$). Investigators created a
301 proxy measure of "current cognitive reserve" to capture dynamic changes in cognitive reserve over
302 time, including intellectual capacity and academic ability.⁴⁶

303 **Key question 1b: Cognitive leisure activities**

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

307 Two systematic reviews^{40,42} investigated the impact of cognitive leisure activities on the
308 incidence of Alzheimer's-type dementia. Di Marco and colleagues included six, Sajeev and colleagues
309 12 primary studies on cognitive leisure activities in their systematic reviews. Both systematic reviews
310 concluded that leisure activities protect against dementia. Due to different categorization of
311 cognitive leisure activities and a high heterogeneity between studies, quantitative analyses were not
312 possible in the two reviews. The effect estimates of included studies ranged from hazard ratios [HR]

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2 313 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
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4 314 reduced risks of Alzheimer's-type dementia when carrying out leisure activities. Sajeev et al.⁴²
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6 315 performed an extensive bias analysis indicating that it is unlikely that the observed positive effects of
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8 316 cognitively stimulating activities on dementia incidence are exclusively explained by unmeasured
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10 317 confounders or reverse causation.

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13 318 One review⁴⁴ assessed both incidence of mild cognitive impairment and Alzheimer's-type
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15 319 dementia and cognitive test performance. The authors conducted five meta-analyses based on
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17 320 groups for outcomes and reported effect estimates (risk ratio [RR], odds ratio [OR], and hazard ratio
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19 321 [HR]). Four out of five meta-analyses revealed statistically significant results showing that cognitive
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21 322 leisure activities were associated with a reduction of dementia incidence (RR = 0.61, 95% CI: 0.42-
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23 323 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
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25 324 impairment incidence (OR = 0.69, 95% CI: 0.56 – 0.85). However, one meta-analysis, combining three
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27 325 cohort studies did not reach statistical significance (HR = 0.85, 95% CI: 0.71-1.02) for reduction of
28
29 326 cognitive impairment. A narrative analysis of primary studies assessing cognitive test performance
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31 327 showed a statistically significant improvement of memory, speed of processing, language, and
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33 328 executive functioning and overall later life cognition.

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36 329 Two other included studies^{41 43}, both rated as high risk of bias, focused on cognitive test
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38 330 performance. Opdebeeck et al.⁴¹ reported a benefit in overall cognitive abilities for the group
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40 331 involving in cognitive leisure activities (standardized mean difference [SMD] of 0.26 (95% confidence
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42 332 interval [CI]: 0.21-0.32). The cognitive domains included memory, working memory, executive
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44 333 function, visuospatial ability, and language. According to the review by Toril et al. ⁴³, playing video
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46 334 games enhanced several cognitive functions. They observed a SMD of 0.37 (95% CI 0.26 – 0.48) for
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48 335 global cognitive function (combining results for memory, attention, reaction time and executive
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50 336 functions), showing a benefit for the intervention group.

51 337 **Key question 2: Harms**

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54 338 We found no evidence regarding harms of continuing education or cognitive leisure activities.
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2 339 **Key question 3: Subgroups**
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5 340 Toril and colleagues⁴³ performed several subgroup analyses. The study revealed that the age
6
7 341 of the participants and the number of video game training sessions significantly changed the effect
8
9 342 size. Older participants (between 71 and 80 years) seemed to benefit more from computer training
10
11 343 than younger participants (60 to 70 years). For the improvement of cognitive test performance,
12
13 344 shorter training sessions (1-6 weeks) seemed to show an advantage over longer training
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15 345 interventions (7-12 weeks). By contrast, for incidence of Alzheimer's-type dementia, DiMarco et al.⁴⁰
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17 346 and Sajeev et al.⁴² infer from their data that greater participation in cognitive leisure activities over a
18
19 347 longer period of time contributes positively to the protective effect.
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23 348 **Key question 4: Optimal age**
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25 349 No study specifically discussed the optimal age to start with continuing education activities or
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27 350 cognitive leisure activities to prevent mild cognitive impairment or dementia.
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2 351 **DISCUSSION**

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4 352 The evidence assessing the impact of continuing education on the risk of MCI or Alzheimer-
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6 353 type dementia is limited. The only eligible primary study (Tasmanian Healthy Brain project)⁴⁵ is still
7
8 354 ongoing but preliminary findings after four years of follow-up demonstrated that the dynamic nature
9
10 355 of cognitive reserve permits improvements through education even at an advanced age.
11
12 356 Nevertheless, these early findings have to be viewed cautiously. In addition, selection bias could
13
14 357 potentially distort results of the Tasmanian Healthy Brain project because participants voluntarily
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16 358 opted for university courses or no further education. The available publications did not explain
17
18 359 sufficiently how baseline differences such as comorbid diseases were taken into consideration during
19
20 360 the analyses.
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24 361 Because of the limited direct evidence, we focused on cognitive leisure activities as proxies
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26 362 for formal continuing education. Overall, the available evidence consistently indicates beneficial
27
28 363 effects of cognitive leisure activities by improving the cognitive function of older adults and reducing
29
30 364 the incidence of MCI and Alzheimer's-type dementia. These findings could be explained by the
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32 365 neuroplasticity of the human brain, which refers to the ability of the brain to adapt to every new
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34 366 stimulus by forming dendritic connections, creating morphological changes and increasing cognitive
35
36 367 reserve.⁴⁹⁻⁵¹ Neuroplasticity is an intrinsic property of the human brain that allows us to learn and
37
38 368 adapt to environmental changes. Depending on the stimuli, the changes can be positive or
39
40 369 negative.⁴⁹⁻⁵¹ The concept of neuroplasticity is interrelated with the concept of cognitive reserve
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42 370 which refers to morphological changes that support cognitive functioning.⁵¹
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46 371 The magnitudes of beneficial effects, however, varied across systematic reviews and
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48 372 confidence intervals encompassed effect sizes that would not be clinically relevant. Consequently, we
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50 373 rated the certainty of evidence as low or very low which means that future studies are likely to have
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52 374 a substantial impact on these findings.
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55 375 To the best of our knowledge, our study was the first assessing the impact of continuing
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57 376 education on MCI and Alzheimer's-type dementia. It is also the first overview of systematic reviews
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59 377 presenting an up-to-date summary of currently available research in the field of cognitive leisure
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2 378 activities and dementia. Nevertheless, our work has several limitations. First, in the overview of
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4 379 systematic reviews we had to rely on the quality of included systematic reviews which often had
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6 380 methodological shortcomings (e.g. no risk of bias assessment, no dual screening etc.). Second, most
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8 381 of the included studies were observational studies, which are prone to selection bias because
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10 382 participants self-select the group. Risk factors for MCI or dementia in participants selecting leisure
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12 383 activities or further education might be systematically different from participants in the control
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14 384 groups. For example, people who eventually suffer from preclinical dementia stages might be more
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16 385 likely to avoid cognitive leisure activities, which would lead to reverse causation. Third, many primary
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18 386 studies within the reviews used self-reported questionnaires that could be challenging for people
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20 387 who start having cognitive deficits. Finally, the variation of leisure activity categorization across
21
22 388 studies made meta-analysis difficult and sometimes impossible. For example, “visiting a library” was
23
24 389 classified as a cognitive activity by one author but as a physical activity by another. Some studies
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26 390 assessed current participation in activities, others participation at younger ages. Additionally, some
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28 391 studies assessed the frequency of participation, others the time devoted to activities and some the
29
30 392 total number of leisure activities. Consequently, due to these limitations, the comparability of results
31
32 393 among studies was limited. A standardization of measures and methods would be necessary to help
33
34 394 synthesize evidence in the future and make more reliable recommendations.

395 **Implication for future research, policy and practice**

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

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2 404 Disability (FINGER)⁵³, a randomized controlled trial, with a multi-domain approach (diet, exercise,
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4 405 cognitive training, vascular risk monitoring) supports the hypothesis that simultaneous changes in
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6 406 several risk factors can lead to a protective effect on cognition.
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9 407 Further research is needed to address the evidence gap regarding continuing education and
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11 408 the extent to which it acts as a protective factor. A study similar to the Tasmanian Healthy Brain
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13 409 Project³⁹, but conducted as a randomized controlled trial, would be ideal because it would
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15 410 adequately handle known and unknown confounders. Computers and Internet could play a more
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17 411 significant role in future prevention trials. Older adults could, for instance, be randomized to attend
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19 412 online courses and communicate with professors and other students in virtual classrooms. This
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21 413 approach could save time, money, and increase the potential participant pool.
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23

24 414 **Conclusion**

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26 415 Although no firm conclusions about the effects of continuing education to prevent MCI and
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28 416 dementia can be drawn, data from preliminary and indirect evidence indicate that continuing
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30 417 education could potentially have important preventive effects. Physicians and policymakers should
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32 418 promote a healthy lifestyle, which also includes being cognitively active throughout late life.
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12
13 425 **Availability of data and materials:** All extracted data are included in the manuscript. There are no
14
15 426 additional datasets available.

16
17 427 **Competing interests:** All authors declare that they have no competing interest.

18
19 428 **Author Contributions:** All authors made substantial contribution to the conception and design of this
20
21 429 study. GG, NM, MK, CG and SA developed the concept of the study. As an information specialist, IK
22
23 430 developed the search strategy. GW, FKA, NM and BT conducted the literature review, abstracted
24
25 431 data and graded the strength of evidence. NM wrote the first draft of the manuscript; all authors
26
27 432 reviewed the manuscript and provided comments. All authors have given approval for this version to
28
29 433 be published.
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35 435 **Figure Legends:**

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37 436 **Figure 1:** Analytic framework for continuing education to prevent mild cognitive impairment and
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39 437 Alzheimer's-type dementia

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41 438 **Figure 2:** Flow diagram of systematic review of continuing education for the prevention of mild
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43 439 cognitive impairment and Alzheimer's-type dementia

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45 440 **Figure 3:** Flow diagram of overview of systematic reviews of cognitive leisure activities for the
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47 441 prevention of mild cognitive impairment and Alzheimer's-type dementia
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1
2 442 **List of abbreviations**
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- 5 443 AD = Alzheimer Disease
6 444 aMCI = Amnesic Mild Cognitive Impairment
7 445 AMSTAR = Assessing the Methodological Quality of Systematic Reviews
8 446 CEDEFOP = European Centre for the Development of Vocational Training
9 447 CENTRAL = Cochrane Central Register of Controlled Trials
10 448 DSM = Diagnostic and Statistical Manual of Mental Disorders
11 449 GRADE = Grading of Recommendations Assessment, Development and Evaluation
12 450 HR = Hazard Ratio
13 451 ICD = International Classification of Diseases
14 452 MCI = Mild Cognitive Impairment
15 453 MMSE = Mini-Mental State Examination
16 454 OECD = Organisation for Economic Co-operation and Development
17 455 OR = Odds Ratio
18 456 PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
19 457 ROBINS-I = Risk of Bias in non-randomized studies – of interventions
20 458 RR = Relative Risk
21 459 SD = Standard Deviation
22 460 SMD = Standardized mean difference
23 461 UNESCO = United Nations Educational, Scientific and Cultural Organization
24 462 WHO = World Health Organisation
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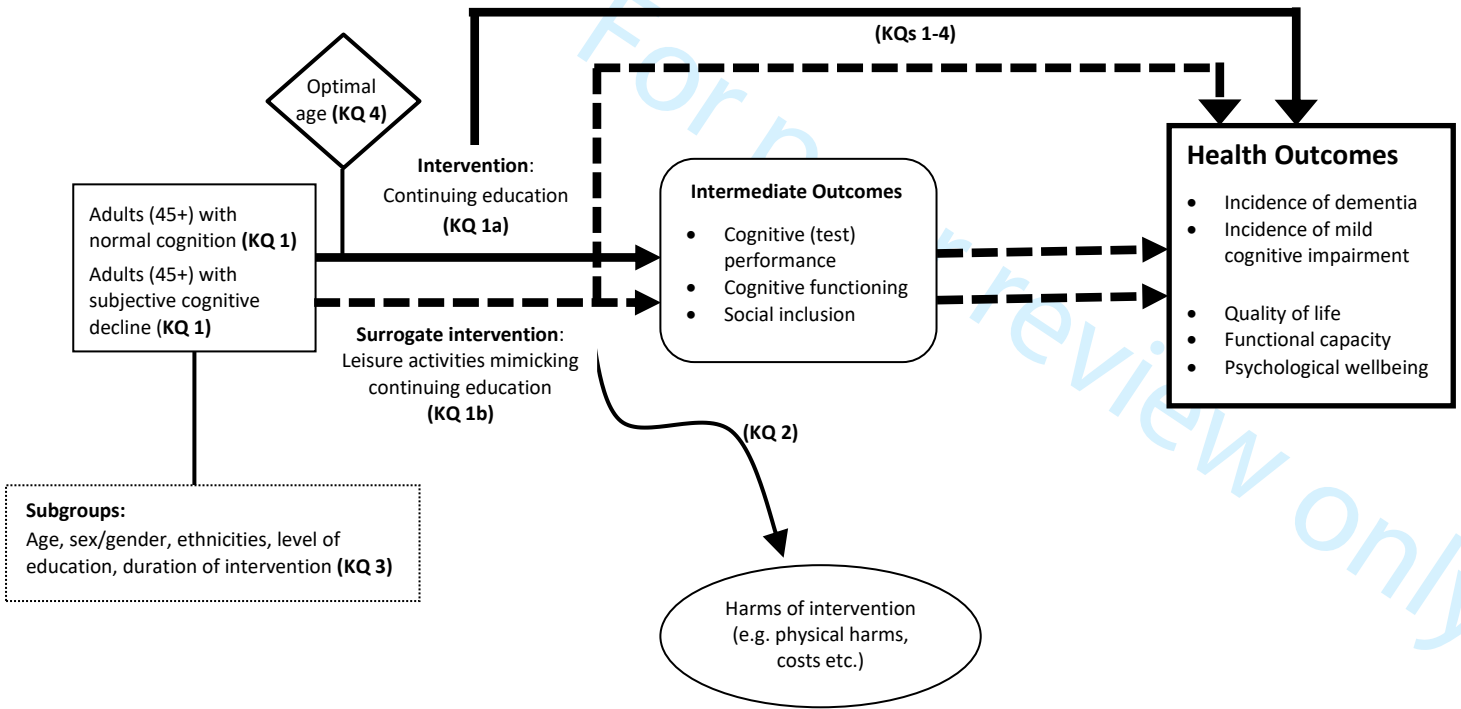
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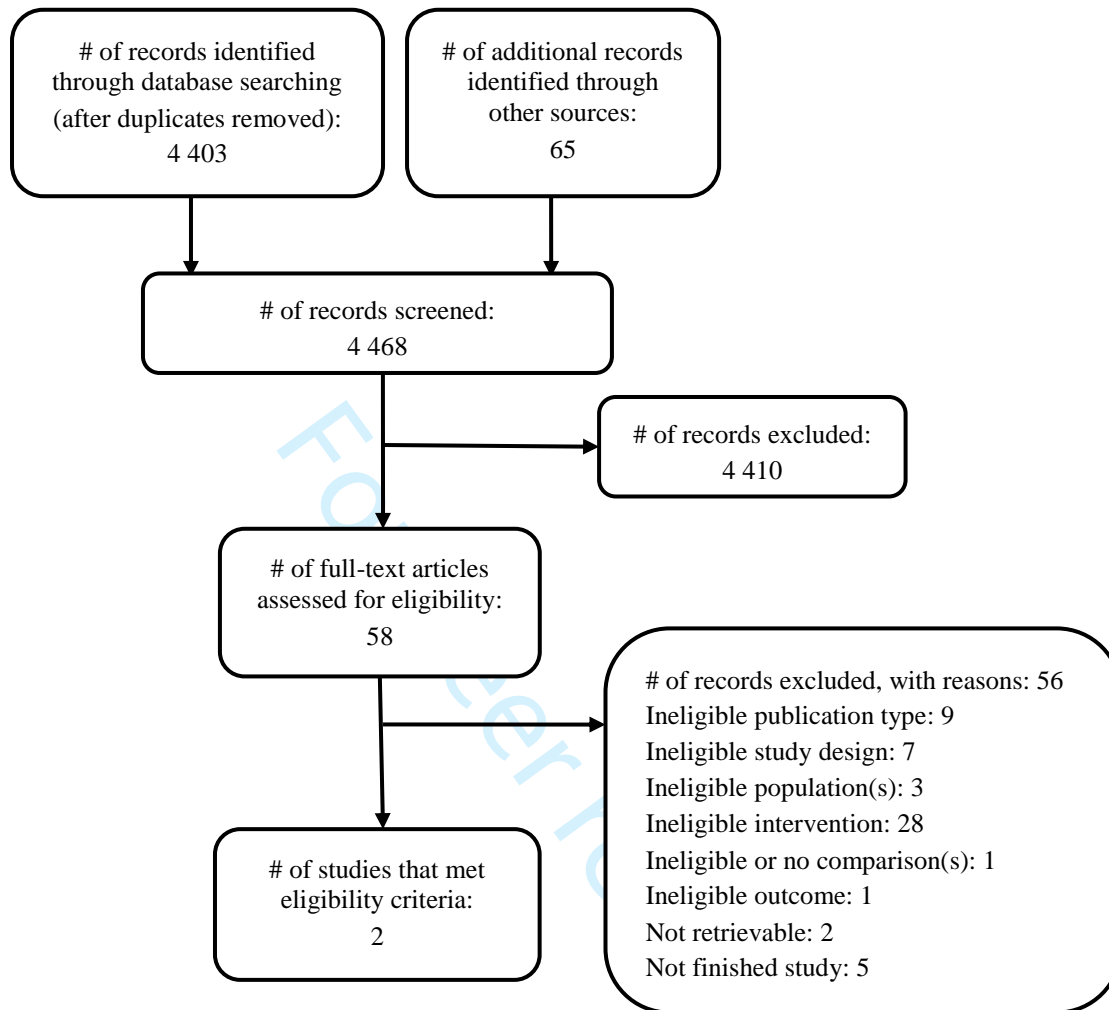
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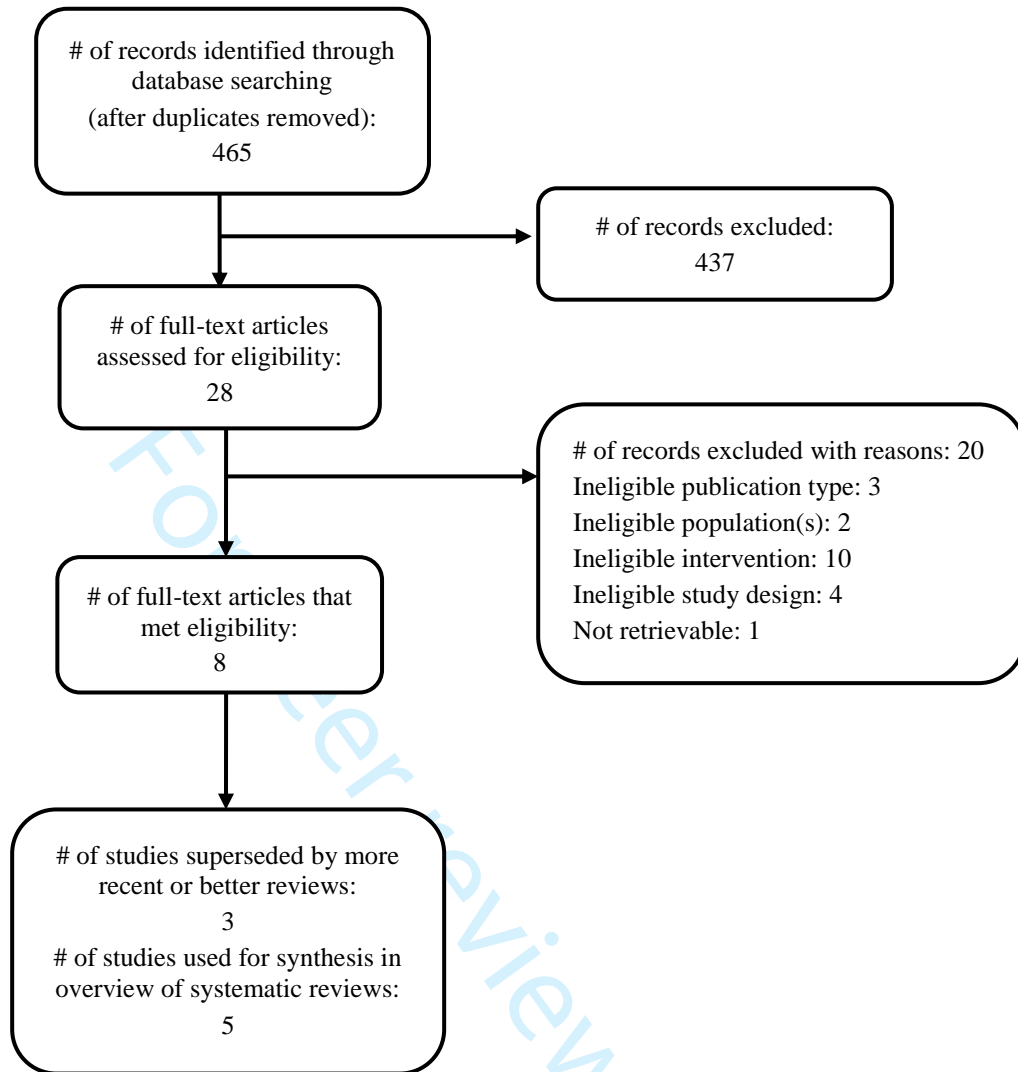
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PRISMA 2009 Checklist

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

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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)
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Page 1 of 2

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.

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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

1			
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4		"lifelong learning" OR "life-long	
5		learning" OR ((continuing OR	
6		adult) N2 (education OR	
7		training))	Search modes - Find all my
8	S16		search terms 106290
9		S12 OR S13 OR S14 OR S15 OR	Search modes - Find all my
10	S17	S16	search terms 27,763
11			Search modes - Find all my
12	S18	S11 AND S17	search terms 667
13			Search modes - Find all my
14	S19	MH "Animal Studies"	search terms 39763
15			Search modes - Find all my
16	S20	S18 NOT S19	search terms 618
17			Search modes - Find all my
18		MH "Named Groups by Age+"	
19		NOT (MH "Middle Age" OR MH	Search modes - Find all my
20	S21	"Aged+")	search terms 55371
21			Search modes - Find all my
22	S22	S20 NOT S21	search terms 552
23			Limiters - Published Date:
24	S23	S22	19900101-20171231 557
25			
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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

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3	S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	290,595
4				
5	S18	S11 AND S17	Search modes - Find all my search terms	753
6				
7	S19	MH "Animal Studies"	Search modes - Find all my search terms	43,810
8				
9	S20	S18 NOT S19	Search modes - Find all my search terms	691
10				
11	S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	595,044
12				
13	S22	S20 NOT S21	Search modes - Find all my search terms	617
14				
15	S23	S22	Limiters - Published Date: 20170101-	78
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17	S24	S22 AND EM 20170701-	Search modes - Find all my search terms	66
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19	S25	S23 OR S24	Search modes - Find all my search terms	95
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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

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4	S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8046
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6		TI (learn* OR class OR classes OR		
7	S16	course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	555016
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9		TI (cognitiv* N2 (stimulat* OR		
10	S17	activit*))	Search modes - Find all my search terms	94
11				
12	S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	76187
13				
14	S19	"lifelong learning" or "life-long learning"	Search modes - Find all my search terms	10135
15				
16	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
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19	S21	S10 AND S20	Search modes - Find all my search terms	286
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22	S22	S21	Limiters - Date Published: 19900101-20171231	234
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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

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2				
3	S17	T1 (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	102
4				
5	S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	77,861
6				
7	S19	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	17
8				
9	S20	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	10,521
10				
11	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
12				
13	S22	S10 AND S21	Search modes - Find all my search terms	309
14				
15	S23	S22	Limiters - Date Published: 20170101-	16
16				
17	S24	S22 AND EM 20170701-	Search modes - Find all my search terms	0
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19	S25	S23 OR S24	Search modes - Find all my search terms	16
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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
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Intervention type:	Non-pharmacological
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Intervention:	Contains any word	learning education educational
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18 Studies found

ALOIS (9 April 2018)

Not searched website down

DART-Europe (16 May 2017)

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

DART-Europe (8 April 2018)

search	results
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimulation") 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

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2			
3	26	(integrative research review* or research integration).tw. or scoping	167686
4		review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as	
5		topic).hw.) or (evidence adj3 review*).ti,ab,kf.	
6			
7	27	21 or 22 or 23 or 24 or 25 or 26	412039
8	28	27 not (case report/ or letter.pt.)	401602
9	29	20 and 28	243
10	30	remove duplicates from 29	229
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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 metasynt*).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)	345120
		2
#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 metasynt*: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 metasynt*	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 metasynt*		
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

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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

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2			
3	S16	(DE "Drug Therapy")	Search modes - Find all my search terms 127,11
4			
5	S17	S15 NOT S16	Search modes - Find all my search terms 3,161
6			
7	S18	DE "Meta Analysis"	Search modes - Find all my search terms 4,026
8			
9	S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynt*	Search modes - Boolean/Phrase 27,695
10			
11	S20	(systematic* OR quantitativ* OR methodologic*)	Search modes - Find all my search terms 27,454
12		N4 (review* OR overview* OR synthes*)	
13	S21	TI (systematic OR structured OR evidence OR trials)	Search modes - Find all my search terms 16,949
14		AND TI (review OR overview OR look OR examination OR update* OR summary)	
15	S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms 51,681
16			
17	S23	S17 AND S22	Search modes - Find all my search terms 73
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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

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3	S13	S11 NOT S12	Search modes - Find all my search terms	3,706
4				
5	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
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8				
9				
10	S15	S13 NOT S14	Search modes - Find all my search terms	3,539
11				
12	S16	(DE "Drug Therapy")	Search modes - Find all my search terms	129,812
13				
14				
15	S17	S15 NOT S16	Search modes - Find all my search terms	3,481
16				
17	S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,152
18				
19	S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	30,127
20				
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22				
23	S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	30,748
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25				
26	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
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31	S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	56,448
32				
33	S23	S17 AND S22	Search modes - Find all my search terms	84
34				
35	S24	RD 201707-	Search modes - Find all my search terms	148,956
36				
37				
38	S25	DT 201707-	Search modes - Find all my search terms	100,982
39				
40	S26	S24 OR S25	Search modes - Find all my search terms	159,715
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43	S27	S23 AND S26	Search modes - Find all my search terms	13
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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

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3	#14 (garden* or horticultur*):ti,kw	125
4	#15 (play* or game* or gaming):ti,kw	3653
5	#16 (creativ* or painting or drawing or reading):ti,kw	3482
6	#17 (voluntary or volunteer* or extracurricular):ti,kw	20037
7	#18 (cognitiv* near/2 (activity or activities)):ti,kw	80
8	#19 {or #8-#18}	44252
9	#20 #7 and #19	1838
10	#21 [mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
11	#22 #20 not #21 Publication Year from 2017 to 2018, in Cochrane Reviews	1
12	(Reviews and Protocols) and Technology Assessments	
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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 "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

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4	Stanford University, 2012	Activities for Cognitive Enhancement of Seniors	Ineligible intervention
5	Then et al., 2016	Education as protector against dementia, but what exactly do we mean by education?	Ineligible intervention
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7	University Hospital 2016	Long-term Effects of Interventional Strategies to Prevent Cognitive Decline in Elderly	Ineligible intervention
8	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
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10	Vemuri et al., 2014	Association of lifetime intellectual enrichment with cognitive decline in the older population	Ineligible intervention
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12	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
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14	Yaffe et al., 2009	Predictors of maintaining cognitive function in older adults: the Health ABC study	Ineligible intervention
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16	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
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18	Jonaitis et al., 2013	Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease	Ineligible populations
19	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
20	National University,	Choral Singing For the Prevention of Dementia	not finished study
21			
22	Marquez et al., 2017	Regular Latin Dancing and Health Education may Improve Cognition of Late Middle-Aged and Older Latinos	Ineligible comparison;
23	University Hospital 2018	Prospective Population Based Cohort Study on Cognitive and Cardiovascular Aging (MonaLisaPredor)	not finished study;
24			
25	Janssen Research Development 2018	Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research: Prospective Readiness Cohort Study	not finished study
26	ACTRN126170008 58392 2017	Ageing and Folk Dances from the Basque Country: Functional and neuropsychological changes. A controlled trial.	Ineligible intervention
27			
28	Biasutti et al., 2018	Assessing a cognitive music training for older participants: a randomised controlled trial	Ineligible population
29			
30	Centre de Recherche del'Institut Universitaire de Geriatrie, 2018	Impact of a Cognitive Intervention Enriched With Leisure Activities in Persons With Subjective Cognitive Decline	Not finished study
31			
32	Chan et al., 2016	Training Older Adults to Use Tablet Computers: Does It Enhance Cognitive Function?	Ineligible study design
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34	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
35			
36	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
37	NCT02919748, 2016	Choral Singing For the Prevention of Dementia	Not finished study
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39	Ramos et al., 2017	Does learning a language in the elderly enhance switching ability?	Ineligible outcome
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41	Wang et al., 2017	Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study	Ineligible intervention
42	ZanESCO et al., 2018	Mental training of attention through intensive meditation: Longitudinal behavioral and electrophysiological investigations of visual sustained attention and response inhibition	Not retrievable
43	Zhu et al., 2017	Leisure activities, education, and cognitive impairment in Chinese older adults: A population-based longitudinal study	Ineligible intervention
44	2017	Study suggests late-life activities reduce the risk of mild cognitive impairment	Ineligible study design
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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 retrievable
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 superseded 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 superseded 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 superseded 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	Ineligible 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

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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)	No 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. I² = 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)	No 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

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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)	No 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, x² test p=0.09, b. differences in interventions (definition of cognitive leisure activities varies across studies), c. high heterogeneity, x² 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)
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Page 1 of 2

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
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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.

Page 2 of 2

BMJ Open

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

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Neurology, Geriatric medicine, Public health, Mental health
Keywords:	Systematic review, Dementia < NEUROLOGY, mild cognitive impairment, PREVENTIVE MEDICINE, continuing education

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Manuscripts

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2 1 **Continuing Education for the Prevention of Mild Cognitive Impairment and**
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5 2 **Alzheimer's-Type Dementia: A Systematic Review and Overview of Systematic**
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7
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20 35 **Key words:** systematic review, dementia, mild cognitive impairment, prevention, continuing
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22 36 education
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39 **ABSTRACT**

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

42 **Design:** Systematic review and overview of systematic reviews.

43 **Data sources:** We systematically searched MEDLINE, PsycINFO, EMBASE, CENTRAL, CINAHL and
44 Scopus for published studies and gray literature databases for unpublished studies from January
45 1990 to April 2018.

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

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

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

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2 65 **Systematic review registration:** PROSPERO CRD42017063944
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9 68 **Strengths and Limitations of this study:**

- 10
11 69 • This is the first systematic review assessing the benefits and harms of continuing education
12 on the prevention of mild cognitive impairment or Alzheimer's type dementia.
13 70
14
15 71 • This is the first overview of systematic reviews presenting an up-to-date summary of
16 currently available research in the field of cognitive leisure activities and dementia.
17 72
18
19 73 • The certainty of evidence is low, indicating that future studies might have a substantial
20 impact on results of our review.
21 74
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23 75 • Measurements and types of cognitive leisure activities differed widely across studies and
24 quantitative analysis were often not possible.
25 76
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27 77 • The majority of included systematic reviews have serious methodological shortcomings.
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80 INTRODUCTION

81 In 2012, the World Health Organization (WHO) named the prevention and control of
82 neurocognitive disorders such as mild cognitive impairment or Alzheimer's-type dementia a global
83 public health priority.¹ Alzheimer's-type dementia is the most common form of dementia.¹ In 2018,
84 50 million people worldwide lived with Alzheimer's disease or another closely related form of
85 dementia.² As a consequence of the rapidly aging world population, the prevalence of dementia is
86 projected to rise up to 152 million people in 2050.²

87 The progressive loss of independent functioning of people with Alzheimer's-type dementia,
88 leads to an enormous social and economic burden. In 2018, the U.S. economic burden associated
89 with Alzheimer's type dementia was estimated to be 277 billion U.S. Dollars.³ The total global costs
90 for dementia were about a trillion US dollar in 2018.²

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

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

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

1
2 106 activity, and smoking.^{7,8} In addition, potential predictors of dementia are chronic medical conditions
3
4 107 such as cardiovascular diseases, diabetes, obesity, cancers, depression, thyroid disorder, or genetic
5
6 108 factors.⁹ Some studies, however, found a protective association of cognitively stimulating activities,
7
8 109 such as learning a new language in middle age, with a slower cognitive decline during late life.¹⁰⁻¹⁴
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10 110 Such results underpin the “cognitive reserve hypothesis”.¹⁵⁻¹⁷ According to this theory, through every
11
12 111 activity that stimulates the brain, the cognitive reserve gets boosted and the resistance towards any
13
14 112 dementia-related brain pathology increases.¹⁸ In animal trials, an enriched environment was
15
16 113 associated with increased cortical thickness.¹⁹ Epidemiological research on humans has shown that
17
18 114 education²⁰ and probably also other forms of intellectual stimulation, during the whole lifespan, are
19
20 115 associated with a lower risk to develop dementia.^{21, 22} A larger cognitive reserve acquired by
21
22 116 continuing education activities, thus, might protect against cognitive decline.^{18, 23}
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26 117 Continuing education activities are structured learning activities offered by educational
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28 118 institutes. These activities are designed to help individuals satisfy learning needs and interests after
29
30 119 compulsory schooling, to enrich knowledge, to develop and improve abilities and skills, and to foster
31
32 120 personality, social competences, families, networks, health, and professional life. Continuing
33
34 121 education is voluntary, based on topics and courses that are not directly connected to any special job
35
36 122 position or vocational training.²⁴⁻²⁹ Cognitive leisure activities (e.g., learning a new language) often
37
38 123 mimic continuing education activities but are not taking place within the framework of an
39
40 124 educational institution.
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44 125 **Rationale**

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47 126 To date, the preventive effect of continuing education on cognitive impairment and Alzheimer’s-type
48
49 127 dementia has not been assessed in an objective and systematic way. The aim of our review was to
50
51 128 summarize the evidence investigating the preventive effects of continuing education on the
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53 129 development of cognitive impairment and Alzheimer’s-type dementia.
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57 130 Our systematic review addressed the following questions:
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- 1
2 131 **Key question 1a:** In adults 45 years of age or older with normal cognition or merely subjective
3
4 132 cognitive impairment, does continuing education lead to a reduction in the risk of mild cognitive
5
6 133 impairment or Alzheimer's-type dementia compared with no continuing education?
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8
9 134 **Key question 1b:** (In case no evidence on continuing education is available or the evidence is sparse):
10
11 135 In adults 45 years of age or older with normal cognition or merely subjective cognitive impairment,
12
13 136 do cognitive leisure activities lead to a reduction in the risk of mild cognitive impairment or
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15 137 Alzheimer's-type dementia compared with no cognitive leisure activities?
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17
18 138 **Key question 2:** What are potential harms of continuing education?
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20
21 139 **Key question 3:** Do benefits and harms differ by subgroups based on age, sex/gender, race or
22
23 140 ethnicities, level of education, or duration of intervention?
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26 141 **Key question 4:** What is the optimal age to start continuing education to prevent mild cognitive
27
28 142 impairment or dementia?
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34 144 **METHODS**

36 145 **Design**

38 146 Throughout this manuscript we followed the PRISMA (Preferred Reporting Items for
39
40 147 Systematic Reviews and Meta-Analyses) statement³⁰ (see supplementary file 1). The protocol of this
41
42 148 systematic review was registered in PROSPERO (International Prospective Register of Systematic
43
44 149 Reviews) (Registration number CRD42017063944) and published previously.³¹ Figure 1 depicts the
45
46 150 analytic framework that guided our systematic review.

49 151 [Figure 1 about here]

52 152 For this systematic review, we define continuing education as structured learning activities
53
54 153 and programs provided by formal and non-formal educational institutions for persons beyond the
55
56 154 age of compulsory schooling (in most countries 16 years and older).²⁴⁻²⁹

59 155 We addressed our research questions with two different methodological approaches:
60

1
2 156 1) We performed a systematic review of primary studies to assess the preventive
3
4 157 effects and potential harms of continuing education provided by formal and non-formal
5
6 158 institutions (key questions 1a, 2, 3, and 4).
7

8 159 2) We conducted an overview of systematic reviews to determine the preventive effects
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10 160 and potential harms of related leisure activities (e.g. playing cards, reading books, etc., key
11
12 161 question 1b).
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15 162 We chose this two-step approach because studies in the field of continuing education and
16
17 163 dementia are very rare. Certain leisure activities, however, are able to mimic continuing education
18
19 164 regarding content (e.g. learning a new language privately versus learning a new language as an
20
21 165 organized educational activity). Leisure activities are not our primary focus of interest but can be
22
23 166 considered as proxy interventions for continuing education in some circumstances.
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29 168 **Study selection**

30 31 169 **Eligibility criteria for the systematic review**

32
33 170 The population of interest were adults 45 years or older, without a clinical diagnosis of
34
35 171 cognitive impairment at the time of study recruitment, which included people with subjective
36
37 172 cognitive impairment. Eligible interventions comprised of all cognitive activities that are provided by
38
39 173 formal and non-formal educational institutions. These activities include classes, courses, and
40
41 174 trainings that are based on individual interests and that are attended voluntarily. We included
42
43 175 randomized controlled trials, nonrandomized controlled trials, prospective controlled cohort studies,
44
45 176 retrospective controlled cohort studies, and case-control studies. All nonrandomized studies needed
46
47 177 to have a minimum sample size of 300 or more participants.
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51 178 Eligible studies had a minimum follow up time of 1 year and a minimum duration of
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53 179 intervention of 3 months. We excluded studies that investigated formal (vocational) education (e.g.
54
55 180 School or College), physical activities, and all job-related courses and trainings.
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2 181 Outcomes of interest included patient-relevant health outcomes such as incidence of
3
4 182 dementia, incidence of MCI, psychological wellbeing, functional capacity, quality of life, and other
5
6 183 relevant health outcomes; in addition, we included intermediate outcomes such as cognitive
7
8 184 functioning, cognitive (test) performance, or social inclusion. For the purpose of our study, mild
9
10 185 cognitive impairment refers to “amnesic” mild cognitive impairment (aMCI), meaning that memory
11
12 186 loss is the predominant symptom.³²

16 187 **Eligibility criteria for the overview of systematic reviews**

18 188 Eligibility criteria for population and outcomes for the overview of systematic reviews were
19
20 189 the same as for the systematic review. Eligible interventions were leisure activities that are
21
22 190 cognitively stimulating and mimic the content of continuing education but in an informal setting. Just
23
24 191 as in the systematic review, we excluded physical activities. Eligible study designs were exclusively
25
26 192 systematic reviews and meta-analyses. We excluded reviews with searches conducted before 2013.

27
28 193 Further details about our inclusion and exclusion criteria can be found in our protocol³¹ and
29
30 194 in the supplementary file 2.

35 195 **Search strategy**

36
37 196 We systematically searched Ovid MEDLINE, Cochrane Library, Embase, PsycINFO, CINAHL
38
39 197 (Cumulative Index to Nursing and Allied Health Literature), ALOIS (the Cochrane Dementia and
40
41 198 Cognitive Improvement Group Specialized Register), and ERIC (Education Resources Information
42
43 199 Center) from January 1990 to April 2018 to identify relevant publications (see supplementary file 3
44
45 200 for the search strategy). For the overview of reviews, we searched Epistemonikos from inception to
46
47 201 April 2018 in addition to the above mentioned databases (see supplementary file 4).

48
49 202 An experienced information specialist developed an appropriate search strategy using a
50
51 203 combination of medical subject headings (MeSH®) and title and abstract keywords, limiting the
52
53 204 search to human-only studies without applying any language limitations. The electronic Ovid Medline
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55 205 search strategy was peer-reviewed by another information specialist following the PRESS (peer
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2 206 review of the electronic search strategy) statement.³³ For the systematic review, we searched for
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4 207 gray literature in ClinicalTrials.gov, the World Health Organization's International Clinical Trials
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6 208 Registry Platform, web pages of relevant organizations, and a dissertation database ("Digital Access
7
8 209 to Research Theses", DART-Europe). Additionally, in an attempt to avoid retrieval bias, we manually
9
10 210 searched the reference lists of landmark studies and background articles on this topic to look for any
11
12 211 relevant citations that our electronic searches might have missed. We imported all citations into an
13
14 212 electronic database (EndNote X.8) and deleted duplicates.
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18 213 **Study selection**

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20 214 Two review authors independently screened abstracts and relevant full text articles for
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22 215 eligibility, using Covidence Software.³⁴ They resolved disagreements by discussion or by consultation
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24 216 with a third author.
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28 217 **Data abstraction**

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30 218 We designed, pilot-tested, and used a data abstraction form to gather pertinent information
31
32 219 from each article. One author extracted relevant data from each study that met our inclusion criteria.
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34 220 A second author of the team cross-checked data abstractions for completeness and accuracy. We
35
36 221 extracted study information (author, publication year, years covered by searches, location/setting,
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38 222 number of included studies and included study designs), sample size, study characteristics
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40 223 (population, interventions, and comparators), outcome measurements, and results. For systematic
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42 224 reviews we abstracted summary estimates of meta-analyses whenever available.
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47 225 **Risk of bias assessment**

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49 226 Two investigators independently assessed the risk of bias of included studies. They resolved
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51 227 any disagreements by consensus or by consulting a third team member. For eligible non-randomized
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53 228 studies we used the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool.³⁵ For
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55 229 the assessment of eligible systematic reviews, we used the AMSTAR (Assessing the Methodological
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230 Quality of Systematic Reviews) tool.³⁶ Detailed risk of bias ratings of included articles are given in
231 supplementary file 5.

232 **Data synthesis and statistical analysis**

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

239 **Certainty of evidence**

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

243 **Patient involvement**

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

245

246 **RESULTS**

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

252 [Figure 2 and figure 3 about here]

253 **Study characteristics**

254 **Systematic Review**

1
2 255 We included two publications^{38 39} that present interim findings of the same medium risk of
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4 256 bias prospective cohort study, namely the Tasmanian Healthy Brain Project that plans to follow
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6 257 participants for 10-20 years.⁴⁵ The two publications analysed different aspects of cognitive
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8 258 functioning of the same 459 participants who did or did not engage in a 12 month, part-time or full-
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10 259 time university-level education. Participants' mean age was 59.6±7 (mean±SD) years in the
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12 260 intervention group and 62.4±6 years in the control group with a follow-up period of 4 years.
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14 261 Participants completed a neuropsychological test battery, consisting of 14 tests each year.⁴⁵
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16
17 262 In this study, selection bias is likely because participants voluntarily opted for university
18
19 263 courses or no further education. It is not clear if investigators used appropriate methods to adjust for
20
21 264 potential confounders (see supplementary file 5 for risk of bias ratings).
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25 265 **Overview of Reviews**

26
27 266 All five included systematic reviews investigated the benefits of cognitive leisure activities in
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29 267 adults over the age of 45 years.⁴⁰⁻⁴⁴ Four studies included any cognitive leisure activities in their
30
31 268 analyses (e.g. reading books, doing crosswords, attending cultural events, knitting, painting), one
32
33 269 study⁴³ specifically focused on the benefits of playing video games in older adults. The number of
34
35 270 participants investigated in the reviews ranged from 913⁴³ to 24,554.⁴¹
36
37

38 271 We rated three of the included systematic reviews^{40 42 43} as high and two studies^{41 44} as
39
40 272 medium risk of bias. Reasons for the high risk of bias ratings were lack of critical appraisal of included
41
42 273 studies, single review of the literature, and insufficient literature searches (see supplementary file 5).
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45 274 We graded the evidence for all meta-analysis outcomes with low certainty of evidence
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47 275 mostly because of high inconsistency and indirectness among studies (see supplementary file 7).
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50 276 We present characteristics of included studies⁴⁰⁻⁴⁴ in table 1 and table 2.
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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

286 **Outcomes**

287 **Key question 1a: Continuing education**

288 Two interim analyses of the Tasmanian Healthy Brain Project focused on language
289 processing³⁸ and cognitive reserve³⁹ after 4 years of follow-up. To date, no results on the incidence of
290 mild cognitive impairment or Alzheimer's-type dementia are available yet. Both studies reported
291 beneficial effects of continuing education. Thow and colleagues³⁸ showed that attending university
292 courses over a period of 12 months statistically significantly ($p<0.05$) improved the language
293 processing capacity in the intervention group compared to the control group. No statistically
294 significant differences were detected for episodic memory, working memory, and executive function
295 between groups. In all analyses, authors accounted for age and prior cognitive reserve (education,
296 pre-existing intellectual capacity, life-experience).

297 Lenehan and coworkers³⁹ demonstrated by conducting growth mixture modeling that the
298 cognitive reserve statistically significantly increased in 92.5% of participants in the intervention group
299 (n=359) compared to 55.7% of participants in the control group (n=100). Investigators created a
300 proxy measure of "current cognitive reserve" to capture dynamic changes in cognitive reserve over
301 time, including intellectual capacity and academic ability.⁴⁶

302 **Key question 1b: Cognitive leisure activities**

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

306 Two systematic reviews^{40,42} investigated the impact of cognitive leisure activities on the
307 incidence of Alzheimer's-type dementia. Di Marco and colleagues included six, Sajeev and colleagues
308 12 primary studies on cognitive leisure activities in their systematic reviews. Both systematic reviews
309 concluded that leisure activities protect against dementia. Due to different categorization of
310 cognitive leisure activities and a high heterogeneity between studies, quantitative analyses were not
311 possible in the two reviews. The effect estimates of included studies ranged from hazard ratios [HR]

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2 312 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
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4 313 reduced risks of Alzheimer's-type dementia when carrying out leisure activities. Sajeev et al.⁴²
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6 314 performed an extensive bias analysis indicating that it is unlikely that the observed positive effects of
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8 315 cognitively stimulating activities on dementia incidence are exclusively explained by unmeasured
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10 316 confounders or reverse causation.

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13 317 One review⁴⁴ assessed both incidence of mild cognitive impairment and Alzheimer's-type
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15 318 dementia and cognitive test performance. The authors conducted five meta-analyses based on
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17 319 groups for outcomes and reported effect estimates (risk ratio [RR], odds ratio [OR], and hazard ratio
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19 320 [HR]). Four out of five meta-analyses revealed statistically significant results showing that cognitive
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21 321 leisure activities were associated with a reduction of dementia incidence (RR = 0.61, 95% CI: 0.42-
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23 322 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
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25 323 impairment incidence (OR = 0.69, 95% CI: 0.56 – 0.85). However, one meta-analysis, combining three
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27 324 cohort studies did not reach statistical significance (HR = 0.85, 95% CI: 0.71-1.02) for reduction of
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29 325 cognitive impairment. A narrative analysis of primary studies assessing cognitive test performance
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31 326 showed a statistically significant improvement of memory, speed of processing, language, and
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33 327 executive functioning and overall later life cognition.

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36 328 Two other included studies^{41 43}, both rated as high risk of bias, focused on cognitive test
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38 329 performance. Opdebeeck et al.⁴¹ reported a benefit in overall cognitive abilities for the group
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40 330 involving in cognitive leisure activities (standardized mean difference [SMD] of 0.26 (95% confidence
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42 331 interval [CI]: 0.21-0.32). The cognitive domains included memory, working memory, executive
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44 332 function, visuospatial ability, and language. According to the review by Toril et al. ⁴³, playing video
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46 333 games enhanced several cognitive functions. They observed a SMD of 0.37 (95% CI 0.26 – 0.48) for
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48 334 global cognitive function (combining results for memory, attention, reaction time and executive
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50 335 functions), showing a benefit for the intervention group.

51 336 **Key question 2: Harms**

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59 337 We found no evidence regarding harms of continuing education or cognitive leisure activities.
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2 338 **Key question 3: Subgroups**
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4 339 Toril and colleagues⁴³ performed several subgroup analyses. The study revealed that the age
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7 340 of the participants and the number of video game training sessions significantly changed the effect
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9 341 size. Older participants (between 71 and 80 years) seemed to benefit more from computer training
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11 342 than younger participants (60 to 70 years). For the improvement of cognitive test performance,
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13 343 shorter training sessions (1-6 weeks) seemed to show an advantage over longer training
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15 344 interventions (7-12 weeks). By contrast, for incidence of Alzheimer's-type dementia, DiMarco et al.⁴⁰
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17 345 and Sajeev et al.⁴² infer from their data that greater participation in cognitive leisure activities over a
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19 346 longer period of time contributes positively to the protective effect.
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23 347 **Key question 4: Optimal age**
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25 348 No study specifically discussed the optimal age to start with continuing education activities or
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27 349 cognitive leisure activities to prevent mild cognitive impairment or dementia.
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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

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2 377 activities and dementia. Nevertheless, our work has several limitations. First, in the overview of
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4 378 systematic reviews we had to rely on the quality of included systematic reviews which often had
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6 379 methodological shortcomings (e.g. no risk of bias assessment, no dual screening etc.). Second, most
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8 380 of the included studies were observational studies, which are prone to selection bias because
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10 381 participants self-select the group. Risk factors for MCI or dementia in participants selecting leisure
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12 382 activities or further education might be systematically different from participants in the control
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14 383 groups. For example, people who eventually suffer from preclinical dementia stages might be more
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16 384 likely to avoid cognitive leisure activities, which would lead to reverse causation. Third, many primary
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18 385 studies within the reviews used self-reported questionnaires that could be challenging for people
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20 386 who start having cognitive deficits. Finally, the variation of leisure activity categorization across
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22 387 studies made meta-analysis difficult and sometimes impossible. For example, “visiting a library” was
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24 388 classified as a cognitive activity by one author but as a physical activity by another. Some studies
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26 389 assessed current participation in activities, others participation at younger ages. Additionally, some
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28 390 studies assessed the frequency of participation, others the time devoted to activities and some the
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30 391 total number of leisure activities. Consequently, due to these limitations, the comparability of results
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32 392 among studies was limited. A standardization of measures and methods would be necessary to help
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34 393 synthesize evidence in the future and make more reliable recommendations.

394 **Implication for future research, policy and practice**

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

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2 403 Disability (FINGER)⁵³, a randomized controlled trial, with a multi-domain approach (diet, exercise,
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4 404 cognitive training, vascular risk monitoring) supports the hypothesis that simultaneous changes in
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6 405 several risk factors can lead to a protective effect on cognition.
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9 406 Further research is needed to address the evidence gap regarding continuing education and
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11 407 the extent to which it acts as a protective factor. A study similar to the Tasmanian Healthy Brain
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13 408 Project³⁹, but conducted as a randomized controlled trial, would be ideal because it would
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15 409 adequately handle known and unknown confounders. Computers and Internet could play a more
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17 410 significant role in future prevention trials. Older adults could, for instance, be randomized to attend
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19 411 online courses and communicate with professors and other students in virtual classrooms. This
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21 412 approach could save time, money, and increase the potential participant pool.
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24 413 **Conclusion**

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26 414 Although no firm conclusions about the effects of continuing education to prevent MCI and
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28 415 dementia can be drawn, data from preliminary and indirect evidence indicate that continuing
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30 416 education could potentially have important preventive effects.
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14
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20 426 **Author Contributions:** All authors made substantial contribution to the conception and design of this
21
22 427 study. GG, NM, MK, CG and SA developed the concept of the study. As an information specialist, IK
23
24 428 developed the search strategy. GW, FKA, NM and BT conducted the literature review, abstracted
25
26 429 data and graded the strength of evidence. NM wrote the first draft of the manuscript; all authors
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28 430 reviewed the manuscript and provided comments. All authors have given approval for this version to
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30 431 be published.

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35 433 **Figure Legends:**

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38 434 **Figure 1:** Analytic framework for continuing education to prevent mild cognitive impairment and
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40 435 Alzheimer's-type dementia

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42 436 **Figure 2:** Flow diagram of systematic review of continuing education for the prevention of mild
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44 437 cognitive impairment and Alzheimer's-type dementia

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46 438 **Figure 3:** Flow diagram of overview of systematic reviews of cognitive leisure activities for the
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48 439 prevention of mild cognitive impairment and Alzheimer's-type dementia

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2 440 **List of abbreviations**
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- 5 441 AD = Alzheimer Disease
6 442 aMCI = Amnesic Mild Cognitive Impairment
7 443 AMSTAR = Assessing the Methodological Quality of Systematic Reviews
8 444 CEDEFOP = European Centre for the Development of Vocational Training
9 445 CENTRAL = Cochrane Central Register of Controlled Trials
10 446 DSM = Diagnostic and Statistical Manual of Mental Disorders
11 447 GRADE = Grading of Recommendations Assessment, Development and Evaluation
12 448 HR = Hazard Ratio
13 449 ICD = International Classification of Diseases
14 450 MCI = Mild Cognitive Impairment
15 451 MMSE = Mini-Mental State Examination
16 452 OECD = Organisation for Economic Co-operation and Development
17 453 OR = Odds Ratio
18 454 PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses
19 455 ROBINS-I = Risk of Bias in non-randomized studies – of interventions
20 456 RR = Relative Risk
21 457 SD = Standard Deviation
22 458 SMD = Standardized mean difference
23 459 UNESCO = United Nations Educational, Scientific and Cultural Organization
24 460 WHO = World Health Organisation
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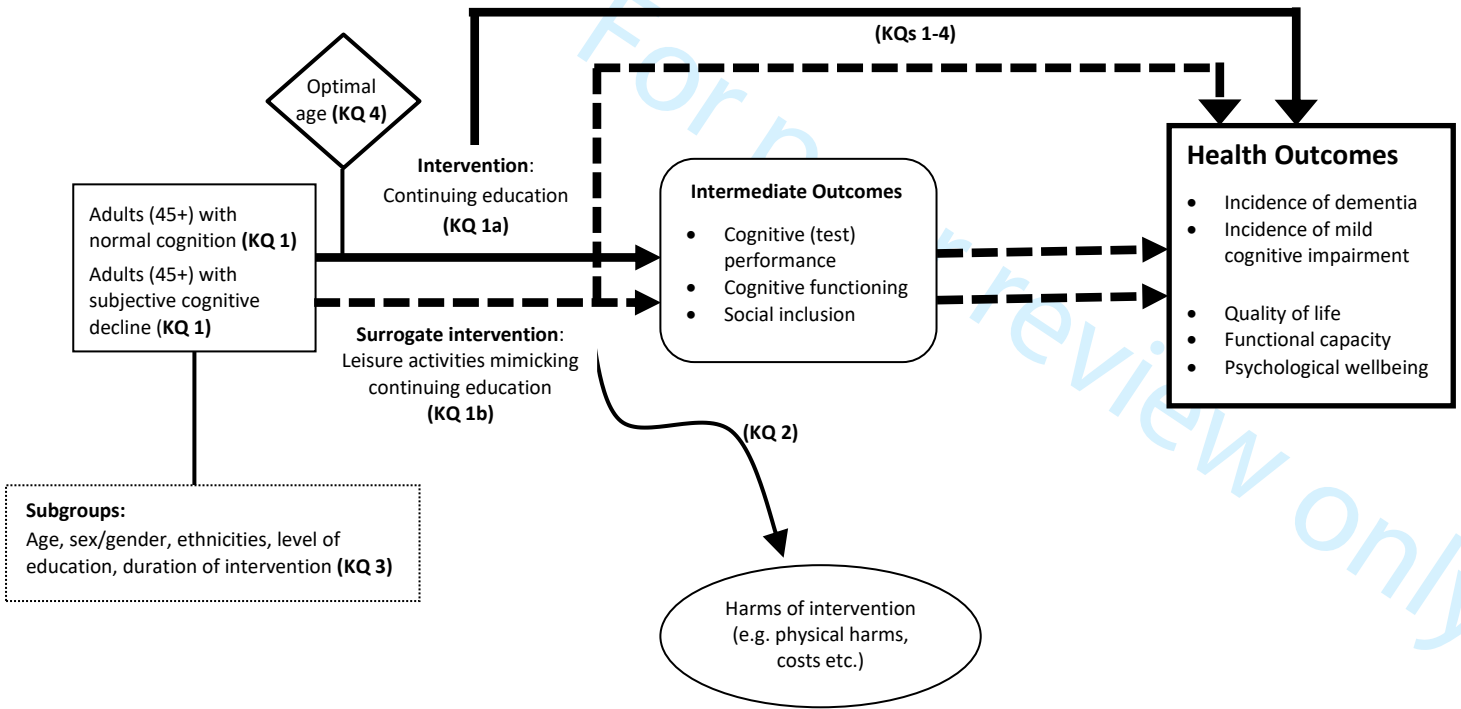
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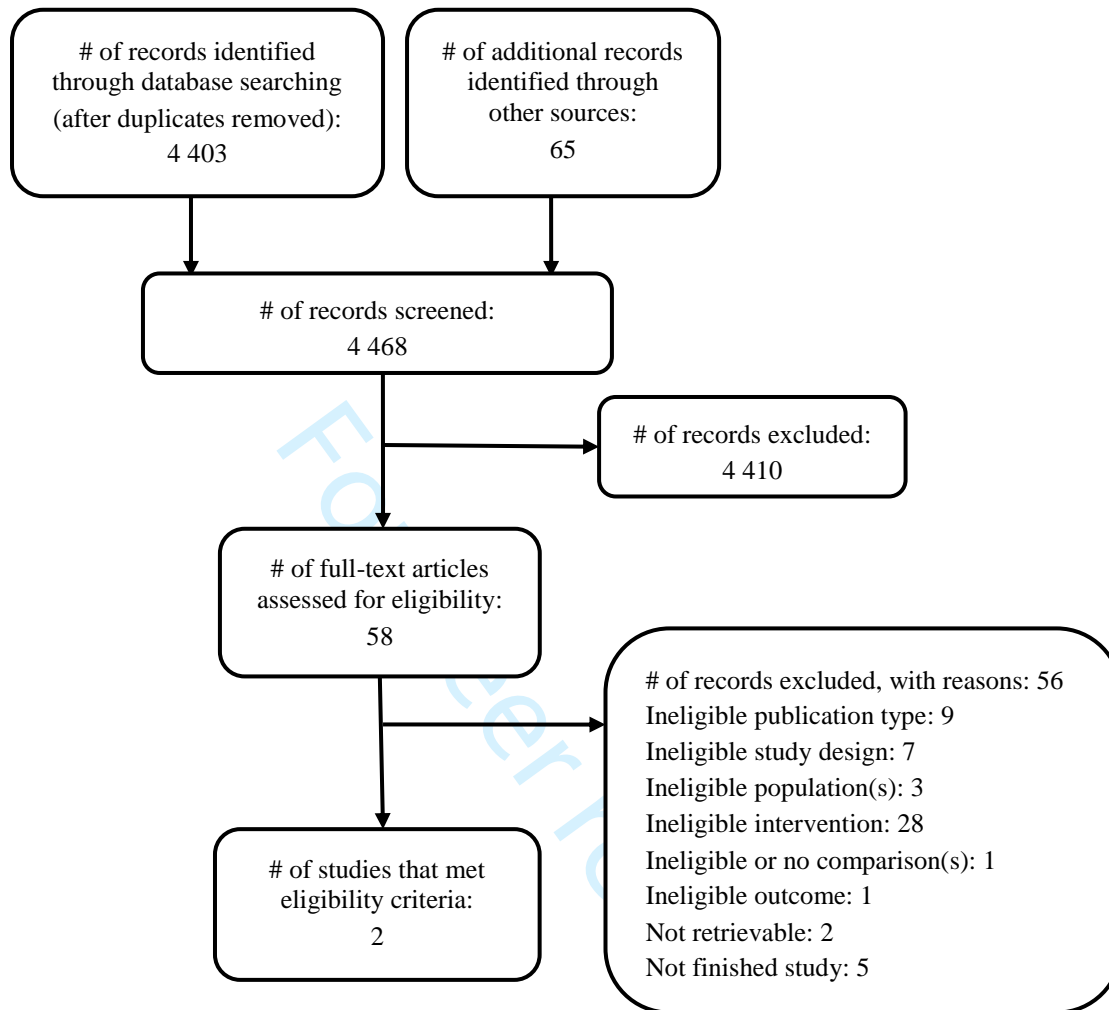
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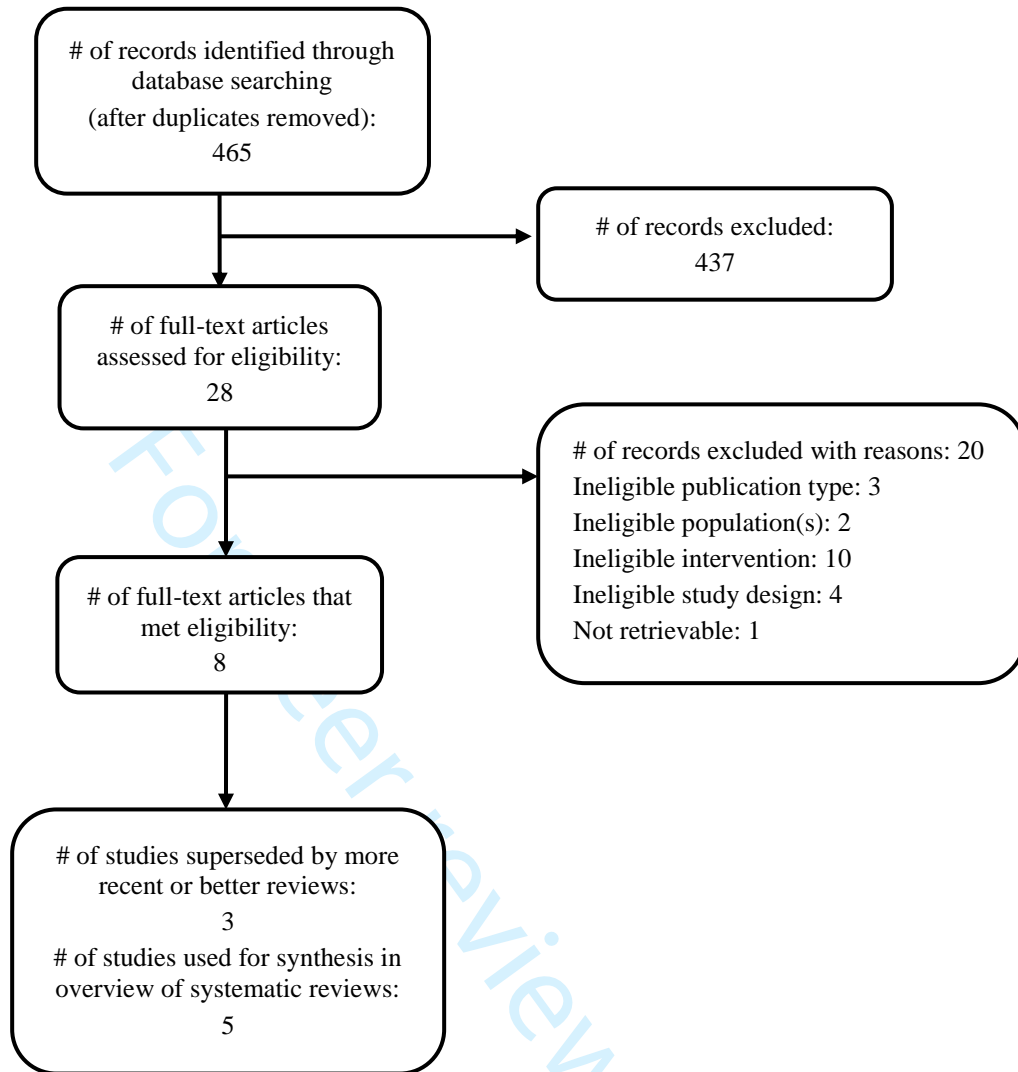
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PRISMA 2009 Checklist

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)
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Page 1 of 2

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.

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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

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4		"lifelong learning" OR "life-long	
5		learning" OR ((continuing OR	
6		adult) N2 (education OR	
7		training))	Search modes - Find all my
8	S16		search terms 106290
9		S12 OR S13 OR S14 OR S15 OR	Search modes - Find all my
10	S17	S16	search terms 27,763
11			Search modes - Find all my
12	S18	S11 AND S17	search terms 667
13			Search modes - Find all my
14	S19	MH "Animal Studies"	search terms 39763
15			Search modes - Find all my
16	S20	S18 NOT S19	search terms 618
17			Search modes - Find all my
18		MH "Named Groups by Age+"	
19		NOT (MH "Middle Age" OR MH	Search modes - Find all my
20	S21	"Aged+")	search terms 55371
21			Search modes - Find all my
22	S22	S20 NOT S21	search terms 552
23			Limiters - Published Date:
24	S23	S22	19900101-20171231 557
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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

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3	S17	S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	290,595
4				
5	S18	S11 AND S17	Search modes - Find all my search terms	753
6				
7	S19	MH "Animal Studies"	Search modes - Find all my search terms	43,810
8				
9	S20	S18 NOT S19	Search modes - Find all my search terms	691
10				
11	S21	MH "Named Groups by Age+" NOT (MH "Middle Age" OR MH "Aged+")	Search modes - Find all my search terms	595,044
12				
13	S22	S20 NOT S21	Search modes - Find all my search terms	617
14				
15	S23	S22	Limiters - Published Date: 20170101-	78
16				
17	S24	S22 AND EM 20170701-	Search modes - Find all my search terms	66
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19	S25	S23 OR S24	Search modes - Find all my search terms	95
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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

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4	S15	DE "Continuing Education Units" OR DE "Lifelong Learning"	Search modes - Find all my search terms	8046
5				
6		TI (learn* OR class OR classes OR		
7	S16	course* OR educat* OR school* OR train* OR seminar* OR tutor*)	Search modes - Find all my search terms	555016
8				
9		TI (cognitiv* N2 (stimulat* OR		
10	S17	activit*))	Search modes - Find all my search terms	94
11				
12	S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	76187
13				
14	S19	"lifelong learning" or "life-long learning"	Search modes - Find all my search terms	10135
15				
16	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
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19	S21	S10 AND S20	Search modes - Find all my search terms	286
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22	S22	S21	Limiters - Date Published: 19900101-20171231	234
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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

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3	S17	T1 (cognitiv* N2 (stimulat* OR activit*))	Search modes - Find all my search terms	102
4				
5	S18	((continuing OR adult) N2 (education OR training))	Search modes - Find all my search terms	77,861
6				
7	S19	"late life" N2 (activity OR activities OR learn* OR school* OR educat* OR training)	Search modes - Find all my search terms	17
8				
9	S20	"lifelong learning" OR "life-long learning"	Search modes - Find all my search terms	10,521
10				
11	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
12				
13	S22	S10 AND S21	Search modes - Find all my search terms	309
14				
15	S23	S22	Limiters - Date Published: 20170101-	16
16				
17	S24	S22 AND EM 20170701-	Search modes - Find all my search terms	0
18				
19	S25	S23 OR S24	Search modes - Find all my search terms	16
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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
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Intervention type:	Non-pharmacological
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Intervention:	Contains any word	learning education educational
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18 Studies found

ALOIS (9 April 2018)

Not searched website down

DART-Europe (16 May 2017)

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

DART-Europe (8 April 2018)

search	results
(dementia OR alzheimer* OR "cognitive impairment") AND (education* OR "mental activity" OR "mental activities" OR "cognitive stimulation") 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

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3	26	(integrative research review* or research integration).tw. or scoping	167686
4		review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as	
5		topic).hw.) or (evidence adj3 review*).ti,ab,kf.	
6			
7	27	21 or 22 or 23 or 24 or 25 or 26	412039
8	28	27 not (case report/ or letter.pt.)	401602
9	29	20 and 28	243
10	30	remove duplicates from 29	229
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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 metasynt*).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 metasynt*: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)	345120
		2
#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 metasynt*: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 metasynt*		
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

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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

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3	S16	(DE "Drug Therapy")	Search modes - Find all my search terms
4			127,11
5	S17	S15 NOT S16	Search modes - Find all my search terms
6			3,161
7	S18	DE "Meta Analysis"	Search modes - Find all my search terms
8			4,026
9	S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynt*	Search modes - Boolean/Phrase
10			27,695
11	S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms
12			27,454
13	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
14			16,949
15	S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms
16			51,681
17	S23	S17 AND S22	Search modes - Find all my search terms
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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

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3	S13	S11 NOT S12	Search modes - Find all my search terms	3,706
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5	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
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10	S15	S13 NOT S14	Search modes - Find all my search terms	3,539
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12	S16	(DE "Drug Therapy")	Search modes - Find all my search terms	129,812
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15	S17	S15 NOT S16	Search modes - Find all my search terms	3,481
16				
17	S18	DE "Meta Analysis"	Search modes - Find all my search terms	4,152
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19	S19	meta-analys* OR meta analys* OR metaanalys* OR meta synth* OR meta-synth* OR metasynth*	Search modes - Boolean/Phrase	30,127
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23	S20	(systematic* OR quantitativ* OR methodologic*) N4 (review* OR overview* OR synthes*)	Search modes - Find all my search terms	30,748
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26	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
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31	S22	S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms	56,448
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33	S23	S17 AND S22	Search modes - Find all my search terms	84
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35	S24	RD 201707-	Search modes - Find all my search terms	148,956
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38	S25	DT 201707-	Search modes - Find all my search terms	100,982
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40	S26	S24 OR S25	Search modes - Find all my search terms	159,715
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43	S27	S23 AND S26	Search modes - Find all my search terms	13
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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

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3	#14 (garden* or horticultur*):ti,kw	125
4	#15 (play* or game* or gaming):ti,kw	3653
5	#16 (creativ* or painting or drawing or reading):ti,kw	3482
6	#17 (voluntary or volunteer* or extracurricular):ti,kw	20037
7	#18 (cognitiv* near/2 (activity or activities)):ti,kw	80
8	#19 {or #8-#18}	44252
9	#20 #7 and #19	1838
10	#21 [mh "age groups"] not ([mh aged] or [mh "middle aged"])	109483
11	#22 #20 not #21 Publication Year from 2017 to 2018, in Cochrane Reviews	1
12	(Reviews and Protocols) and Technology Assessments	
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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 "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

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4	Stanford University, 2012	Activities for Cognitive Enhancement of Seniors	Ineligible intervention
5	Then et al., 2016	Education as protector against dementia, but what exactly do we mean by education?	Ineligible intervention
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7	University Hospital 2016	Long-term Effects of Interventional Strategies to Prevent Cognitive Decline in Elderly	Ineligible intervention
8	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
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10	Vemuri et al., 2014	Association of lifetime intellectual enrichment with cognitive decline in the older population	Ineligible intervention
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12	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
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14	Yaffe et al., 2009	Predictors of maintaining cognitive function in older adults: the Health ABC study	Ineligible intervention
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16	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
17			
18	Jonaitis et al., 2013	Cognitive activities and cognitive performance in middle-aged adults at risk for Alzheimer's disease	Ineligible populations
19	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
20	National University,	Choral Singing For the Prevention of Dementia	not finished study
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22	Marquez et al., 2017	Regular Latin Dancing and Health Education may Improve Cognition of Late Middle-Aged and Older Latinos	Ineligible comparison;
23	University Hospital 2018	Prospective Population Based Cohort Study on Cognitive and Cardiovascular Aging (MonaLisaPredor)	not finished study;
24			
25	Janssen Research Development 2018	Cognitive Health in Ageing Register: Investigational, Observational and Trial Studies in Dementia Research: Prospective Readiness Cohort Study	not finished study
26	ACTRN126170008 58392 2017	Ageing and Folk Dances from the Basque Country: Functional and neuropsychological changes. A controlled trial.	Ineligible intervention
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28	Biasutti et al., 2018	Assessing a cognitive music training for older participants: a randomised controlled trial	Ineligible population
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30	Centre de Recherche del'Institut Universitaire de Geriatrie, 2018	Impact of a Cognitive Intervention Enriched With Leisure Activities in Persons With Subjective Cognitive Decline	Not finished study
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32	Chan et al., 2016	Training Older Adults to Use Tablet Computers: Does It Enhance Cognitive Function?	Ineligible study design
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34	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
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36	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
37	NCT02919748, 2016	Choral Singing For the Prevention of Dementia	Not finished study
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39	Ramos et al., 2017	Does learning a language in the elderly enhance switching ability?	Ineligible outcome
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41	Wang et al., 2017	Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study	Ineligible intervention
42	Zanesco et al., 2018	Mental training of attention through intensive meditation: Longitudinal behavioral and electrophysiological investigations of visual sustained attention and response inhibition	Not retrievable
43	Zhu et al., 2017	Leisure activities, education, and cognitive impairment in Chinese older adults: A population-based longitudinal study	Ineligible intervention
44	2017	Study suggests late-life activities reduce the risk of mild cognitive impairment	Ineligible study design
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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 retrievable
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 superseded 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 superseded 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 superseded 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	Ineligible 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)	No 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. I² = 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)	No 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

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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)	No 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, x² test p=0.09, b. differences in interventions (definition of cognitive leisure activities varies across studies), c. high heterogeneity, x² 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)
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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
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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.

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