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[Intervention Protocol]

Exergaming for dementia and mild cognitive impairment

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of exergame applications on physical and cognitive outcomes, and activities of daily living (ADL), in people with dementia and mild cognitive impairment (MCI).

BACKGROUND

Description of the condition

Dementia is a major cause of disability and dependency among the older population, and has an extremely negative impact on family, caregivers, community, and residential care services (Shah 2016; Wortmann 2012). It currently affects about 5% of the older population, which is 46.8 million people worldwide, but this figure is forecast to rise over the next decades to approximately 74.7 million by 2030 (World Alzheimer Report 2015).

Dementia is an umbrella term for a syndrome caused by several diseases, usually of a chronic or progressive nature. It is characterised by significant cognitive decline in one or more cognitive domains (e.g. attention, executive functioning, learning and memory, language, perceptual-motor function, and social cognition). This decline negatively impacts and significantly affects independence (e.g. personal activities of daily living, such as housework, managing money, shopping, washing, dressing, personal hygiene, feeding, etc. (APA 2013)). Alzheimer's disease is the most common form of dementia, accounting for approximately 70% of dementia cases. Vascular dementia, dementia with Lewy bodies, dementia in Parkinson's disease, and frontotemporal dementia are other forms of dementia (APA 2013). Mixed pathologies are common.

Mild cognitive impairment (MCI) is a also syndrome of cognitive decline, but less severe than dementia. The main criteria for MCI are a subjective concern about decline in cognitive functioning, and an objective alteration of cognitive functions (e.g. memory, executive functioning, attention language, visuospatial abilities), measured using neuropsychological tests. The key criterion that distinguishes MCI from dementia is the preservation of independence in daily activities, even though people with MCI might be less efficient (Langa 2014). MCI has a prevalence of 10% to 20% of the older adult population (Langa 2014). A meta-analysis of inception cohort studies identified that 32% of people with MCI developed dementia after an average of 4.57 years of follow-up (Mitchell 2009). Conversion rates from MCI to dementia depend largely on the type of population being studied. For example, participants from clinical settings and those from community settings, both with MCI, have different conversion rates. After an average of 4.57 years, the community samples converted to dementia at a rate of 21.9%, while 39.2% of the clinical samples progressed to dementia (Mitchell 2009).

Besides impairments in cognitive functioning, people with dementia and MCI often experience balance and gait problems, are at high risk of falls, and are more sedentary than healthy controls (Allan 2005; Eriksson 2008; Hartman 2018; Taylor 2013).

There are currently limited options for either treating MCI or dementia, or for delaying progression from MCI to dementia. For dementia, approved drugs (e.g. acetylcholinesterase inhibitors, memantine) show small effects on cognition and activities of daily living (ADL) in the short term (Owens 2020; Winblad 2016). In the case of MCI, there is no evidence that drug therapy (e.g. donepezil or memantine) improves general cognitive functioning (Owens 2020). Non-pharmacological interventions, such as regular physical exercise and cognitive training have been identified as potentially effective interventions in reducing the likelihood of developing dementia or MCI, reducing symptoms, or cognitive decline (Bahar-Fuchs 2019; Forbes 2015; Gallaway 2017; Heyn 2004; Kane 2017; Lam 2018; Sallis 2016; Selkoe 2012; Song 2018; Wang 2019). However, the extent of their effectiveness remains unclear, as there is a lack of consensus regarding the magnitude of the effects, and the quality of the evidence.

Description of the intervention

There is growing evidence that combining physical and cognitive exercise training significantly improves global cognitive function. A meta-analysis, which included data from 10 randomised controlled trials (RCT) and 742 participants, reported small to medium improvements in global cognitive function with combined cognitive and physical interventions, and medium to large improvements in ADL for people with MCI and dementia, compared to control conditions Karssemeijer 2017. However, people with dementia and MCI are more sedentary and have more balance and gait problems, which can result in more falls compared with cognitively healthy older adults (Allan 2005; Eriksson 2008; Hartman 2018; Taylor 2013), it might be more difficult for them to engage in physical activities outside the house. Deterioration in emotional control, social behaviour, or motivation (APA 2013; WHO 2019), which can also appear in dementia, might result in lack of initiative and interest in physical and cognitive activities (Clarke 2008; Crombie 2004). Other barriers that may reduce older adults' participation in physical activity are the availability and cost of programmes, the reliability and affordability of public transportation, the weather, and concerns about neighbourhood safety (Belza 2004).

A new intervention, which focuses on physical exercise, can incorporate cognitive elements, and can be carried out in the comfort and security of a person's own home, is virtual reality (VR)-based exercise training, also known as exergaming (Van Santen 2018). Using various technology devices and software (e.g. PCs, gaming consoles, TV screens or projectors, head mounted displays (HMD), controllers, motion tracking sensors), a game-like environment (e.g. virtual football court or ski slope), or a more familiar environment (e.g. a virtual city familiar to the participant) is generated. The person is immersed in this virtual environment via motion-tracking sensors, or infra-red cameras that capture and project their image and movements in real time on the HMD or on a screen. Using controllers and motion-tracking technology that records their movement, the person interacts with, and controls the computer-generated environment, by performing various tasks, usually following rules, keeping score, etc. For example, they virtually ski down the slope; in order to do this, they have to reproduce body movements that are typical for a skiing session.

Virtual reality can also facilitate the combination of physical exercise with cognitive exercise. An example of an exergame that combines both physical and cognitive aspects is cycle training. Participants cycle in a virtual environment (VE) while performing activities known to target specific cognitive functions (e.g. working memory), such as learning a list of neighbourhood errand locations (e.g. doctor, pharmacy, grocery), and having to follow the correct route to reach that location (Anderson-Hanley 2017; Anderson-Hanley 2018).

It has been proposed that exergames can improve and stimulate physical activity among people with dementia with better adherence rates than traditional physical activities, with no adverse effects (Karssemeijer 2019a; Karssemeijer 2019b; Van Santen

2018; Wiloth 2018). Exergames were found to produce similar energy expenditure, heart rate, and oxygen consumption levels to traditional physical activities, which makes them potentially effective as a form of light to moderate intensity physical activity (Peng 2011). Technology-driven tasks, using VR or exergames, require substantial cognitive resources to accomplish tasks, such as navigation, and they offer both cognitive and physical stimulation (Green 2006; Green 2008; Neguţ 2016). High adherence rates, relatively low cost compared to other training programmes, such as gyms, and a safe training environment (e.g. at home) can increase accessibility, especially among vulnerable populations, such as individuals with dementia and MCI.

Clinical trials have reported conflicting results on the effects of exergaming on both physical (e.g. Karssemeijer 2019b; Hughes 2014; Padala 2012; Padala 2017), and cognitive outcomes in people with dementia and MCI (e.g. Amjad 2019; Hughes 2014; Karssemeijer 2019a; Padala 2012; Padala 2017; Park 2018).

How the intervention might work

Meta-analytical studies have shown that physical exercise has a positive effect on cognitive functions and ADL in people with dementia and MCI, but this is supported with low-quality evidence, assessed by tools such as the GRADE approach (Forbes 2015; Song 2018; Wang 2019). Multiple pathways have been proposed to explain the facilitating effect of physical activity on cognition: mainly, a reduction of risk factors associated with cardiovascular disease, insulin resistance, obesity, hypertension, and inflammation (Bamidis 2014; Sofi 2011). A second protective mechanism is the neurotrophic effect of physical exercise, which leads to increased neural growth due to a release of neurotrophins, and growth of synapses and dendritic receptors (Bamidis 2014; Gómez-Pinilla 1998; Sofi 2011). Neurotrophins facilitate brain plasticity mechanisms (e.g. neurogenesis, synaptogenesis and angiogenesis; (Bamidis 2014)).

Various interventions designated to enhance cognition have been developed (e.g. cognitive stimulation, rehabilitation, and cognitive training). Cognitive stimulation designates interventions that aim to improve global cognitive status, social functioning and orientation, using a wide range of activities and discussions. Cognitive stimulation programmes are typically delivered in clinics, residential, or day care settings (Bahar-Fuchs 2019; Woods 2012). Cognitive rehabilitation includes interventions that focus on groups of cognitive abilities required for daily tasks, activities, and social functioning. The main focus of cognitive rehabilitation interventions is on improving performance in daily life, therefore, rehabilitation typically takes place in the participant's natural environment (Bahar-Fuchs 2019; Tardif 2011; Woods 2012). Cognitive training contains standardised tasks that target specific cognitive domains (e.g. attention, memory). The tasks and the environment are highly structured (Bahar-Fuchs 2019; Tardif 2011). Cognitive training and rehabilitation are typically delivered individually, while stimulation is usually delivered in small group settings (Bahar-Fuchs 2019; Woods 2012). Several meta-analyses found that cognitive stimulation and training improved general cognition in people with dementia, but the quality of the evidence was low (Aguirre 2013; Bahar-Fuchs 2019; Woods 2012). Some RCTs found that cognitive rehabilitation for people with dementia improved global performance, everyday functioning, and satisfaction (Clare 2010; Clare 2019; Regan 2017).

The underlying mechanisms proposed to account for positive effects of training or stimulation on cognition are mostly related to brain plasticity, i.e. to the brain's capacity to modify its structure and function, even at an older age, through several mechanisms: neurogenesis, synaptogenesis, and angiogenesis (Hill 2011). For example, at a structural level, positive effects of cognitive training result in an increase of brain volume, cortical thickness, and density and consistency of white matter tracts (Bamidis 2014; Draganski 2004). Imaging studies have shown that the brains of people with MCI and dementia retain plasticity, and thus, could potentially benefit from cognitive stimulation or training (Belleville 2011; Hill 2011).

It has been proposed that combining physical and cognitive training would facilitate greater changes in brain plasticity (Bamidis 2014; Fissler 2013). According to Fissler 2013, combining the two forms of training might lead to synergistic effects. Physical activity facilitates plasticity by enhancing neurogenesis and synaptic plasticity, and cognitive activity guides the plastic modifications by increasing the number and survival rate of newly born cells, and integrating these new cells into an existing neural network (Bamidis 2014; Fissler 2013). Indeed, combining physical and cognitive training improved cognitive functioning, ADL, and mood among people with MCI and dementia compared with controls, with low to moderate effect sizes (Karssemeijer 2017). Functional neuroimaging studies provide further evidence in favour of the positive effect of combining physical and cognitive training, by showing an increase in the volume of the brain grey matter, and increased brain activity in multiple regions (Bamidis 2014).

There are several characteristics of exergames that may make them suitable for training and rehabilitating both physical and cognitive abilities.

First, exergames can offer realistic experiences, thus accommodating principles of rehabilitation (Levin 2015). For example, learning improves if the tasks are meaningful, specific, and repetitive, and if the task difficulty is increased over time (Kleim 2008; Levin 2015). The technical and software capabilities of exergames allow the number of stimuli and the difficulty of tasks to be adjusted according to the needs and abilities of the player, while maintaining stimulus control and consistency (Mrakic-Sposta 2018; Mura 2018). Feedback is a key component for motor learning, and facilitates quick self-correction (Bortone 2018; Da Fonseca 2017; Ferreira 2018), and exergame platform systems can provide real-time, strategic, and goal-directed feedback (Mrakic-Sposta 2018; Rizzo 2019).

Second, exergames can also provide environmental enrichment. Previous research in animal and human studies pointed out the positive effect of enriched environments on motor and cognitive performance (Clemenson 2015a; Freund 2013; Gelfo 2011; Harvey 2009; Kondo 2008; Maguire 1998; Morgan 2013; Nozari 2014; Zhao 2014). Other studies have also linked performance of various tasks (e.g. navigation) in enriched environments with morphological changes to the brain (e.g. greater cerebral weight and length; (Bayne 2018; Clemenson 2015b; Harvey 2009; Maguire 1998)), and enhanced brain plasticity (Fares 2013).

Third, because exergaming incorporates gaming elements, it has the potential to increase motivation (Howard 2017; Rizzo 2005). It has been proposed that VR platforms, including exergaming, can offer more gratifying experiences than traditional rehabilitation

interventions, which might offer unclear rewards (Howard 2017). For example, research showed that the use of VR applications in rehabilitation may increase a person's willingness to accept their treatment plan, as the enjoyment component increased their adherence to the intervention, most likely because of the gaming experience (Rose 2018).

Why it is important to do this review

Evidence is accumulating for the effectiveness of exergaming in improving physical or cognitive outcomes (or both) in older adults (Larsen 2013; Tahmosybayat 2017), people with Parkinson's disease (Garcia-Agundez 2019; Harris 2015), and people with neurological disabilities (Mura 2018; Rosly 2017). However, the effect of exergaming on physical, cognitive outcomes, and ADL in people with dementia and MCI remains unclear. The results of RCTs are contradictory, and we are not aware of any previous meta-analyses. Also, due to increased heterogeneity of measures used for various physical and cognitive domains, synthesising the results using a meta-analytical approach will enable us to obtain a clearer picture of the effectiveness of exergaming on global physical, cognitive domains, and ADL.

OBJECTIVES

To assess the effects of exergame applications on physical and cognitive outcomes, and activities of daily living (ADL), in people with dementia and mild cognitive impairment (MCI).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) that compare an exergame intervention with a control condition (e.g. waiting list, treatment as usual, or a non-specific intervention not expected to have an effect on key outcomes), or with an alternative intervention (e.g. traditional physical, cognitive, or combined physical and cognitive interventions).

If the exergame intervention is used in addition to conventional treatment (e.g. pharmaceutical therapy), the control and comparison groups should receive the same conventional treatment.

Where participants are exposed to all treatments, we will treat studies with a cross-over design as parallel designs, so we will extract only the first-period scores if possible; otherwise we will include the study and explain the absence of data (Elbourne 2002).

Types of participants

The study will include adults (18 years or older), diagnosed as having dementia or mild cognitive impairment (MCI).

Participants with dementia should have been diagnosed using internationally recognised criteria, e.g. DSM-5 or DSM-IV (APA 1995; APA 2013), and ICD-10 (WHO 1992). We will include people with any subtype or severity of dementia.

To classify the severity of dementia, we will use internationally recognised classifications (e.g. mild dementia: a score of 1 on the Clinical Dementia Rating (CDR) scale (Morris 1993), between 21 and 26 on the Mini Mental State Examination (MMSE; (Folstein 1975)), or between 18 and 25 on the Montreal Cognitive Assessment (MoCA, Nasreddine 2005); moderate dementia: a score of 2 on the CDR, between 10 and 20 on the MMSE, and between 10 and 17 on the MoCA). We will use the same classification systems to categorise severe dementia; however, we do not expect to identify trials that included people with severe dementia, due to difficulties in implementing the intervention.

For MCI, we will accept a diagnosis provided by the study authors, based on criteria proposed by Petersen 1999, the National Institute on Aging-Alzheimer's Association (Albert 2011), International Working Group on Mild Cognitive Impairment (Winblad 2004), MCI Working Group of the European Consortium on Alzheimer's Disease (Portet 2006), or similar criteria. This includes, for example, a diagnostic assessment, subjective memory complaints, or both, with reduced scores on cognitive tests, such as the MMSE or the MoCA. In addition, the authors of the study should describe an attempt to exclude dementia (e.g. Gates 2019). We will record the definitions used by study authors, consider criteria as a possible source of heterogeneity, and perform sensitivity analysis if necessary.

If studies include a heterogeneous group of participants (e.g. other neurological diseases, such as stroke, traumatic brain injury, both dementia and MCI), we will include these studies only if data for each subgroup of participants are available separately (e.g. dementia and MCI), or we can obtain these data from authors.

Types of interventions

Interventions

We will focus on exergame interventions designed to improve physical and cognitive outcomes, and activities of daily living (ADL), in people with MCI and dementia. Eligible exergaming interventions are those in which the participant engages in physical activity of at least moderate intensity, with or without an additional cognitive element, using an interactive, immersive or non-immersive virtual reality platform (Norton 2010). Exergaming interventions may be of any frequency and duration, delivered in any setting (e.g. delivered in a clinic or at the participant's home).

As defined by the World Health Organization (WHO), physical activity refers to all movement produced by skeletal muscles that requires energy expenditure (WHO 2020). The level of energy expenditure varies on a continuum from low to high (Caspersen 1985). We will use published guidelines to identify levels of intensity of physical activity (Norton 2010). Norton 2010 proposed the following categories of intensity, based on energy expenditure: sedentary – sitting or lying with low additional movement (e.g. watching TV or riding a car), and low energy requirement; light – an aerobic activity that does not cause a noticeable change in breathing rate, can be sustained for at least 60 minutes (e.g. domestic or occupational tasks, such as ironing, washing, cooking, eating); moderate – an aerobic activity that can be performed while maintaining an uninterrupted conversation, may last between 30 and 60 minutes (e.g. gentle swimming, social tennis, golf, cycling at regular pace, carrying light loads); high – an aerobic activity that cannot sustain a conversation without interruption, and can last for about 30 minutes (e.g. jogging, cycling, aerobics, competitive tennis); very high – an aerobic activity that cannot be sustained for longer than about 10 minutes, and has a relative intensity level of at least 90% maximum heart

rate; but such activities occur rarely in daily life. We will only consider interventions of at least moderate intensity. Exergaming interventions must include physical activity, which substantially simulates a recognised sport or dance form, or which includes a structured set of physical activities, designed or chosen to improve some. or all of: aerobic fitness, muscle strength, balance, and coordination.

Exergaming interventions inevitably include some cognitive activity, although this may be non-specific, e.g. interacting within the game, following rules, keeping score. For example, the Wii skiing game asks players to choose their route when they descend the slope, follow the route, and avoid obstacles and falling down. Based on their performance, they collect points. The player's performance is monitored, and they get instant feedback. We regard this as a form of cognitive stimulation. In addition, exergames may include more specific tasks, which would amount to cognitive rehabilitation, training, or both. For example, participants must learn a list of neighbourhood errand locations (e.g., doctor, pharmacy, grocery) and have to follow the correct route on a virtual bike to reach the locations (Anderson-Hanley 2017; Anderson-Hanley 2018). This targets working memory and the real-life task of completing a shopping trip.

We will include any interventions that use an immersive or non-immersive virtual reality (VR)-based platform, using the definitions provided by Rizzo 2017. Immersive VR contains platforms, such as head mounted displays (HMD) and connected automated virtual environments (CAVE), which occlude the view of the outside world. Non-immersive VR uses platforms that deliver content via standard TV screens, desktop monitors, projectors, etc. The key feature of non-immersive systems is that the user's view does not occlude the outside world. Given this definition, interactive gaming platforms, such as Wii, Xbox, and Sony PlayStation are considered non-immersive VR.

Interaction may be achieved via any type of technology that allows real-time interaction, by capturing and projecting the participant's image, movements, or both, in real time on a screen. The interaction should be "beyond what is typically afforded with standard mouse and keyboard interface devices" (Rizzo 2017). This can include controllers, motion tracking sensors, or infra-red cameras. We will only consider virtual environments (VE) in which the interaction is in real time (e.g. while walking on a treadmill, the speed is adjusted in line with the person's own pace, and by considering the direction in which the participant is heading). We will exclude VEs in which the user does not interact in real time with the VE (e.g. cycling in front of a TV set, with no changes in VE dictated by the user's behaviour).

Comparators

The comparator interventions may be:

(a) inactive control (no intervention, such as a waiting list, where participants in the control group receive the exergame intervention at the end of the study; or treatment as usual, where participants received usual care only);

(b) active control (intervention involves equivalent contact with the researchers, typically for an equivalent number of sessions or visits, and participants receive similar levels of contact with the researchers, but the intervention is not hypothesised to have any specific effect on the study outcomes, such as relaxation, or watching documentaries or movies);

(c) alternative treatment control (another treatment hypothesised to have a specific effect on the study outcomes, such as physical activity, cognitive stimulation therapy, cognitive training, music therapy, dance therapy, multisensory stimulation, multimodal training, reminiscence therapy, etc.).

Types of outcome measures

We will consider the following broad category of physical and cognitive outcomes, and ADL, measured by any validated instrument that covers multiple or single domains, at the end of the intervention (at post-test), and at follow-up. We will consider a validated instrument to be any measure that has been published or used in other studies; we will exclude measures created by the research team. Biomarker and economic outcomes are beyond the scope of this review.

Primary outcomes

a) Global physical functioning: we will combine all physical measures from each study

b) Global cognitive functioning: we will combine all outcomes measuring cognitive outcomes from all available studies

c) Global ADL performance: we will combine all ADL outcomes from each study

Secondary outcomes

We will treat the following outcomes as secondary outcomes. We will classify outcomes according to well established classifications (e.g. Laver 2017; Lezak 2012):

a) Physical functioning outcomes including:

- Lower limb function, using measures, such as walk tests – 10-minute walk test, Timed Up and Go Test, Sit to Stand Test;
- Upper limb function, using measures, such as the Fugl Myer Assessment, Box and Block Test;
- Balance and postural control, including assessments, such as the Berg Balance Scale;
- Motor function, measured with the Gross Motor Function Test, Motor Assessment Scale.

b) Cognitive functioning outcomes including:

- General cognition, using measures such as the Mini Mental State Examination, Montreal Cognitive Assessment Test;
- Attention, processing speed, and working memory, using the Wechsler Adult Intelligence Scale (WAIS)-digit span, Corsi Block-tapping Test, WAIS- digits backward, N-Back tasks, Continuous Performance Test;
- Perception (e.g. visual inattention, visual scanning, visual recognition and organisation; auditory perception, inattention) measured using the Behavioral Inattention Test, Line Bisection Tests, Cancellation tasks, Judgment of Line Orientation, Face Recognition, Wepman's Auditory Discrimination Test;
- Memory (e.g. verbal, visual, incidental, and prospective memory), using measures such as the California Verbal Learning

Test, Rey-Osterrieth Complex Figure Test, Wechsler Memory Scale, Rivermead Behavioural Memory Test;
- Verbal functions and language skills (e.g. aphasia, auditory comprehension, naming, vocabulary and verbal comprehension), measured with the Boston Diagnostic Aphasia Examination, Putney Auditory Comprehension Screening Test, Boston Naming Test, WAIS-vocabulary, Token Test;
- Reasoning, measured with the WAIS-Similarities, Category test, D-KEFS- Twenty Questions, Color Form Sorting Test;
- Executive function (e.g. volition, planning and decision making, purposive action, verbal, letter, category fluency, perseveration), measured using tests, such as the Patient Competency Rating Scale, Self-Ordered Pointing Test, Tower tests, Multiple Errands Test, Iowa Gambling Task, Wisconsin Card Sorting Test-Perseveration, Trail Making Tests, Stroop test, etc.

c) ADL outcomes including:

- ADL measures, such as the Barthel Index scale, Functional Independence Measure;
- Instrumental activities of daily living (IADL) including measures such as the Instrumental Activities of Daily Living Scale.

d) Quality of life (e.g. Quality of Life in Alzheimer's Disease);

e) Physical activity (e.g. Physical Activity Scale for the Elderly);

f) Frailty (e.g. Evaluative Frailty Index for Physical Activity);

g) Adverse effects (e.g. motion sickness, disorientation, headaches, pain, fatigue, injury);

h) Falls that occur during the use of the intervention;

i) Falls outside of the use of the intervention;

j) Measures of enjoyment and satisfaction with the programme;

k) Feasibility and treatment adherence (number of dropouts);

l) Caregiver outcomes (e.g. burden).

Search methods for identification of studies

Electronic searches

We will search ALOIS, the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialized register (www.medicine.ox.ac.uk/alois).

ALOIS is maintained by the Information Specialists for the Cochrane Dementia and Cognitive Improvement Group, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through:

1. Searching a number of major healthcare databases: MEDLINE, Embase, CINAHL, and PsycINFO;
2. Searching a number of trial registers: ClinicalTrials.gov; the World Health Organization's International Clinical Trials Register Platform (ICTRP), which covers ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials; and the Netherlands National Trials Register, plus others;
3. Searching the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
4. Searching grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched for ALOIS, go to the ALOIS web site (www.medicine.ox.ac.uk/alois).

To view details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement, and cognitive enhancement trials, go to the Cochrane Dementia and Cognitive Improvement Group's website (dementia.cochrane.org/searches).

We will run additional searches in MEDLINE, Embase, PsycINFO, CINAHL, Latin American and Caribbean Health Science Information database (LILACs), ClinicalTrials.gov, and ICTRP to ensure that the searches for this review are as comprehensive and as up to date as possible. The MEDLINE Ovid search strategy that we will use for the retrieval of reports of trials can be seen in Appendix 1.

We will not set language, publication date, or publication type restrictions on the searches. We will attempt to obtain reliable translations of relevant non-English publications (either from the study authors or other sources). If this is not possible, we will exclude the study, including a clear rationale.

Searching other resources

We will screen the reference lists of included studies for additional trials, as well as all identified review papers related to exergame interventions in people with MCI and dementia. We will also contact the corresponding authors of identified ongoing trials for additional references and unpublished data.

Data collection and analysis

Selection of studies

We will prepare a complete list of search results, with duplicate records removed. Two authors (AV and TP) will independently screen all titles and abstracts identified from searches to determine which may meet the inclusion criteria. We will retrieve in full text any papers identified as potentially relevant by at least one author. At this stage, we will link multiple reports of the same study. We will discuss any disagreements on eligibility at this stage with a third review author (KP). Two review authors (AV and TP) will independently screen full-text articles against eligibility criteria, and will resolve discrepancies by discussion with a third author to reach consensus (KP). If necessary, we will contact primary study authors to clarify study eligibility criteria. We will list as excluded studies, all potentially relevant papers excluded from the review at this stage, and provide reasons in the 'Characteristics of excluded studies' table.

We will collate information that comes from multiple reports of the same study (e.g. studies reported in more than one publication, such as journal articles and conference abstracts) under a single study identifier; the study will be the unit of interest (Li 2019). We will report the screening and selection process using a PRISMA flow chart (Mohler 2009).

Data extraction and management

Two review authors (AV and TP) will extract data independently from included studies. They will resolve any discrepancies by discussion until consensus is reached, or through consultation with a third author (KP), where necessary. We will extract data into a spreadsheet file, and later transfer and manage it in Comprehensive Meta-Analysis 3 (Borenstein 2013) and Review Manager Web (RevMan Web 2020).

We will extract the following: study identification data (e.g. authors, year of publication, country of origin, sources of funding); details of the study (aim of intervention, study design, description of comparison group, study outcomes, settings); population (e.g. diagnosis, age, gender, education, dementia severity, and medication use); details about intervention and comparators (e.g. nature, intensity, frequency, and duration).

For dichotomous outcomes (e.g. experience of severe simulator sickness), we will extract the number of participants with each outcome, at each time point. For continuous outcomes, we will extract the number of participants for each condition, means, and standard deviations. We will also extract data regarding a priori moderators: type of exergame platform used: commercial versus customised; type of technology: VR-based (e.g. head mounted display headsets, such as Oculus Rift) versus monitor display (e.g. Wii Fit, Sports), and adverse events (e.g. fatigue, dizziness).

One reviewer (AV) will enter the extracted data into Comprehensive Meta-Analysis 3 and Review Manager Web, and the second review author (TP), working independently, will check them for accuracy against the original data reported in primary studies.

We will extract the number of participants with each condition for whom the outcome was measured, as well as the mean and standard deviation (SD) of the change from baseline, for each outcome at each time point for each condition (e.g. intervention and control condition). We will conduct the same analyses as for any other type of continuous outcome variable (Higgins 2019b). If change scores are not reported, we will manually calculate change scores by subtracting the baseline scores from the post-test or post-intervention score (Higgins 2019b). We will compute the SDs of change scores on the assumption that the correlation between measurements at baseline and those at subsequent time points is r = 0.00, which overestimates the SD of change, but is more conservative (e.g.Bahar-Fuchs 2019). We will pay attention to the direction of the scales.

Assessment of risk of bias in included studies

Two review authors (AV and TP) will independently assess the risk of bias of included studies using the Cochrane 'Risk of bias 2 (RoB 2)' tool (Higgins 2019a). We will assess the following 'Risk of bias' domains: random sequence generation; allocation concealment; blinding (participants, personnel); blinding (outcome assessment); incomplete outcome data (e.g. more than 20% missing participants between baseline and post-test); selective reporting of outcomes (Higgins 2019a). We will rate the studies at low, high, or unknown risk of bias for each domain. We will resolve any disagreements by a discussion with a third review author (DSF) to reach consensus.

We will assess the impact of risk of bias by conducting sensitivity analyses. For this, we will exclude studies with high or unclear risk of bias, and compare effect estimates with analyses in which all studies were included.

We expect that participants and personnel will not be blinded in many, or all studies, because exergaming interventions are difficult to blind. Another Cochrane Review that investigated the effectiveness of virtual reality for physical rehabilitation of people with stroke considered that blinding of participants and personnel was more strongly related to the type and intrinsic characteristics of the intervention and less to the study quality (Laver 2017). We expect outcome assessors to be blinded to treatment allocation, but we will not exclude studies if they are at high or unclear risk in this domain.

Measures of treatment effect

For measures of treatment effect for continuous measures, we will calculate the mean difference (MD) and 95% confidence interval (CI) when studies used the same rating scale to measure a particular outcome, or standardised mean difference (SMD) (the between-group difference in mean values divided by the pooled SD) and 95% CI if different scales were used to measure the same outcome. We will use change from baseline scores.

For dichotomous outcomes (e.g. adverse events, such as experience of severe symptoms of simulator sickness, or no experience of such symptoms), we will express the treatment effect as a risk ratio (RR) with a 95% CI.

Unit of analysis issues

We anticipate the following unit of analysis issues: cross-over trial designs, studies with multiple conditions (multi-arm trials), repeated observations on participants, and multiple measures of the same outcome using different measurement scales.

For cross-over trials, we will only use data from the first treatment period (before cross over), due to risk of carry-over effects (Higgins 2011).

For studies with multiple conditions, we will combine all relevant experimental groups into a single group, and all relevant control groups into a single comparator group (Higgins 2019b; Higgins 2019c).

For primary outcomes (global physical functioning, cognitive functioning, and ADL performance), we will calculate global composite scores directly from all relevant measures or tests included in each study; this may include, where relevant, more than one score derived from the same test. We will do this using Comprehensive Meta-Analysis 3 (CMA) software to derive one SMD (Hedges's g) and one SE for each study at each assessment point (e.g. immediate post-test and follow-up; (Borenstein 2013)). We will enter these into Review Manager Web using the generic inverse variance method to obtain pooled effect estimates across studies. We will use the same procedure to obtain estimates of effects for secondary outcomes.

For repeated assessments, we plan to conduct separate comparisons (a) immediately after the intervention has finished (post-test) and (b) at follow-up. As follow-up may vary in duration, and multiple assessments may be made within the follow-up period, we will only consider follow-up in the short- (three months)

to medium-term (12 months), and will use data from the latest assessment within this time period.

Dealing with missing data

We will attempt to contact study authors to obtain missing or unreported data (participant, outcome, or summary data). Any discrepancies between the number of participants who commenced and completed the study will be addressed in our assessment of the incomplete outcome data domain (attrition bias). We will also perform sensitivity analyses to investigate the impact of including studies at high risk of attrition bias on treatment effect estimates.

Assessment of heterogeneity

We will identify significant heterogeneity using the Chi^2 and I^2 statistics. Based on the Chi^2 statistic, significant heterogeneity will be identified if $P < 0.10$ (Deeks 2019). We will use the I^2 statistic to estimate the level of heterogeneity: low (I^2 < 40%), moderate (I^2 = 40% to 60%), substantial (I^2 = 60% to 90%), considerable (I^2 > 90%). If we detect moderate or substantial heterogeneity (an I^2 between 40% and 90%), we will investigate the sources of heterogeneity by conducting subgroup analyses, and a random-effects meta-analysis (Deeks 2019). However, if fewer than three studies are available for meta-analysis (Neguţ 2016), we will use a fixed-effect model (Borenstein 2009).

If we encounter one or both of the following situations, we will not pool results, but will report results narratively for that comparison and outcome (Deeks 2019):

- detect considerable heterogeneity (I^2 > 90);
- low number of studies (< 2 studies; Bahar-Fuchs 2019; Hafdi 2020; Kudlicka 2019).

Assessment of reporting biases

For the primary outcomes, we will assess publication bias associated with small study size by a visual inspection of the funnel plots, if the number of studies included in the pooled analysis is larger than 10 (Deeks 2019). We will also use the Duval and Tweedie's trim-and-fill procedure (Duval 2000).

Data synthesis

We will conduct separate comparisons for people with dementia and MCI. For each outcome of interest, depending on data availability, we will undertake the following separate comparisons:

- Exergaming versus control (i.e. no treatment, standard treatment, waiting list, or non-specific active control) at the end of therapy (i.e. immediately post-intervention, post-test) for people with dementia
- Exergaming versus control (i.e. no treatment, standard treatment, waiting list, or non-specific active control) at follow-up (i.e. up to 12 months following the end of intervention) for people with dementia
- Exergaming versus alternative treatment at the end of therapy (i.e. immediately post-intervention, post-test) for people with dementia
- Exergaming versus alternative treatment at follow-up (i.e. up to 12 months following the end of intervention) for people with dementia
- Exergaming versus control (i.e.no treatment, standard treatment, waiting list, or non-specific active control) at the end of therapy (e.g. immediately post-intervention, post-test) for people with MCI
- Exergaming versus control (i.e. no treatment, standard treatment, waiting list, or non-specific active control) at follow-up (e.g. up to 12 months following the end of intervention) for people with MCI
- Exergaming versus alternative treatment at the end of therapy (i.e. immediately post-intervention, post-test) for people with MCI
- Exergaming versus alternative treatment at follow-up (i.e. up to 12 months following the end of intervention) for people with MCI

We will decide if it is appropriate to pool data for each outcome, based on a qualitative assessment of the similarity of the included studies in terms of participants, settings, intervention, comparison, and outcome measures. Because we anticipate variability in the interventions (e.g. various platforms of exergaming) or participants (e.g. dementia severity) of included studies, we will use a random-effects model for meta-analysis (Deeks 2019). If we are able to pool data from at least two studies, we will conduct meta-analyses in RevMan Web (Review Manager 2020), as well as in Comprehensive Meta-Analysis 3 (Borenstein 2013).

Subgroup analysis and investigation of heterogeneity

For each outcome, we will conduct subgroup analyses if heterogeneity (I^2) is higher than 40%, and there are at least three studies per subgroup.

We aim to conduct the following subgroup comparisons, when there are sufficient data:

- Severity of dementia: mild versus moderate versus severe
- Intervention characteristics: physical activity with or without the addition of specific cognitive training or rehabilitative tasks (beyond the basic performance of the game);
- Type of control intervention (for the comparisons of exergaming versus control): inactive control (no intervention or treatment as usual) versus active control (intervention involving equivalent contact with the researchers but not hypothesised to have any specific effect on the study outcomes);
- Type of exergame platform used: commercial versus customised;
- Type of technology: VR-based (e.g. head mounted display headsets such as Oculus Rift) versus monitor display (e.g. Wii Fit, Sports);
- Length of intervention: the total time of the intervention in minutes: 0 to 360 minutes (6 hours) versus 361 to 720 minutes (12 hours) versus more than 720 minutes;
- Length of follow-up period: 0 to one month versus one to three months versus four to six months versus longer than six months.

Sensitivity analysis

To assess the robustness of our results, we will perform the following sensitivity analyses for our primary outcomes.

- Compare the results of studies at higher and lower risk of bias. Low quality studies will be those that have a high risk of bias in at

least two critical domains, except for blinding participants and personnel.

- Compare the results of dose-matched studies (intervention and control interventions have an equal dose of time and frequency) versus non-dose-matched studies (intervention and control interventions have unequal dose of time and frequency).
- Compare the results of studies that used strict criteria to define MCI (e.g. criteria proposed by Petersen 2009) versus studies that relied on cutoff scores from at least one objective neuropsychological measure (e.g. MoCA, MMSE, CDR, etc.).
- Compare the results of our meta-analyses with change scores and those with post-intervention scores only.
- Compare the results of studies with high statistical power and studies with low statistical power. Powered studies will be those that have a post hoc achieved power larger than 0.80. Post hoc achieved power will be calculated using GPower software (Faul 2007).

Summary of findings and assessment of the certainty of the evidence

We will assess the certainty of the evidence with the GRADE approach. In short, the algorithm for assigning GRADE levels of evidence is based on five essential domains: risk of bias, unexplained heterogeneity or inconsistency of results, indirectness of evidence, imprecision of results, high probability of publication bias. For RCTs, the GRADE assessment starts at a high level of certainty. Based on weakness in each domain, the certainty of a body of evidence is downgraded by one or two levels for each domain. Four ratings are possible: high, moderate, low, and very low, which describe the levels of the certainty associated with an outcome. High certainty of evidence implies that further research is very unlikely to change our confidence in the estimate of effect. Moderate certainty indicates that further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate. Low certainty indicates that further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate. Very low certainty implies uncertainty about the estimate.

Using GRADEpro GDT software (GRADEpro GDT), we will generate 'Summary of findings' tables for the following comparisons:

- Exergaming and control (e.g. no/standard treatment/wait-list or active control) at the end of therapy (e.g. immediately post intervention/post-test) for people with dementia
- Exergaming and control (e.g. no/standard treatment/wait-list or active control) at follow-up (e.g. up to 12 months following the end of intervention) for people with dementia
- Exergaming and alternative treatment at the end of therapy (e.g. immediately post intervention/post-test) for people with dementia.
- Exergaming and alternative treatment at follow-up (e.g. up to 12 months following the end of intervention) for people with dementia.
- Exergaming and control (e.g. no/standard treatment/wait-list or active control) at the end of therapy (e.g. immediately post intervention/post-test) for people with MCI
- Exergaming and control (e.g. no/standard treatment/wait-list or active control) at follow-up (e.g. up to 12 months following the end of intervention) for people with MCI
- Exergaming and alternative treatment at the end of therapy (e.g. immediately post intervention/post-test) for people with MCI
- Exergaming and alternative treatment at follow-up (e.g. up to 12 months following the end of intervention) for people with MCI

We will include the following outcomes in each 'Summary of findings' table:

- Global physical functioning
- Global cognitive functioning
- Global ADL outcomes
- Adverse effects

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REFERENCES

Additional references

Aguirre 2013

Aguirre E, Woods RT, Spector A, Orrell M. Cognitive stimulation for dementia: a systematic review of the evidence of effectiveness from randomised controlled trials. *Ageing Research Reviews* 2013;**12**(1):253-62. [DOI: 10.1016/j.arr.2012.07.001]

Albert 2011

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 2011;**7**(3):270-9. [DOI: 10.1016/j.jalz.2011.03.008]

Allan 2005

Allan LM, Ballard CG, Burn DJ, Kenny RA. Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. *Journal of the American Geriatrics Society* 2005;**53**(10):1681-7. [DOI: 10.1111/j.1532-5415.2005.53552.x]

Amjad 2019

Amjad I, Toor H, Niazi IK, Pervaiz S, Jochumsen M, Shafique M, et al. Xbox 360 Kinect cognitive games improve slowness, complexity of EEG, and cognitive functions in subjects with mild cognitive impairment: a randomized control trial. *Games for Health Journal* 2019;**8**(2):144-52. [DOI: 10.1089/g4h.2018.0029]

Anderson-Hanley 2017

Anderson-Hanley C, Maloney M, Barcelos N, Striegnitz K, Kramer A. Neuropsychological benefits of neuro-exergaming for older adults: a pilot study of an interactive physical and cognitive exercise system (iPACES). *Journal of Aging and Physical Activity* 2017;**25**(1):73-83. [DOI: 10.1123/japa.2015-0261]

Anderson-Hanley 2018

Anderson-Hanley C, Stark J, Wall KM, VanBrakle M, Michel M, Maloney M, et al. The interactive physical and cognitive exercise system (iPACes™): effects of a 3-month in-home pilot clinical trial for mild cognitive impairment and caregivers. *Clinical Interventions in Aging* 2018;**13**:1565–77. [DOI: 10.2147/CIA.S160756]

APA 1995

American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders (DSM-4®). 4th edition. Washington, DC: American Psychiatric Association, 1995.

APA 2013

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders (DSM-5®). 5th edition. Washington, DC: American Psychiatric Association, 2013.

Bahar-Fuchs 2019

Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No: CD013069. [DOI: 10.1002/14651858.CD013069]

Bamidis 2014

Bamidis PD, Vivas AB, Styliadis C, Frantzidis C, Klados M, Schlee W, et al. A review of physical and cognitive interventions in aging. *Neuroscience and Biobehavioral Reviews* 2014;**44**:206-20. [DOI: 10.1016/j.neubiorev.2014.03.019]

Bayne 2018

Bayne K. Environmental enrichment and mouse models: current perspectives. *Animal Models and Experimental Medicine* 2018;**1**(2):82-90. [DOI: 10.1002/ame2.12015]

Belleville 2011

Belleville S, Clement F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain* 2011;**134**(6):1623-34. [DOI: 10.1093/brain/awr037]

Belza 2004

Belza B, Walwick J, Shui-Thornton S, Schwartz S, Taylor M, LeGerfo J. Older adult perspectives on physical activity and exercise: voices from multiple cultures. Preventing Chronic Disease 2004;**1**(4):1-12.

Borenstein 2009

Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to Meta-analysis. Chichester, UK: John Wiley & Sons, 2009.

Borenstein 2013 [Computer program]

Comprehensive Meta-analysis. Borenstein M, Hedges LV, Higgins JP, Rothstein HR, Version 3. Englewood, NJ: Biostat, 2013. Available at www.meta-analysis.com/pages/new_v3.php.

Bortone 2018

Bortone I, Leonardis D, Mastronicola N, Crecchi A, Bonfiglio L, Procopio C, et al. Wearable haptics and immersive virtual reality rehabilitation training in children with neuromotor impairments. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2018;**26**(7):1469-78. [DOI: 10.1109/TNSRE.2018.2846814]

Caspersen 1985

Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports* 1985;**100**(2):126-31.

Clare 2010

Clare L, Linden DE, Woods RT, Whitaker R, Evans SJ, Parkinson CH, et al. Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease: a single-blind randomized controlled trial of clinical efficacy. *The American Journal of Geriatric Psychiatry* 2010;**18**(10):928-39. [DOI: 10.1097/JGP.0b013e3181d5792a]

Clare 2019

Clare L, Kudlicka A, Oyebode JR, Jones RW, Bayer A, Leroi I, et al. Individual goal-oriented cognitive rehabilitation to improve everyday functioning for people with early-stage dementia: a multicentre randomised controlled trial (the GREAT trial). *International Journal of Geriatric Psychiatry* 2019;**34**(5):709-21. [DOI: 10.1002/gps.5076]

Clarke 2008

Clarke DE, van Reekum R, Simard M, Streiner DL, Conn D, Cohen T, et al. Apathy in dementia: clinical and sociodemographic correlates. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2008;**20**(3):337-47.

Clemenson 2015a

Clemenson GD, Deng W, Gage FH. Environmental enrichment and neurogenesis: from mice to humans. *Current Opinion in Behavioral Sciences* 2015;**4**:56-62. [DOI: 10.1016/j.cobeha.2015.02.005]

Clemenson 2015b

Clemenson GD, Stark CE. Virtual environmental enrichment through video games improves hippocampal-associated memory. *Journal of Neuroscience* 2015;**35**(49):16116-25. [DOI: 10.1523/JNEUROSCI.2580-15.2015]

Crombie 2004

Crombie IK, Irvine L, Williams B, McGinnis AR, Slane PW, Alder EM, et al. Why older people do not participate in leisure time physical activity: a survey of activity levels, beliefs and deterrents. *Age and Ageing* 2004;**33**(3):287-92. [DOI: 10.1093/ageing/afh089]

Da Fonseca 2017

da Fonseca EP, da Silva NM, Pinto EB. Therapeutic effect of virtual reality on post-stroke patients: randomized clinical trial. *Journal of Stroke and Cerebrovascular Diseases* 2017;**26**(1):94-100. [DOI: 10.1016/j.jstrokecerebrovasdis.2016.08.035]

Deeks 2019

Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook.

Draganski 2004

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Changes in grey matter induced by training. *Nature* 2004;**427**(6972):311-2. [DOI: doi.org/10.1038/427311a]

Duval 2000

Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;**56**:455–63. [DOI: 10.1111/j.0006-341X.2000.00455.x]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9. [DOI: 10.1093/ije/31.1.140]

Eriksson 2008

Eriksson S, Gustafson Y, Lundin-Olsson L. Risk factors for falls in people with and without a diagnose of dementia living in residential care facilities: a prospective study. *Archives of Gerontology and Geriatrics* 2008;**46**(3):293-306. [DOI: 10.1016/j.archger.2007.05.002]

Fares 2013

Fares RP, Belmeguenai A, Sanchez PE, Kouchi HY, Bodennec J, Morales A, et al. Standardized environmental enrichment supports enhanced brain plasticity in healthy rats and prevents cognitive impairment in epileptic rats. *PloS One* 2013;**8**(1):e53888. [DOI: 10.1371/journal.pone.0053888]

Faul 2007

Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods* 2007;**39**:175-91. [DOI: 10.3758/BF03193146]

Ferreira 2018

Ferreira V, Carvas N Jr, Artilheiro MC, Pompeu JE, Hassan SA, Kasawara KT. Interactive video gaming improves functional balance in poststroke individuals: meta-analysis of randomized controlled trials. *Evaluation & the Health Professions* 2018;**43**(1):23-32. [DOI: 10.1177/0163278718784998]

Fissler 2013

Fissler P, Küster O, Schlee W, Kolassa I-T. Novelty interventions to enhance broad cognitive abilities and prevent dementia: synergistic approaches for the facilitation of positive plastic change. *Progress in Brain Research* 2013;**207**:403-34. [DOI: 10.1016/B978-0-444-63327-9.00017-5]

Folstein 1975

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;**12**(3):189–98. [DOI: 10.1016/0022-3956(75)90026-6]

Forbes 2015

Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No: CD006489. [DOI: 10.1002/14651858.CD006489.pub4]

Freund 2013

Freund J, Brandmaier AM, Lewejohann L, Kirste I, Kritzler M, Krüger A, et al. Emergence of individuality in genetically identical mice. *Science* 2013;**340**(6133):756-9. [DOI: 10.1126/science.1235294]

Gallaway 2017

Gallaway PJ, Miyake H, Buchowski MS, Shimada M, Yoshitake Y, Kim AS, et al. Physical activity: a viable way to reduce the risks

of mild cognitive impairment, Alzheimer's disease, and vascular dementia in older adults. *Brain Sciences* 2017;**7**(2):22. [DOI: 10.3390/brainsci7020022]

Garcia-Agundez 2019

Garcia-Agundez A, Folkerts A-K, Konrad R, Caserman P, Tregel T, Goosses M, et al. Recent advances in rehabilitation for Parkinson's Disease with exergames: a systematic review. *Journal of Neuroengineering and Rehabilitation* 2019;**16**(1):17. [DOI: 10.1186/s12984-019-0492-1]

Gates 2019

Gates NJ, Rutjes AW, Di Nisio M, Karim S, Chong LY, March E, et al. Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No: CD012277. [DOI: 10.1002/14651858.CD012277.pub3]

Gelfo 2011

Gelfo F, Cutuli D, Foti F, Laricchiuta D, De Bartolo P, Caltagirone C, et al. Enriched environment improves motor function and increases neurotrophins in hemicerebellar lesioned rats. *Neurorehabilitation and Neural Repair* 2011;**25**(3):243-52. [DOI: 10.1177/1545968310380926]

Gómez-Pinilla 1998

Gómez-Pinilla F, So V, Kesslak J P. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. *Neuroscience* 1998;**85**(1):53-61. [DOI: 10.1016/S0306-4522(97)00576-9]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed prior to 13 January 2021. Hamilton, ON: McMaster University (developed by Evidence Prime). Available at gradepro.org.

Green 2006

Green CS, Bavelier D. The cognitive neuroscience of video games. *Digital Media: Transformations in Human Communication* 2006;**1**(1):211-23.

Green 2008

Green CS, Bavelier D. Exercising your brain: a review of human brain plasticity and training-induced learning. *Psychology and Aging* 2008;**23**(4):692-701. [DOI: 10.1037/a0014345]

Hafdi 2020

Hafdi M, Hoevenaar-Blom MP, Richard E. Multi-domain interventions for the prevention of dementia and cognitive decline. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No: CD013572. [DOI: 10.1002/14651858.CD013572]

Harris 2015

Harris DM, Rantalainen T, Muthalib M, Johnson L, Teo W-P. Exergaming as a viable therapeutic tool to improve static and dynamic balance among older adults and people with idiopathic Parkinson's Disease: a systematic review and meta-analysis. *Frontiers in Aging Neuroscience* 2015;**7**(167):1-12. [DOI: 10.3389/fnagi.2015.00167]

Hartman 2018

Hartman YA, Karssemeijer EG, van Diepen LA, Rikkert MG, Thijssen DH. Dementia patients are more sedentary and less physically active than age-and sex-matched cognitively healthy older adults. *Dementia and Geriatric Cognitive Disorders* 2018;**46**(1-2):81-9. [DOI: 10.1159/000491995]

Harvey 2009

Harvey CD, Collman F, Dombeck DA, Tank DW. Intracellular dynamics of hippocampal place cells during virtual navigation. *Nature* 2009;**461**:941–6. [DOI: 10.1038/nature08499]

Heyn 2004

Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of Physical Medicine and Rehabilitation* 2004;**85**(10):1694-704. [DOI: 10.1016/j.apmr.2004.03.019]

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2019a

Higgins JPT, Savović J, Page MJ, Sterne JAC. Revised Cochrane 'risk-of-bias' tool for randomized trials (RoB 2). Available from www.methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials.

Higgins 2019b

Higgins JPT, Li T, Deeks JJ. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook.

Higgins 2019c

Higgins JPT, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook.

Hill 2011

Hill NL, Kolanowski AM, Gill DJ. Plasticity in early Alzheimer's disease: an opportunity for intervention. *Topics in Geriatric Rehabilitation* 2011;**27**(4):257–67.

Howard 2017

Howard MC. A meta-analysis and systematic literature review of virtual reality rehabilitation programs. *Computers in Human Behavior* 2017;**70**:317-27. [DOI: 10.1016/j.chb.2017.01.013]

Hughes 2014

Hughes TF, Flatt JD, Fu B, Butters MA, Chang CCH, Ganguli M. Interactive video gaming compared with health education in older adults with mild cognitive impairment: a feasibility study.

International Journal of Geriatric Psychiatry 2014;**29**(9):890-8. [DOI: 10.1002/gps.4075]

Kane 2017

Kane RL, Butler M, Fink HA, Brasure M, Davila H, Desai P, et al. Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Mar. Report No.: 17-EHC008-EF. Available from www.ncbi.nlm.nih.gov/books/NBK442425/. [PMID: 28759193]

Karssemeijer 2017

Karssemeijer EG, Aaronson JA, Bossers W, Smits T, Olde Rikkert MG, Kessels RP. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: a meta-analysis. *Ageing Research Reviews* 2017;**40**:75-83. [DOI: 10.1016/j.arr.2017.09.003]

Karssemeijer 2019a

Karssemeijer EG, Aaronson JA, Bossers WJ, Donders R, Olde Rikkert MG, Kessels RP. The quest for synergy between physical exercise and cognitive stimulation via exergaming in people with dementia: a randomized controlled trial. *Alzheimer's Research & Therapy* 2019;**11**:1-13. [DOI: 10.1186/s13195-018-0454-z]

Karssemeijer 2019b

Karssemeijer EG, Bossers WJ, Aaronson JA, Sanders LM, Kessels RP, Olde Rikkert MG. Exergaming as a physical exercise strategy reduces frailty in people with dementia: a randomized controlled trial. *Journal of the American Medical Directors Association* 2019;**20**(12):1502-8.e1. [DOI: 10.1016/j.jamda.2019.06.026]

Kleim 2008

Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research* 2008;**51**:S225–39. [DOI: 10.1044/1092-4388(2008/018)]

Kondo 2008

Kondo M, Gray LJ, Pelka GJ, Christodoulou J, Tam PP, Hannan AJ. Environmental enrichment ameliorates a motor coordination deficit in a mouse model of Rett syndrome–Mecp2 gene dosage effects and BDNF expression. *European Journal of Neuroscience* 2008;**27**(12):3342-50. [DOI: 10.1111/j.1460-9568.2008.06305.x]

Kudlicka 2019

Kudlicka A, Martyr A, Bahar-Fuchs A, Woods B, Clare L. Cognitive rehabilitation for people with mild to moderate dementia. *Cochrane Database of Systematic Reviews* 2019, Issue 8. Art. No: CD013388. [DOI: 10.1002/14651858.CD013388]

Lam 2018

Lam FM, Huang M-Z, Liao L-R, Chung RC, Kwok TC, Pang MC. Physical exercise improves strength, balance, mobility, and endurance in people with cognitive impairment and dementia: a systematic review. *Journal of Physiotherapy* 2018;**64**(1):4-15. [DOI: 10.1016/j.jphys.2017.12.001]

Langa 2014

Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. *JAMA* 2014;**312**(23):2551-61. [DOI: 10.1001/jama.2014.13806]

Larsen 2013

Larsen LH, Schou L, Lund HH, Langberg H. The physical effect of exergames in healthy elderly—a systematic review. *GAMES FOR HEALTH: Research, Development, and Clinical Applications* 2013;**2**(4):205-12. [DOI: 10.1089/g4h.2013.0036]

Laver 2017

Laver KE, Lange B, George S, Deutsch JE, Saposnik G, Crotty M. Virtual reality for stroke rehabilitation.. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No: CD008349. [DOI: 10.1002/14651858.CD008349.pub4]

Levin 2015

Levin MF, Weiss PL, Keshner EA. Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles. *Physical Therapy* 2015;**95**(3):415-25. [DOI: 10.2522/ptj.20130579]

Lezak 2012

Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological Assessment. 5th edition. New York, NY: Oxford University Press, 2004.

Li 2019

Li T, Higgins JPT, Deeks JJ. Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from training.cochrane.org/handbook.

Maguire 1998

Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J. Knowing where and getting there: a human navigation network. *Science* 1998;**280**(5365):921-4. [DOI: 10.1126/science.280.5365.921]

Mitchell 2009

Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatrica Scandinavica* 2009;**119**(4):252-65. [DOI: 10.1111/j.1600-0447.2008.01326.x]

Mohler 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**(b2535):1-8. [DOI: 10.1136/bmj.b2535]

Morgan 2013

Morgan C, Novak I, Badawi N. Enriched environments and motor outcomes in cerebral palsy: systematic review and meta-analysis. *Pediatrics* 2013;**132**(2):e735-46. [DOI: doi.org/10.1542/peds.2012-3985]

Morris 1993

Morris JC. The Clinical Dementia Rating (CDR). Current version and scoring rules. *Neurology* 1993;**43**:2412-4. [DOI: 10.1212/WNL.43.11.2412-a]

Mrakic-Sposta 2018

Mrakic-Sposta S, Di SS, Franchini F, Arlati S, Zangiacomi A, Greci L, et al. Effects of combined physical and cognitive virtual reality-based training on cognitive impairment and oxidative stress in MCI patients: a pilot study. *Frontiers in Aging Neuroscience* 2018;**10**(282):1-11. [DOI: 10.3389/fnagi.2018.00282]

Mura 2018

Mura G, Carta MG, Sancassiani F, Machado S, Prosperini L. Active exergames to improve cognitive functioning in neurological disabilities: a systematic review and meta-analysis. *European Journal of Physical and Rehabilitation Medicine* 2018;**54**(3):450-62. [DOI: 10.23736/s1973-9087.17.04680-9]

Nasreddine 2005

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;**53**(4):695–9. [DOI: 10.1111/j.1532-5415.2005.53221.x]

Neguţ 2016

Neguţ A, Matu S-A, Sava FA, David D. Task difficulty of virtual reality-based assessment tools compared to classical paper-and-pencil or computerized measures: a meta-analytic approach. *Computers in Human Behavior* 2016;**54**:414-24. [DOI: 10.1016/j.chb.2015.08.029]

Norton 2010

Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. *Journal of Science and Medicine in Sport* 2010;**13**(5):496-502. [DOI: 10.1016/j.jsams.2009.09.008]

Nozari 2014

Nozari M, Shabani M, Hadadi M, Atapour N. Enriched environment prevents cognitive and motor deficits associated with postnatal MK-801 treatment. *Psychopharmacology* 2014;**231**(22):4361-70. [DOI: 10.1007/s00213-014-3580-8]

Owens 2020

Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Screening for cognitive impairment in older adults: US Preventive Services Task Force re: commendation statement. *JAMA* 2020;**323**(8):757-63. [DOI: 10.1001/jama.2020.0435]

Padala 2012

Padala KP, Padala PR, Malloy TR, Geske JA, Dubbert PM, Dennis RA, et al. Wii-fit for improving gait and balance in an assisted living facility: a pilot study. *Journal of Aging Research* 2012;**597573**:1-6. [DOI: 10.1155/2012/597573]

Padala 2017

Padala KP, Padala PR, Lensing SY, Dennis RA, Bopp MM, Roberson PK, et al. Home-based exercise program improves balance and fear of falling in community-dwelling older adults with mild Alzheimer's disease: a pilot study. *Journal of Alzheimer's Disease* 2017;**59**(2):565-74. [DOI: 10.3233/JAD-170120]

Park 2018

Park J-H, Park J-H. Does cognition-specific computer training have better clinical outcomes than non-specific computer training? A single-blind, randomized controlled trial. *Clinical Rehabilitation* 2018;**32**(2):213-22. [DOI: 10.1177/0269215517719951]

Peng 2011

Peng W, Lin J-H, Crouse J. Is playing exergames really exercising? A meta-analysis of energy expenditure in active video games. *Cyberpsychology, Behavior, and Social Networking* 2011;**14**(11):681-8. [DOI: 10.1089/cyber.2010.0578]

Petersen 1999

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology* 1999;**53**(3):303-8. [DOI: 10.1001/archneur.56.3.303]

Petersen 2009

Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. *Archives of Neurology* 2009;**66**(12):1447-55. [DOI: 10.1001/archneurol.2009.266]

Portet 2006

Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 2006;**77**(6):714-8. [DOI: 10.1136/jnnp.2005.085332]

Regan 2017

Regan B, Wells Y, Farrow M, O'Halloran P, Workman B. MAXCOG—maximizing cognition: a randomized controlled trial of the efficacy of goal-oriented cognitive rehabilitation for people with mild cognitive impairment and early Alzheimer disease. *The American Journal of Geriatric Psychiatry* 2017;**25**(3):258-69. [DOI: 10.1016/j.jagp.2016.11.008]

Review Manager 2020 [Computer program]

The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. The Cochrane Collaboration, 2020.

RevMan Web 2020 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 2.1.0. The Cochrane Collaboration, 2020. Available at revman.cochrane.org.

Rizzo 2005

Rizzo AS, Kim GJ. A SWOT analysis of the field of virtual reality rehabilitation and therapy. *Presence:*

Teleoperators & Virtual Environments 2005;**14**(2):119-46. [DOI: 10.1162/1054746053967094]

Rizzo 2017

Rizzo A, Koenig ST. Is clinical virtual reality ready for primetime? *Neuropsychology* 2017;**31**(8):877-99. [DOI: 10.1037/neu0000405]

Rizzo 2019

Rizzo AS. Clinical virtual reality in mental health and rehabilitation: a brief review of the future! Infrared Technology and Applications XLV 2019 May 13;**11002**:110020Q. [DOI: 10.1117/12.2524302]

Rose 2018

Rose T, Nam CS, Chen KB. Immersion of virtual reality for rehabilitation – review. *Applied Ergonomics* 2018;**69**:153-61. [DOI: 10.1016/j.apergo.2018.01.009]

Rosly 2017

Rosly MM, Rosly HM, OAM Davis GM, Husain R, Hasnan N. Exergaming for individuals with neurological disability: a systematic review. *Disability and Rehabilitation* 2017;**39**(8):727-35. [DOI: 10.3109/09638288.2016.1161086]

Sallis 2016

Sallis JF, Bull F, Guthold R, Heath GW, Inoue S, Kelly P, et al. Progress in physical activity over the Olympic quadrennium. *Lancet* 2016;**388**(10051):1325-36. [DOI: 10.1016/S0140-6736(16)30581-5]

Selkoe 2012

Selkoe DJ. Preventing Alzheimer's disease. *Science* 2012;**337**(6101):1488-92. [DOI: 10.1126/science.1228541]

Shah 2016

Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, et al. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurology* 2016;**15**(12):1285-94. [DOI: 10.1016/S1474-4422(16)30235-6]

Sofi 2011

Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of Internal Medicine* 2011;**269**(1):107-17. [DOI: 10.1111/j.1365-2796.2010.02281.x]

Song 2018

Song D, Doris SF, Li PW, Lei Y. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: a systematic review and meta-analysis. *International Journal of Nursing Studies* 2018;**79**:155-64. [DOI: 10.1016/j.ijnurstu.2018.01.002]

Tahmosybayat 2017

Tahmosybayat R, Baker K, Godfrey A, Caplan N, Barry G. A systematic review and meta-analysis of outcome measures to assess postural control in older adults who undertake exergaming. *Maturitas* 2017;**98**:35-45. [DOI: 10.1016/j.maturitas.2017.02.003]

Tardif 2011

Tardif S, Simard M. Cognitive stimulation programs in healthy elderly: a review. *International Journal of Alzheimer's Disease* 2011;**2011**(378934):1-13. [DOI: 10.4061/2011/378934]

Taylor 2013

Taylor ME, Delbaere K, Lord SR, Mikolaizak AS, Close JC. Physical impairments in cognitively impaired older people: implications for risk of falls. *International Psychogeriatrics* 2013;**25**(1):148-56. [DOI: 10.1017/S1041610212001184]

Van Santen 2018

Van Santen J, Dröes R-M, Holstege M, Henkemans OB, Van Rijn A, De Vries R, et al. Effects of exergaming in people with dementia: results of a systematic literature review. *Journal of Alzheimer's Disease* 2018;**63**(2):741-60. [DOI: 10.3233/JAD-170667]

Wang 2019

Wang S, Yin H, Wang X, Jia Y, Wang C, Wang L, et al. Efficacy of different types of exercises on global cognition in adults with mild cognitive impairment: a network meta-analysis. *Aging Clinical and Experimental Research* 2019;**31**(10):1391-400. [DOI: 10.1007/s40520-019-01142-5]

WHO 1992

World Health Organization (WHO). International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Geneva, Switzerland: World Health Organisation, 1992.

WHO 2019

World Health Organization (WHO). ICD-11. International Classification of Diseases 11th revision. Geneva, Switzerland: World Health Organization, Division of Mental Health, 2019.

WHO 2020

World Health Organization (WHO). Physical activity. Available at who.int/news-room/fact-sheets/detail/physical-activity.

Wiloth 2018

Wiloth S, Werner C, Lemke NC, Bauer J, Hauer K. Motor-cognitive effects of a computerized game-based training method in people with dementia: a randomized controlled trial. *Aging & Mental Health* 2018;**22**(9):1130-41. [DOI: 10.1080/13607863.2017.1348472]

Winblad 2004

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine* 2004;**256**(3):240-6. [DOI: 10.1111/j.1365-2796.2004.01380.x]

Winblad 2016

Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurology* 2016;**15**(5):455-532. [DOI: 10.1016/S1474-4422(16)00062-4]

Woods 2012

Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No: CD005562. [DOI: 10.1002/14651858.CD005562.pub2]

World Alzheimer Report 2015

World Alzheimer Report 2015: The Global Impact of Dementia. www.alz.co.uk/research/WorldAlzheimerReport2015.pdf.

Wortmann 2012

Wortmann M. Dementia: a global health priority-highlights from an ADI and World Health Organization report. *Alzheimer's Research & Therapy* 2012;**4**(5):40-3. [DOI: 10.1186/alzrt143]

Zhao 2014

Zhao C, Jou J, Wolff L, Sun H, Gage FH. Spine morphogenesis in newborn granule cells is differentially regulated in the outer and middle molecular layers. *Journal of Comparative Neurology* 2014;**522**(12):2756-66. [DOI: 10.1002/cne.23581]

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Dementia/

2 Delirium/

3 Wernicke Encephalopathy/

4 Neurocognitive Disorders/

5 exp *Cognition Disorders/

6 "Benign senescent forgetfulness".ti,ab.

7 "CDR 0.5".ti,ab.

8 "clinical dementia rating scale 0.5".ti,ab.

9 "cognit* impair*".ti,ab.

10 "GDS 3".ti,ab.

11 "major neurocognitive disorder".ti,ab.

12 "mild neurocognit* disorder*".ti,ab.

13 "organic brain disease".ti,ab.

14 "organic brain syndrome".ti,ab.

15 "preclinical AD".ti,ab.

16 "pre-clinical AD".ti,ab.

17 "preclinical alzheimer*".ti,ab.

18 "pre-clinical alzheimer*".ti,ab.

19 "stage 3 GDS".ti,ab.

20 ("global deterioration scale" and "stage 3").ti,ab.

21 ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or insufficient* or chronic)).ti,ab.

22 aMCI.ti,ab.

23 MCIa.ti,ab.

24 (lewy* adj2 bod*).ti,ab.

25 (prodrom* adj2 dement*).ti,ab.

26 alzheimer*.ti,ab.

27 dement*.ti,ab.

28 MCI.ti,ab.

29 or/1-28

30 exp Video Games/

31 exp Exercise Therapy/mt [Methods]

32 Virtual Reality Exposure Therapy/

33 Virtual Reality/

34 exp Exercise Therapy/is [Instrumentation]

35 "active gaming".ti,ab.

36 "active video gaming".ti,ab.

37 "Bright Arm Duo".ti,ab.

38 "Clinical Arcade".ti,ab.

39 "cognitive-aerobic bicycle training".ti,ab.

40 "computer game*".ti,ab.

41 "computer based".ti,ab.

42 "computer generated environment".ti,ab.

43 "Dance Dance Revolution".ti,ab.

44 "digital gam*".ti,ab.

45 "exercise gaming".ti,ab.

46 "exer-gam*".ti,ab.

47 "gaming console*".ti,ab.

48 "infra red camera*".ti,ab.

49 "interactive gaming".ti,ab.

50 "motion tracking".ti,ab.

51 "play station".ti,ab.

52 "Sony EyeToy".ti,ab.

53 "video based".ti,ab.

54 "video gam*".ti,ab.

55 "virtual city".ti,ab.

56 "virtual environment".ti,ab.

57 "virtual reality".ti,ab.

58 exergam*.ti,ab.

59 gaming.ti,ab.

60 IREX.ti,ab.

61 Kinect*.ti,ab.

62 Nintendo.ti,ab.

63 playstation.ti,ab.

64 videogam*.ti,ab.

65 Wii.ti,ab.

66 Xbox.ti,ab.

67 "X box".ti,ab.

68 "computer interaction".ti,ab.

69 "exercise bike".ti,ab.

70 "sports game*".ti,ab.

71 gamecycle.ti,ab.

72 immersive.ti,ab.

73 "serious game*".ti,ab.

74 treadmill.ti,ab.

75 or/30-74

76 29 and 75

77 randomized controlled trial.pt.

78 controlled clinical trial.pt.

79 randomized.ab.

80 placebo.ab.

81 drug therapy.fs.

82 randomly.ab.

83 trial.ab.

84 groups.ab.

85 or/77-84

86 exp animals/ not humans.sh.

87 85 not 86

88 76 and 87

HISTORY

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CONTRIBUTIONS OF AUTHORS

Alexandra Voinescu drafted the protocol. All co-authors reviewed the draft and contributed to revisions.

DECLARATIONS OF INTEREST

Alexandra Voinescu: none known

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