


BMJ Open Effects of reducing sedentary behaviour duration by increasing physical activity, on cognitive function, brain function and structure across the lifespan: a systematic review protocol

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ABSTRACT

Introduction Greater engagement in sedentary behaviours has been related to poorer cognitive functions in epidemiological research. However, the effects of reducing sedentary behaviour duration on cognitive function, brain function, and structure remain poorly understood. This systematic review aims to synthesise the evidence on the effects of reducing sedentary behaviour duration by increasing time spent in physical activity on cognitive function, brain structure and function in apparently healthy children, adolescents and adults.

Methods and analysis The protocol follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The literature search will be conducted (search dates: August–September 2022) across six databases: PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature (via EBSCO Host), PsycINFO (via ProQuest), SPORTDiscus and Web of Science (Science and Social Science Citation Index). The inclusion criteria are as follows: randomised and non-randomised experimental studies as defined by the Cochrane Handbook, published in English, in peer-reviewed journals, and as theses or dissertations. References of included papers will be screened for additional studies. Acute and chronic interventions targeting children (≥ 4 years), adolescents, younger adults (≥ 18 –40 years), middle-aged (40–64 years) and older adults (65+ years) will be eligible. Methodological quality will be assessed with the Effective Public Health Practice Project quality assessment tool for quantitative studies. Qualitative synthesis will be stratified by intervention type (acute vs chronic), intervention content (reducing sedentary time or interrupting prolonged sitting) and outcome (cognitive, brain structure and function).

Ethics and dissemination No primary data collection will be conducted as part of this systematic review. Study findings will be disseminated through peer-reviewed publications, conference presentations and social media.
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INTRODUCTION

Sedentary lifestyles are ubiquitous in Western countries among adults^{1–3} and children alike^{1 3–5}, and this trend remains on

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A comprehensive synthesis of acute and chronic effects of reducing sedentary behaviour duration by increasing time spent in physical activity on cognitive functions, brain function and structure in apparently healthy adults and children.
- ⇒ A rigorous systematic review methodology follows the guidelines of the Preferred Reporting Items for Systematic Reviews and employs the Effective Public Health Practice Project quality assessment tool to evaluate the risk of bias.
- ⇒ The heterogeneity of cognitive outcomes is accounted for by a structured synthesis based on the cognitive typology according to the involvement of controlled processes.
- ⇒ The generalisability of study results is limited to healthy children and adults.

the rise.^{1 6} Growing evidence suggests that greater engagement in sedentary behaviours (e.g., ≥ 8 hours/day) increases the risk of mortality,^{7 8} cardiovascular disease⁹ and type 2 diabetes.¹⁰ Several of these health risks are distinct from being physically inactive because accounting for individual differences in moderate-to-vigorous physical activity (MVPA) attenuates but does not abolish the risk in a large proportion of the population.^{7 8} Sedentary behaviour is defined as any waking behaviour performed while sitting, reclining or lying down with low energy expenditure of ≤ 1.5 metabolic equivalents.¹¹ It can be broadly characterised by its duration, context (e.g., school or work), and type (e.g., TV viewing vs computer use).^{11 12} Negative physical health consequences have been related to sedentary behaviour duration.^{7 8} Accordingly, the Human Movement Framework¹³ has focused on the compromising health consequences of sedentary behaviour associated with low

energy expenditure and the lack of benefits to physical fitness.^{14 15} While evidence on the adverse physical health consequences of sedentary behaviour duration is growing, its effects on cognitive and brain health remain poorly understood.

Emergent epidemiological and intervention studies suggest that sedentary behaviour duration is related to poorer cognitive functions, including fluid intelligence, short-term memory¹⁶ and executive functions (EFs).^{17 18} EFs refer to cognitive processes, which underpin goal-directed behaviour, and include inhibitory control (the ability to control distractions and to act on an impulse), working memory (WM, the ability to hold and manipulate information in mind) and set-shifting (switching between tasks and mental sets).^{17 18} A systematic review of cohort and case-control studies¹⁹ suggested that sedentary behaviour is related to impaired cognitive functioning and the risk of dementia among middle-aged and older adults. However, the causality of the relationship could not be ascertained due to the observational evidence. At present, it remains unclear what proportion of negative associations between sedentary behaviours and cognitive functions could be explained by passive behaviour duration or type (e.g., cognitively engaging computer use or cognitively passive television (TV) viewing).¹⁶ Specifically, two out of four reviewed high-quality studies measured TV viewing as a single indicator of sedentary behaviour.¹⁹ However, the associations between sedentary behaviour and cognitive functions can vary with the sedentary behaviour type.¹⁶ TV viewing (a cognitively passive behaviour) has been negatively related to visuospatial and verbal memory, and fluid intelligence. In contrast, computer use (a cognitively engaging behaviour) has been positively associated with these cognitive functions.¹⁶ A systematic review of experimental studies designed to reduce the sedentary time (ST) can help complement previous work by estimating the effect of reducing sedentary behaviour duration on cognitive health. Preliminary experimental findings in children suggest that such reduction can positively affect EFs. Specifically, reducing sitting over several weeks by implementing two daily 4–5 min PA breaks at school improved response inhibition (the ability to inhibit acting on an impulse and an aspect of inhibitory control), and reductions in inclinometer-measured sitting fully mediated this effect.²⁰

Acute experimental studies can provide complementary evidence on the effects of reducing sedentary behaviour duration by increasing PA on cognitive functions over one to several days.^{21–28} Such studies are often conducted using a randomised cross-over design in a laboratory setting where PA dose, energy intake and the type of sedentary behaviours can be controlled, providing a direct estimate of reducing ST by increasing PA (e.g., by interrupting prolonged sitting with short PA bouts) on cognitive functions. For example, substituting an hour of sitting for 30 min of moderate-intensity PA and frequent (every 30 min) but brief (3 min) light-intensity PA breaks improved working memory in older adults relative to 8-hour sitting.²⁸ Likewise, interrupting prolonged sitting every hour with 10–30 min

light-intensity walking or cycling positively affected working memory and set-shifting in younger overweight adults.²⁴ However, null findings have also been reported.^{22 25 26} Two previous systematic reviews found null effects of alternating sitting with standing or walking to a workstation on EFs in working-age adults.^{29 30} However, both reviews included acute studies that measured cognitive performance during standing or PA, compared with during sitting. Thus, their findings capture cognitive responses to an acute bout of standing or PA, essential not to reducing sitting with PA. This is an important distinction because preliminary data suggest that cognitive function can decline over several hours of sitting (3–8 hours).^{28 31} Accordingly, understanding the effects of reducing sitting (e.g., by reallocating a proportion of sitting to PA) on cognitive function would require protocols lasting several hours (compared with acute PA protocols usually lasting 16–35 min³²). Likewise, more than one PA bout would be required to avert a decrement in cognitive performance following several hours of sitting because cognitive benefits of a single PA bout are transient, begin to wane after 20 min,³³ and generally last about an hour.³² In confirmation, two not one 20 min bout of moderate intensity PA delivered at the beginning and mid-morning improved selective attention in younger adolescents.²¹ Selective attention was measured repeatedly over 4.5-hour sitting at school, including 2 hours after the last PA bout. An acute effect of PA could not explain the positive effect of PA on selective attention because when a single PA bout was delivered mid-morning, it did not improve selective attention. How much PA (how often, for how long and at what intensity) is required to prevent decline in cognitive performance over several hours of sitting remains unclear. This question has high public health and practical significance given today's sedentary societies.^{1–3 34–37} Emergent estimates from studies in the USA, UK, Australia, Denmark and Portugal indicate a relatively high percentage of waking time spent in prolonged sedentary bouts by children, adolescents³⁷ and adults.^{36 38} For example, estimates in children ranged between 10% and 45% (where prolonged bout was defined as ST lasting ≥ 10 min).³⁷ Higher estimates were observed in adults in the USA³⁶ and the UK³⁸ with 43% and 49% of waking time spent in sedentary bouts lasting ≥ 30 min.

The effects of passive behaviour duration on brain structure or function remain poorly understood. Findings from a few observational studies among older adults suggest that more ST may be negatively related to white matter integrity^{39 40} and reduced cortical thickness in the medial temporal cortex⁴¹ that subserves long-term memory. These studies support the notion that higher ST may have negative consequences for brain health. White matter integrity declines with ageing,⁴² and this decline is associated with decrements in cognitive performance, including EFs and long-term memory.⁴³ A small number of cross-sectional studies also examined the associations between accelerometer-measured ST and brain activation at rest or during cognitive task engagement. Pindus *et al*⁴⁴ found a negative association between ST and functional connectivity

of the dorsal attention network at rest in younger healthy adults. Dorsal attention network biases information processing towards top-down attentional control.⁴⁵ Thus, these findings suggest decreased readiness to engage top-down control with higher ST. In middle-aged adults with overweight and obesity, higher ST was related to poorer neural efficiency, such that more sedentary adults allocated more attentional resources to the task that varied in cognitive demands without benefit to cognitive performance.⁴⁶ These emergent studies raise the possibility of suboptimal activation in brain regions that support EFs with higher ST already during younger-age and middle-age adulthood. Preliminary data from a longitudinal study further suggest that decreasing ST over several weeks can lead to positive adaptations in global cerebral blood flow (CBF), a global measure of substrate delivery to the brain. Specifically, a 16-week intervention, which reduced daily sitting by an hour, increased global CBF.⁴⁷ Furthermore, acutely interrupting prolonged sitting with PA enhanced global CBF over and above the chronic adaptations in CBF in response to a clinically meaningful reduction in ST (60 min/day).⁴⁷ Thus, a systematic review of experimental evidence will increase our understanding of both chronic and acute effects of reducing ST and prolonged sitting (by increasing PA) on cognitive and brain health.

To the best of our knowledge, no previous systematic review synthesised chronic and acute effects of reducing ST and prolonged sitting on cognitive and brain health across the lifespan in apparently healthy individuals. Previous systematic reviews focused on chronic effects of sedentary behaviours on cognitive functions but included only observational studies,¹⁹ limited the review to specific cognitive functions (memory and working memory),⁴⁸ context (occupational sitting)⁴⁹ or age groups (middle-aged and older adults,¹⁹ older adults⁵⁰ or preschool children⁵¹). For example, Loprinzi⁴⁸ included experimental studies but limited cognitive outcomes to broadly conceptualised memory. In children, Carson *et al.*⁵¹ synthesised the literature on the relationships between duration, type (eg, frequency of TV viewing or video gaming) and patterns of sedentary behaviours and cognitive functions but limited their review to young children (aged ≤ 5 years), and behavioural measures of cognitive function. Only two systematic reviews attempted to capture the measures of brain function and structure in relation to sedentary behaviour. However, they were limited in the scope of cognitive functions measured (i.e., memory)⁴⁸ and population (i.e., older adults).⁵⁰ The proposed systematic review aims to address these gaps and synthesise experimental studies on the acute and chronic effects of reducing sedentary behaviour duration by increasing PA on cognitive functions, brain function and structure. Including studies across a broad age range (from school-aged children to older adults) will facilitate conclusions based on a larger set of studies, given this relatively new field.

Our choice to focus on studies reallocating sedentary behaviours to PA and not standing is based on the hypothesised mechanisms that may underlie its effects

on cognitive and brain health.^{52–54} These mechanisms include reduced lipid metabolism via decreased lipoprotein lipase activity (i.e., an enzyme involved in the regulation of lipid metabolism),⁵⁵ and changes in glycaemic response.^{52–54} Experimental studies in rodents have shown steep reduction in lipoprotein lipase in slow twitch red muscles within hours of forced hind limb unloading (an experimental model to study prolonged sitting). Although this effect is readily reversible with ambulatory movement, repetitive, habitual engagement in high volumes of sitting^{1 3 34 56 57} might chronically downregulate lipoprotein lipase. In turn, attenuated lipoprotein lipase activity may indirectly affect cognitive and brain function by downregulating lipid metabolism.⁵² In confirmation, breaking prolonged sitting (such as sitting continuously for 30 min or more) with PA can acutely (over several hours) decrease triglyceride concentrations.⁵⁸ Higher triglyceride concentrations have been associated with greater visceral fat mass.⁵⁹ In turn, greater visceral fat mass has been related to poorer attentional control, and WM in adolescent girls,⁶⁰ greater age-related decrease in the connectivity of the structural brain network that supports memory performance in younger through to older adults,⁶¹ and white matter lesions, and decreased global cognitive function in healthy elderly.⁶² However, direct evidence on the mediating effect of lipid metabolism on the relationship between high ST, prolonged sitting, cognitive and brain functions is currently lacking. A small number of cross-over randomised controlled studies examined the acute changes in lipid metabolism alongside changes in cognitive performance following a bout of prolonged sitting compared with sitting interrupted with PA breaks (moderate-intensity cycling,²⁶ resistance exercise⁶³) or substituting 50% of ST for light-intensity PA.⁶² These studies reported null effects of the intervention on lipid metabolism (e.g., triglycerides, total cholesterol high-density and low-density lipoprotein) and cognitive functions (e.g., working memory, episodic memory, attentional vigilance). Given the associations between visceral fat mass, cognitive function and brain structure, this specific mechanism may require a chronic intervention approach to allow for changes in lipid profile, visceral fat mass and brain structure to take effect.

Another proposed mechanism to explain the effects of excessive ST on cognitive and brain function is glycaemic control.⁵² Prolonged sitting leads to acute increases in postprandial glycaemia and insulinaemia.⁵⁵ It has been proposed that over time, repeated exposure to prolonged sitting might result in greater compensatory response (larger glucose nadir and glucose excursions) and greater variability in brain glucose levels.⁵⁴ Epidemiological evidence supports the tenet that high engagement in sedentary behaviours may increase the risk of cognitive dysfunction due to type 2 diabetes. In confirmation, greater engagement in ST is related to twofold increase in the risk of type 2 diabetes.^{55 64} In turn, type 2 diabetes is related to global cognitive dysfunction (including EFs, memory and processing speed),⁶⁵ increased risk of vascular and other

unspecified dementias,⁶⁶ white matter lesions,⁶⁷ regional grey matter atrophy in the hippocampus and orbitofrontal cortex (that support memory and inhibitory control, respectively),⁶⁸ and reductions in functional connectivity between brain regions supporting memory and EFs.⁶⁹ Conversely, regularly interrupting prolonged sitting with light to vigorous PA acutely decreases postprandial glycaemia and insulin response.⁵⁴ This effect can partly be explained by increased energy expenditure.⁵⁴ In contrast, standing does not sufficiently increase energy expenditure above resting levels.^{58 70} Indeed, interrupting sitting with standing was not associated with glycaemic control in several acute randomised controlled trials (RCTs).^{71–73} Accordingly, this systematic review will focus on the effects of reducing sedentary behaviour duration by increasing PA (not standing) of any intensity (light to vigorous) on cognitive function, brain function and structure in apparently healthy children, adolescents, younger-aged, middle-aged and older adults.

OBJECTIVES

Accordingly, this systematic review has the following objectives:

1. To synthesise the literature on the acute effects of reducing sedentary behaviour duration by increasing PA (eg, by interrupting prolonged sitting with PA) (interventions) relative to usual practice or a prescribed sedentary comparator on cognitive functions (outcomes).
2. To synthesise the literature on the acute effects of reducing sedentary behaviour duration on brain function (outcomes).
3. To synthesise the evidence from chronic interventions reducing sedentary behaviour duration by increasing PA (interventions) on cognitive functions (outcomes) relative to usual practice, attention control or prescribed sedentary condition (comparator).
4. To synthesise the evidence from chronic interventions on brain structure.
5. To synthesise the evidence from chronic interventions on brain function.

METHODS AND ANALYSIS

This systematic review protocol follows the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA)⁷⁴ and has been registered in PROSPERO (registration number: CRD42020200998).

Inclusion and exclusion criteria for study selection

Type of studies

Acute effects

Experimental studies using RCT and cross-over randomised trials will be included. Due to the paucity of acute interventions testing the effects of reducing ST and/or prolonged ST on cognitive functions and brain function, non-randomised studies of the interventions (NRSI) ranging from quasi-RCTs to pre studies and post studies⁷⁵ will also be included.

Chronic effects

RCTs, cross-over randomised trials, cluster randomised trials and NRSIs (excluding observational studies) will be included. We will include NRSIs due to the dearth of chronic intervention studies in this area and ethical considerations in assigning groups to prolonged or increased ST conditions based on adverse effects of prolonged sitting on glucose homeostasis.⁵⁸

Conference abstracts, poster abstracts, letters, opinion pieces, reviews and unpublished studies other than thesis and dissertations will be excluded.

Type of participants

School-aged children and adolescents (4–17 years),³² younger adults (18–44 years), middle-aged adults (45–64 years)^{76 77} and older adults (≥ 65 years)⁷⁷ will be included. The definition of midlife was based on the cognitive decline on several measures of higher order cognitive functions (e.g., inductive reasoning, episodic memory) observed in mid 40s and early 40s,^{77 78} and the definition of midlife adopted in cancer prevention literature.⁷⁶ Definition of older adulthood has been adopted to align with the transition to retirement, and accelerated cognitive decline compared with middle age.⁷⁷ Children younger than 4 years will not be included due to underdeveloped EFs,^{79–81} consistent with studies of PA and cognition in children.^{82 83}

Exclusion criteria include observational studies, studies assessing participants with physical disability, cancer, any condition that could affect cognitive function including, but not limited to, neurological disorders, neurodegenerative disorders, metabolic syndrome, types 1 and 2 diabetes, cardiovascular disease and mental health conditions. We will include studies that focused on specific ethnic and socioeconomic groups, men and/or women, and adults with overweight and/or obesity.

Type of interventions

Acute interventions

Prospective acute intervention studies testing the effects of reducing and substituting time spent in sedentary behaviours for PA or interrupting prolonged sitting with multiple bouts of PA of any intensity or type (e.g., light walking, high-intensity interval training and strength exercises) will be included. An acute intervention is defined as a condition lasting ≥ 3 hours^{21 84 85} and up to 13 days.⁸⁶ The upper boundary has been adopted because: (1) an acute effect of a single bout of PA on long-term memory can persist for 48 hours,⁸⁷ even though the majority of acute PA studies measure its effect on cognitive and brain function within an hour from PA cessation³²; (2) the effects of a single PA bout on glycaemic control (postprandial insulin) can extend to 72 hours;⁸⁴ (3) studies testing the effects of interrupting prolonged sitting with PA or decreasing daily PA (< 5000 steps) and increasing ST on cognitive functions over 3–7 days found no effects,^{25 86 88} suggesting that 7 days may be insufficient to engender chronic changes in cognition by manipulating ST and (4)

step reduction studies have shown a decrease in cardiorespiratory fitness over 2 weeks.^{89 90} Because cardiorespiratory fitness has been associated with enhanced EFs^{82 91 92} and brain function^{93–95} across the lifespan, physical adaptations to sitting occurring within 2 weeks may be sufficient to stimulate chronic adaptations in cognitive and brain function.

The acute effects of reducing sedentary behaviour duration by increasing PA (eg, by interrupting prolonged sitting with PA) should be defined relative to the end of the sedentary behaviour exposure, which generally varies in acute studies between 3 and 10 hours.^{22–26 28} However, cognitive functions were often assessed during the intervention^{23–25} or during and at the end of the intervention.²⁸ Studies that extended the acute protocol to >1 day,^{25 86 88} measured cognitive functions either during each day²⁵ or the day after each experimental condition.^{86 88} All such studies will be included, and the effect of the timing of cognitive and neurofunctional assessments will be discussed. Studies testing the effects of substituting ST for PA or interrupting prolonged sitting with PA on cognitive functions and brain function will be included. Studies substituting ST for standing only will be excluded because standing may contribute minimally to energy expenditure compared with sitting.^{70 96} Interventions delivered either in the laboratory or in free living including work, school and leisure time will be included. For studies conducted in free living, ST and PA must be measured with motion sensors.

Chronic interventions

We will include prospective intervention studies lasting ≥ 2 weeks,^{89 90} which test the effects of reducing ST by re-allocating ST to PA and/or interrupting prolonged sitting with intermittent bouts of PA. We chose 2 weeks as the boundary for the chronic effect based on step reduction studies, showing decreased cardiorespiratory fitness and whole-body insulin sensitivity within 2 weeks of increasing ST by reducing PA. Importantly, these changes were largely reversed 2 weeks later on resumption of the ambulatory activity.^{89 90} Both cardiorespiratory fitness,^{82 91–95} and better glycaemic control^{97–100} have been related to improved brain function and cognition, lending support to our definition of the chronic effect. Interventions which substitute ST for standing only will be excluded.⁵⁸ Interventions which compare cognitive aspects of screen-based behaviours (e.g., the effects of the pace and content of TV programmes on cognitive functions) without reducing ST will be excluded because they focus on the effects of mental stimulation on cognitive functions^{101 102} and not the duration of sedentary behaviours or sedentary patterns. The exclusion of interventions testing the effects of cognitive aspects of screen-based behaviours was informed by a discontinued systematic review.¹⁰³ In this review, the inclusion of interventions comparing the cognitive effects within the same type of sedentary behaviour (e.g., TV viewing) resulted in too broad a definition of the comparator and difficulty in synthesising the

effects of ST and patterns on brain structure and function. Our approach will address this limitation. Studies assessing the effects of active video gaming on cognitive and brain health will also be excluded because some active video games increase energy expenditure up to moderate intensity,^{104 105} and therefore, they focus on active sitting, which does not conform to the energy expenditure aspect of the sedentary behaviour definition. Eligible long-term interventions will be required to include sensor-measured ST and PA (e.g., using activPAL inclinometer, accelerometers or pedometers).^{25 86 106}

Studies with intervention groups varying in cognitive engagement

We will include studies with multiple intervention arms that vary in the cognitive engagement of PA or sedentary behaviours as long as at least one intervention group introduces reductions in sedentary behaviour and increases in PA relative to the comparator. Such additional intervention arms may include: a group matched on sedentary behaviour duration and PA dose to the intervention group, but different in cognitive engagement from the PA group (e.g., cognitively engaging PA such as movement requiring coordination, rule-based PA games versus cognitively passive PA such as jumping jacks, running or walking) or sedentary behaviour exposure (e.g., reading vs. TV viewing).

Type of comparators

Acute studies

A comparator will include usual practice (e.g., daily behaviour, daily ST at school, work or leisure time) or prescribed sitting.

Chronic intervention studies

Studies using a usual practice as well as sedentary attention-control condition and prescribed ST condition will be included.

Type of outcome measures

Cognitive functions

Cognitive function can be defined as mental activity of information processing which results in mental representations and their transformations.¹⁰⁷ Cognitive processes will be classified using categories described by Lezak¹⁰⁸ as previously adopted by reviews of acute exercise and cognition.^{32 33} We will classify cognitive functions proceeding from the least to most complex in relation to the involvement of controlled processes (i.e., top-down processes that control and schedule perception, memory and action in congruence with current goals): (1) motor speed and motor learning, (2) information processing, (3) attention, (4) memory, (5) cognitive control (ie, EFs such as inhibitory control, working memory and set-shifting) and (6) reasoning and intelligence.^{32 92}

Common tasks that measure these cognitive functions include but are not limited to: simple and choice reaction time tasks (motor speed and information processing), Oddball (attention), Hopkins Verbal Learning Test (memory), Stroop and Eriksen flanker tasks (inhibitory

control), digit backwards, n-back or Operation Span Task (working memory), task switching (set shifting), Wechsler Adult Intelligence Scale (intelligence and reasoning).

Brain structure

Measures of total and region-specific grey and white matter volume will be included, as assessed with MRI and related techniques (eg, diffusion MRI). Measures of total cerebral volume will also be included.

Brain function

Studies measuring neurofunctional correlates of cognitive functions as well as resting state functional connectivity will be included. Specific neuroimaging methods will include but are not limited to electroencephalography and event-related brain potentials, functional near-infrared spectroscopy, functional MRI (fMRI), resting state fMRI and positron emission tomography. Studies assessing the effects of reducing sedentary behaviour duration by substituting some ST for PA or interrupting prolonged sitting with PA on CBF and cerebral perfusion will also be included.

Search methods and identification of studies

Electronic databases

Electronic searches of published and peer-reviewed manuscripts in English will be conducted in PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL via EBSCO Host), PsycINFO (via ProQuest), SPORTDiscus and Web of Science (Science and Social Science Citation Index) from the beginning of the electronic database records. In addition, we will search ProQuest Dissertation and Theses. Study records, including deduplication will be managed using EndNote reference manager.

Search terms will be organised according to exposure and three outcomes: cognitive function, brain structure, and function. Examples of the search terms include: (1) “sedentary behavior”, sedentariness, sitting, “sedentary lifestyle”; (2) “cognitive function”, “information processing”, attention, memory, learning, “executive function”, intelligence, reasoning; (3) “magnetic resonance imaging”, “white matter volume”, “gray matter volume”, “cortical thickness”, “cortical surface area”; and (4) “functional magnetic resonance imaging”, electroencephalography, “event related brain potentials”, magnetoencephalography, “near-infrared spectroscopy”, “positron emission tomography”. All key words will include British as well as American spelling and plurals. Title and abstracts, along with relevant MeSH terms (and their equivalents in respective databases) will be searched (see online supplemental material I for an example of PubMed search strategy).

Reference lists of all included studies and relevant systematic reviews will be screened for additional studies.

Search dates: August–September 2022.

Data collection and analysis

Study selection

After the deduplication of records, two independent reviewers will screen titles and abstracts according to pre-defined inclusion and exclusion criteria. Full texts of studies selected during the title and abstract screening will be reviewed for inclusion and exclusion criteria. Reasons for exclusions will be recorded. Discrepancies between reviewers will be resolved through discussion and consensus or adjudication by a third reviewer if no consensus is reached.

Data extraction

A data extraction form will be developed and piloted prior to implementation according to Cochrane recommendations.¹⁰⁹ Two authors will independently extract the following information in duplicate:

- ▶ Authors, year of publication.
- ▶ Aim of the study.
- ▶ Intervention type (acute/chronic), study design, country.
- ▶ Participant characteristics (age, sex, weight status).
- ▶ Intervention characteristics (e.g., whether an intervention focused on reducing ST and/or prolonged sitting, intervention duration, frequency and duration of intervention sessions, the amount of ST to be reallocated to PA, frequency, duration and intensity of PA, qualitative characteristics of PA, the type(s) of sedentary behaviours that participants engaged in (i.e., cognitively passive vs cognitively engaging sedentary behaviours).
- ▶ Comparator characteristics (including presence/absence of the attention control condition).
- ▶ Additional intervention arms with different cognitive content of PA or sedentary behaviour but matched on sedentary behaviour duration and PA dose to the main intervention arm.
- ▶ Methods used to measure intervention fidelity (ST, type of sedentary behaviours and PA).
- ▶ The moderating effect of sedentary behaviour type.
- ▶ For NRIS studies, information about measured covariates.
- ▶ Main outcomes measured and assessment method.
- ▶ The timing of outcome assessment and follow-up.
- ▶ Data analysis.
- ▶ Key results relevant to the population, intervention, comparison and outcome.

When necessary, we will contact the authors of the included studies to provide further details (e.g., details of the intervention). The discrepancies between the two reviewers will be resolved through discussion and consensus.

Assessment of methodological quality

The risk of bias will be assessed independently by two researchers as recommended by the Cochrane Handbook of Systematic Reviews.¹¹⁰ Disagreements will be resolved through discussion with adjudication of the third

reviewer if consensus cannot be reached. The risk of bias will be assessed using the quality assessment tool for quantitative studies developed by the Effective Public Health Practice Project.¹¹¹ The tool has good intrarater reliability ($\kappa=0.74$) and provides conservative quality ratings compared with similar methods.¹¹¹ It is suitable for the assessment of RCTs as well as NRSIs. The tool consists of eight components evaluating selection bias, study design, confounders, blinding, data collection methods, withdrawals and drop-outs, intervention integrity and appropriateness of data analyses.¹¹¹ Studies are rated as strong in quality if no weak components are present, moderate in quality if one weak component is present and weak otherwise. The scale has been previously applied in systematic reviews of PA and cognitive functions.^{83 112}

Data synthesis and analysis

Narrative synthesis

A narrative synthesis will be conducted following the recommended structure by the Cochrane Handbook of Systematic Reviews¹¹³ and grouped by intervention type (acute and chronic). Studies will be synthesised within each intervention type by the type of outcome: cognitive, followed by neurofunctional outcomes. The relationship between ST and sedentary patterns and brain structure within chronic intervention literature will also be synthesised. If evidence is sufficient, studies explicitly testing the mediating effects of neurofunctional and/or neurostructural intervention-related changes on the relationship between the time spent in sedentary behaviours and cognitive functions will be synthesised separately. Following the results for each cognitive and brain-related outcome, the relationship between cognitive, neurofunctional and neurostructural results will be discussed in relation to the major cognitive function groupings in order to explore possible mechanisms.

Tabulated information by intervention type (acute and chronic) will include study identification (author, year), study design, participant characteristics (age, sex, body mass index, and aerobic fitness), qualitative (e.g., intervention to reduce ST vs intervention to interrupt prolonged sitting or the combination of both; the type of sedentary behaviours^{114 115} that participants engaged in during the intervention), and quantitative intervention characteristics (e.g., intervention duration and frequency of intervention sessions; frequency, duration and intensity of PA bouts), the characteristics of the comparator, outcome type, outcome measure, the timing of cognitive assessment and main results including the effect size and classification of the effect as positive, negative or null. If more than one outcome is reported, the results for each outcome will be presented within a relevant section. Within each category defined by the intervention type, intervention content and outcome, studies will be tabulated in descending order based on study quality. The relationships within each intervention type will be systematically explored. For example, similarities and differences in the effect sizes between studies designed to reduce ST and

those that focus on interrupting prolonged sitting with PA will be compared. We will discuss how PA dose may contribute to these differences. The type of sedentary behaviours defined as cognitively passive vs cognitively engaging sedentary behaviours¹¹⁴⁻¹¹⁶ will be considered in relation to intervention design. Specifically, studies will be compared on how cognitive engagement during the intervention was controlled by design. For example, choosing only cognitively engaging or only cognitively passive sedentary behaviours during an acute intervention; assessment of the moderating effects of sedentary behaviour type by including two sedentary groups (cognitively engaging vs. cognitively passive) in addition to a sedentary behaviour plus PA condition. Finally, we will consider how the timing of cognitive assessment may influence the main findings (e.g., assessing cognitive functions immediately after a PA break in acute studies compared with assessing cognitive functions at a delay following the last PA break).

Critical appraisal of the quality of evidence included in the synthesis will be presented based on the quality assessment tool for quantitative studies. The results of the quality assessment will be tabulated. The robustness of methodologies used to perform study synthesis will also be critically appraised.

Quantitative synthesis

A meta-analysis will not be attempted because our preliminary findings suggest that an insufficient ($N<8$) of RCTs are available, which tested the chronic effects of reducing sedentary behaviour duration by increasing PA on cognitive function, brain structure and function.

Patient and public involvement

Patients or public were not involved in the design of the systematic review protocol.

Ethics and dissemination

No primary data collection will be conducted as part of this systematic review. Thus, ethical approval is not required. The results of the review will be published in a peer-reviewed journal following the recommendations of the PRISMA statement.⁷⁴ We will present the results at scientific meetings and through social media platforms as appropriate.

DISCUSSION

Remaining highly sedentary increases mortality, cardiovascular and metabolic risk, which in the majority of the population is not compensated by engagement in PA.^{7 8} In contrast, relatively little is known about the effects of reducing the duration of sedentary behaviours on cognitive function, brain function and structure. Systematic synthesis of evidence in this new area can provide a guiding framework for future research by identifying research gaps and potentially fruitful areas of enquiry. This systematic review will focus on reducing the duration

of sedentary behaviours by increasing PA because sedentary behaviour duration has been most consistently related to health outcomes,^{7 8 58 117} including cognitive and brain function.^{16 44 118}

While the research into the relationships between sedentary behaviours and cognitive and brain health is growing, the conclusions, which can be drawn from these studies remain limited due to the lack of explicit mechanistic framework supporting intervention design. For example, studies testing the acute effects of interrupting prolonged sitting on cognitive functions use PA,^{22 24} as well as standing breaks (or both)^{88 119} and have yielded mixed results. The discrepancy in findings between these studies may stem from implicit assumptions on the mechanisms that support cognitive improvements associated with interrupting (fragmenting) prolonged sitting: increased energy expenditure or physiological adaptations to an upright posture (e.g., increase in lipoprotein lipase).¹²⁰ Accumulating evidence suggests that the latter may be insufficient to stimulate cognitive gains.^{24 71–73} Consequently, this systematic review will focus on the energy expenditure aspect of reducing sedentary behaviour duration by increasing PA (e.g., by interrupting prolonged sitting with PA) due to its positive effects on postprandial glycaemia and insulinaemia.⁵⁸ Consequently, the heterogeneity of included studies will be reduced.

To better understand the effects of reducing sedentary behaviour duration on cognitive functions, it is necessary to uncover how such interventions affect brain function and structure. Only two previous systematic reviews included measures of brain structure and function.^{48 50} However, their coverage of the literature was limited. The scope of these reviews was either constrained to hippocampal structures supporting long-term, and episodic memory,⁴⁸ or an adopted search strategy was not designed to capture neurofunctional changes, or changes in brain structure due to limited search terms, which included 'biomarkers' and 'neuropathology'.⁵⁰ Neither review included search terms related to structural neuroimaging or brain volume. The synthesis of studies on the effects of reducing time spent in sedentary behaviours (and prolonged sitting) and increasing PA on brain structure can support future mechanistic hypotheses. For example, several recent observational studies in children^{121–123} and adults^{41 124} have shown region-specific decrements in grey matter volume within the hippocampus,¹²⁵ medial temporal lobes,⁴¹ and frontal and parietal regions¹²³ with ST. These brain regions support episodic memory, learning and EFs. Thus, their results suggest that (in addition to increasing MVPA) reductions in ST could be an important intervention target with potential implications for cognitive development and healthy ageing.

The limitations of the current systematic review also need to be recognised. We propose to capture a broad range of studies based on research design (randomised controlled and crossover trials and NRSIs) and intervention characteristics (e.g., acute and chronic). This choice is deliberate, as our aim is to synthesise an emergent

but fast-growing area of research comprehensively. The heterogeneity of intervention designs will be managed by structured review of two main intervention effects: acute and transient effects, and chronic long-lasting effects that may entail changes in brain structure and neurotransmitter systems.⁵² The heterogeneity of research designs will be accounted for within qualitative analyses, with the attention to formally assessed study quality.¹¹¹ By including a broad range of cognitive outcomes, we introduce heterogeneity to the qualitative analyses. However, the comprehensive coverage of cognitive outcomes increases the sensitivity of our search strategy and overcomes the issue of inconsistencies in cognitive terminology within the field of PA and cognitive function.^{32 126} Our approach aligns with a previous review within PA and cognition literature¹²⁷ and is supported by the scoping survey of potential studies to be included in our systematic review. Specifically, cognitive outcomes studied within the literature on PA and cognitive functions can be broadly classified into motor speed, information processing, EFs, memory and intelligence.³² Our scoping search indicates that most studies can be classified within these categories. The inclusion of neurofunctional and neurostructural measures does not increase the heterogeneity in cognitive outcomes because the effects of interventions designed to reduce sedentary behaviour duration by increasing PA on brain structure and function will be synthesised separately. Given that only chronic interventions can lead to changes in brain structure, the heterogeneity of our synthesis will be further limited. Importantly, we balance the inclusion of multiple outcomes with an a priori focus on reducing the time spent in sedentary behaviours (and prolonged sitting) by increasing PA and energy expenditure. We will also limit our systematic review to apparently healthy participants. Lastly, this review will exclude studies that compare the effects of the type but not the duration of sedentary behaviours (e.g., cognitively passive vs cognitively engaging sedentary behaviours^{114 115}). However, when studies that include cognitively engaging vs cognitively passive comparison groups are available, they will be discussed in relation to the moderating effects of sedentary behaviour type on the effects of reducing ST with PA on cognitive and brain functions.

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REFERENCES

- Yang L, Cao C, Kantor ED, *et al.* Trends in sedentary behavior among the US population, 2001-2016. *JAMA* 2019;321:1587-97.
- Loyen A, Verloigne M, Van Hecke L, *et al.* Variation in population levels of sedentary time in European adults according to cross-European studies: a systematic literature review within DEDIPAC. *Int J Behav Nutr Phys Act* 2016;13:71.
- Prince SA, Melvin A, Roberts KC, *et al.* Sedentary behaviour surveillance in Canada: trends, challenges and lessons learned. *Int J Behav Nutr Phys Act* 2020;17:34.
- Arundell L, Fletcher E, Salmon J, *et al.* A systematic review of the prevalence of sedentary behavior during the after-school period among children aged 5-18 years. *Int J Behav Nutr Phys Act* 2016;13:93.
- Steene-Johannessen J, Hansen BH, Dalene KE, *et al.* Variations in accelerometry measured physical activity and sedentary time across Europe - harmonized analyses of 47,497 children and adolescents. *Int J Behav Nutr Phys Act* 2020;17:38.
- Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the globe. *Obes Rev* 2012;13:659-80.
- Ekelund U, Steene-Johannessen J, Brown WJ, *et al.* Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet* 2016;388:1302-10.
- Ekelund U, Tarp J, Steene-Johannessen J, *et al.* Dose-Response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ* 2019;366:l4570.
- Ekelund U, Brown WJ, Steene-Johannessen J, *et al.* Do the associations of sedentary behaviour with cardiovascular disease mortality and cancer mortality differ by physical activity level? A systematic review and harmonised meta-analysis of data from 850 060 participants. *Br J Sports Med* 2019;53:886-94.
- Wilmot EG, Edwardson CL, Achana FA, *et al.* Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia* 2012;55:2895-905.
- Tremblay MS, Aubert S, Barnes JD, *et al.* Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. *Int J Behav Nutr Phys Act* 2017;14:75.
- Chastin SFM, Schwarz U, Skelton DA, *et al.* Development of a consensus taxonomy of sedentary behaviors (sit): report of Delphi round 1. *PLoS One* 2013;8:e82313.
- Pettee Gabriel KK, Morrow JR, Woolsey A-LT. Framework for physical activity as a complex and multidimensional behavior. *J Phys Act Health* 2012;9 Suppl 1:S11-18.
- Dyrstad SM, Anderssen SA, Edvardsen E, *et al.* Cardiorespiratory fitness in groups with different physical activity levels. *Scand J Med Sci Sports* 2016;26:291-8.
- Eriksen L, Grønbaek M, Helge JW, *et al.* Cardiorespiratory fitness in 16 025 adults aged 18-91 years and associations with physical activity and sitting time. *Scand J Med Sci Sports* 2016;26:1435-43.
- Bakrania K, Edwardson CL, Khunti K, *et al.* Associations between sedentary behaviors and cognitive function: cross-sectional and prospective findings from the UK Biobank. *Am J Epidemiol* 2018;187:441-54.
- Vásquez E, Strizich G, Isasi CR, *et al.* Is there a relationship between accelerometer-assessed physical activity and sedentary behavior and cognitive function in US Hispanic/Latino adults? the Hispanic community health Study/Study of Latinos (HCHS/SOL). *Prev Med* 2017;103:43-8.
- Edwards MK, Loprinzi PD. The association between sedentary behavior and cognitive function among older adults may be attenuated with adequate physical activity. *J Phys Act Health* 2017;14:52-8.
- Falck RS, Davis JC, Liu-Ambrose T. What is the association between sedentary behaviour and cognitive function? A systematic review. *Br J Sports Med* 2017;51:800-11.
- Mazzoli E, Salmon J, Teo W-P, *et al.* Breaking up classroom sitting time with cognitively engaging physical activity: behavioural and brain responses. *PLoS One* 2021;16:e0253733.
- Altenburg TM, Chinapaw MJM, Singh AS. Effects of one versus two bouts of moderate intensity physical activity on selective attention during a school morning in Dutch primary schoolchildren: a randomized controlled trial. *J Sci Med Sport* 2016;19:820-4.
- Bergouignan A, Legget KT, De Jong N, *et al.* Effect of frequent interruptions of prolonged sitting on self-perceived levels of energy, mood, food cravings and cognitive function. *Int J Behav Nutr Phys Act* 2016;13:113.
- Chrismas BCR, Taylor L, Cherif A, *et al.* Breaking up prolonged sitting with moderate-intensity walking improves attention and executive function in Qatari females. *PLoS One* 2019;14:e0219565.
- Mullane SL, Buman MP, Zeigler ZS, *et al.* Acute effects on cognitive performance following bouts of standing and Light-intensity physical activity in a simulated workplace environment. *J Sci Med Sport* 2017;20:489-93.
- Vincent GE, Jay SM, Sargent C, *et al.* The impact of breaking up prolonged sitting on glucose metabolism and cognitive function when sleep is restricted. *Neurobiol Sleep Circadian Rhythms* 2018;4:17-23.
- Wanders L, Cuijpers I, Kessels RPC, *et al.* Impact of prolonged sitting and physical activity breaks on cognitive performance, perceivable benefits, and cardiometabolic health in overweight/obese adults: the role of meal composition. *Clin Nutr* 2021;40:2259-69.
- Dunstan DW, Wheeler MJ, Ellis KA, *et al.* Interacting effects of exercise with breaks in sitting time on cognitive and metabolic function in older adults: rationale and design of a randomised crossover trial. *Ment Health Phys Act* 2018;15:11-16.
- Wheeler MJ, Green DJ, Ellis KA, *et al.* Distinct effects of acute exercise and breaks in sitting on working memory and executive function in older adults: a three-arm, randomised cross-over trial to evaluate the effects of exercise with and without breaks in sitting on cognition. *Br J Sports Med* 2020;54:776-81.
- Magnon V, Vallet GT, Auxiette C. Sedentary behavior at work and cognitive functioning: a systematic review. *Front Public Health* 2018;6:239.
- Ojo SO, Bailey DP, Chater AM, *et al.* The impact of active workstations on workplace productivity and performance: a systematic review. *Int J Environ Res Public Health* 2018;15:417.
- Burnet K, Blackwell J, Kelsch E, *et al.* Cerebrovascular function response to prolonged sitting combined with a high-glycemic index meal: a double-blind, randomized cross-over trial. *Psychophysiology* 2021;58:e13830.
- Pontifex MB, McGowan AL, Chandler MC, *et al.* A primer on investigating the after effects of acute bouts of physical activity on cognition. *Psychol Sport Exerc* 2019;40:1-22.
- Chang YK, Labban JD, Gapin JL, *et al.* The effects of acute exercise on cognitive performance: a meta-analysis. *Brain Res* 2012;1453:87-101.
- Loyen A, Clarke-Cornwell AM, Anderssen SA, *et al.* Sedentary time and physical activity surveillance through accelerometer pooling in four European countries. *Sports Med* 2017;47:1421-35.
- Matthews CE, Chen KY, Freedson PS, *et al.* Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am J Epidemiol* 2008;167:875-81.

- 36 Evenson KR, Wen F, Metzger JS, *et al.* Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults. *Int J Behav Nutr Phys Act* 2015;12:20.
- 37 van Ekris E, Wijndaele K, Altenburg TM, *et al.* Tracking of total sedentary time and sedentary patterns in youth: a pooled analysis using the International children's Accelerometry database (ICAD). *Int J Behav Nutr Phys Act* 2020;17:65.
- 38 Jefferis BJ, Sartini C, Shiroma E, *et al.* Duration and breaks in sedentary behaviour: accelerometer data from 1566 community-dwelling older men (British regional heart study). *Br J Sports Med* 2015;49:1591–4.
- 39 Burzynska AZ, Chaddock-Heyman L, Voss MW, *et al.* Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. *PLoS One* 2014;9:e107413.
- 40 Bronas UG, Steffen A, Dion C, *et al.* Sedentary time and white matter hyperintensity volume in older adults. *Med Sci Sports Exerc* 2019;51:1613–8.
- 41 Siddarth P, Burggren AC, Eyre HA, *et al.* Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. *PLoS One* 2018;13:e0195549.
- 42 Kochunov P, Glahn DC, Lancaster J, *et al.* Fractional anisotropy of cerebral white matter and thickness of cortical gray matter across the lifespan. *Neuroimage* 2011;58:41–9.
- 43 Coelho A, Fernandes HM, Magalhães R, *et al.* Signatures of white-matter microstructure degradation during aging and its association with cognitive status. *Sci Rep* 2021;11:4517.
- 44 Pindus DM, Zwilling CE, Jarrett JS, *et al.* Opposing associations between sedentary time and decision-making competence in young adults revealed by functional connectivity in the dorsal attention network. *Sci Rep* 2020;10:13993.
- 45 Dosenbach NUF, Fair DA, Cohen AL, *et al.* A dual-networks architecture of top-down control. *Trends Cogn Sci* 2008;12:99–105.
- 46 Pindus DM, Edwards CG, Walk AM, *et al.* Sedentary time is related to deficits in response inhibition among adults with overweight and obesity: an accelerometry and event-related brain potentials study. *Psychophysiology* 2021;58:e13843.
- 47 Hartman YAW, Tillmans LCM, Benschop DL, *et al.* Long-Term and acute benefits of reduced sitting on vascular flow and function. *Med Sci Sports Exerc* 2021;53:341–50.
- 48 Loprinzi P. The effects of sedentary behavior on memory and markers of memory function: a systematic review. *Phys Sportsmed* 2019;47:387–94.
- 49 Sui W, Smith ST, Fagan MJ, *et al.* The effects of sedentary behaviour interventions on work-related productivity and performance outcomes in real and simulated office work: a systematic review. *Appl Ergon* 2019;75:27–73.
- 50 Olanrewaju O, Stockwell S, Stubbs B, *et al.* Sedentary behaviours, cognitive function, and possible mechanisms in older adults: a systematic review. *Aging Clin Exp Res* 2020;32:969–84.
- 51 Carson V, Kuzik N, Hunter S, *et al.* Systematic review of sedentary behavior and cognitive development in early childhood. *Prev Med* 2015;78:115–22.
- 52 Voss MW, Carr LJ, Clark R, *et al.* Revenge of the “sit” II: Does lifestyle impact neuronal and cognitive health through distinct mechanisms associated with sedentary behavior and physical activity? *Ment Health Phys Act* 2014;7:9–24.
- 53 Vaynman S, Gomez-Pinilla F. Revenge of the “Sit”: How lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. *J Neurosci Res* 2006;84:699–715.
- 54 Wheeler MJ, Dempsey PC, Grace MS, *et al.* Sedentary behavior as a risk factor for cognitive decline? A focus on the influence of glycemic control in brain health. *Alzheimers Dement* 2017;3:291–300.
- 55 Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes* 2007;56:2655–67.
- 56 Matthews CE, Carlson SA, Saint-Maurice PF, *et al.* Sedentary behavior in U.S. adults: fall 2019. *Med Sci Sports Exerc* 2021;53:2512–9.
- 57 Australian Bureau of Statistics. *Australian health survey: physical activity 2011–12*. Canberra, Australia, 2013.
- 58 Loh R, Stamatakis E, Folkerts D, *et al.* Effects of interrupting prolonged sitting with physical activity breaks on blood glucose, insulin and triacylglycerol measures: a systematic review and meta-analysis. *Sports Med* 2020;50:295–330.
- 59 Pou KM, Massaro JM, Hoffmann U, *et al.* Patterns of abdominal fat distribution: the Framingham heart study. *Diabetes Care* 2009;32:481–5.
- 60 Schwartz DH, Leonard G, Perron M, *et al.* Visceral fat is associated with lower executive functioning in adolescents. *Int J Obes* 2013;37:1336–43.
- 61 Zsido RG, Heinrich M, Slavich GM, *et al.* Association of estradiol and visceral fat with structural brain networks and memory performance in adults. *JAMA Netw Open* 2019;2:e196126.
- 62 Ozato N, Saitou S, Yamaguchi T, *et al.* Association between visceral fat and brain structural changes or cognitive function. *Brain Sci* 2021;11:1036.
- 63 Charlett OP, Morari V, Bailey DP. Impaired postprandial glucose and NO improvement in other cardiometabolic responses or cognitive function by breaking up sitting with bodyweight resistance exercises: a randomised crossover trial. *J Sports Sci* 2021;39:792–800.
- 64 Edwardson CL, Gorely T, Davies MJ, *et al.* Association of sedentary behaviour with metabolic syndrome: a meta-analysis. *PLoS One* 2012;7:e34916.
- 65 Geijselaers SLC, Sep SJS, Stehouwer CDA, *et al.* Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol* 2015;3:75–89.
- 66 Benn M, Nordestgaard BG, Tybjaerg-Hansen A, *et al.* Impact of glucose on risk of dementia: Mendelian randomisation studies in 115,875 individuals. *Diabetologia* 2020;63:1151–61.
- 67 Wang D-Q, Wang L, Wei M-M, *et al.* Relationship between type 2 diabetes and white matter hyperintensity: a systematic review. *Front Endocrinol* 2020;11:595962.
- 68 Moulton CD, Costafreda SG, Horton P, *et al.* Meta-Analyses of structural regional cerebral effects in type 1 and type 2 diabetes. *Brain Imaging Behav* 2015;9:651–62.
- 69 Macpherson H, Formica M, Harris E, *et al.* Brain functional alterations in Type 2 Diabetes - A systematic review of fMRI studies. *Front Neuroendocrinol* 2017;47:34–46.
- 70 Mansoubi M, Pearson N, Clemes SA, *et al.* Energy expenditure during common sitting and standing tasks: examining the 1.5 Met definition of sedentary behaviour. *BMC Public Health* 2015;15:516.
- 71 Bailey DP, Locke CD. Breaking up prolonged sitting with Light-intensity walking improves postprandial glycemia, but breaking up sitting with standing does not. *J Sci Med Sport* 2015;18:294–8.
- 72 Yates T, Edwardson CL, Celis-Morales C, *et al.* Metabolic effects of breaking prolonged sitting with standing or light walking in older South Asians and white Europeans: a randomized acute study. *J Gerontol A Biol Sci Med Sci* 2020;75:139–46.
- 73 Larsen RN, Dempsey PC, Dillon F, *et al.* Does the type of activity “break” from prolonged sitting differentially impact on postprandial blood glucose reductions? An exploratory analysis. *Appl Physiol Nutr Metab* 2017;42:897–900.
- 74 Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- 75 Higgins JP, Thomas J, Chandler J. Chapter 24, Including non-randomized studies on intervention effects. In: *Cochrane Handbook for Systematic Reviews of Interventions [Internet]*. Hoboken, NJ: Wiley, 2019: 595–620. <https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604>
- 76 Ory MG, Anderson LA, Friedman DB, *et al.* Cancer prevention among adults aged 45–64 years: setting the stage. *Am J Prev Med* 2014;46:S1–6.
- 77 Singh-Manoux A, Kivimaki M, Glymour MM, *et al.* Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ* 2012;344:d7622.
- 78 Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging* 2009;30:507–14.
- 79 Zelazo PD, Müller U, Frye D, *et al.* The development of executive function in early childhood. *Monogr Soc Res Child Dev* 2003;68:vii–137.
- 80 Bunge SA, Zelazo PD. A brain-based account of the development of rule use in childhood. *Curr Dir Psychol Sci* 2006;15:118–21.
- 81 Davidson MC, Amso D, Anderson LC, *et al.* Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia* 2006;44:2037–78.
- 82 Donnelly JE, Hillman CH, Castelli D, *et al.* Physical activity, fitness, cognitive function, and academic achievement in children: a systematic review. *Med Sci Sports Exerc* 2016;48:1197–222.
- 83 Álvarez-Bueno C, Pesce C, Cervero-Redondo I, *et al.* The Effect of Physical Activity Interventions on Children's Cognition and Metacognition: A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry* 2017;56:729–38.
- 84 Nelson RK, Horowitz JF. Acute exercise ameliorates differences in insulin resistance between physically active and sedentary overweight adults. *Appl Physiol Nutr Metab* 2014;39:811–8.

- 85 Broadney MM, Belcher BR, Berrigan DA, *et al.* Effects of interrupting sedentary behavior with short bouts of moderate physical activity on glucose tolerance in children with overweight and obesity: a randomized crossover trial. *Diabetes Care* 2018;41:2220–8.
- 86 Edwards MK, Loprinzi PD. Effects of a sedentary intervention on cognitive function. *Am J Health Promot* 2018;32:595–605.
- 87 van Dongen EV, Kersten IHP, Wagner IC, *et al.* Physical exercise performed four hours after learning improves memory retention and increases hippocampal pattern similarity during retrieval. *Curr Biol* 2016;26:1722–7.
- 88 Duvivier BMFM, Schaper NC, Koster A, *et al.* Benefits of substituting sitting with standing and walking in free-living conditions for cardiometabolic risk markers, cognition and mood in overweight adults. *Front Physiol* 2017;8:353.
- 89 Pišot R, Marusic U, Biolo G, *et al.* Greater loss in muscle mass and function but smaller metabolic alterations in older compared with younger men following 2 wk of bed rest and recovery. *J Appl Physiol* 2016;120:922–9.
- 90 McGlory C, von Allmen MT, Stokes T, *et al.* Failed recovery of glycemic control and myofibrillar protein synthesis with 2 wk of physical inactivity in overweight, prediabetic older adults. *J Gerontol A Biol Sci Med Sci* 2018;73:1070–7.
- 91 Kramer AF, Colcombe S. Fitness effects on the cognitive function of older adults: a meta-analytic Study-Revisited. *Perspect Psychol Sci* 2018;13:213–7.
- 92 Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* 2003;14:125–30.
- 93 Chaddock L, Pontifex MB, Hillman CH, *et al.* A review of the relation of aerobic fitness and physical activity to brain structure and function in children. *J Int Neuropsychol Soc* 2011;17:975–85.
- 94 Kao S-C, Cadenas-Sanchez C, Shigeta TT, *et al.* A systematic review of physical activity and cardiorespiratory fitness on P3b. *Psychophysiology* 2020;57:e13425.
- 95 Talukdar T, Nikolaidis A, Zwilling CE, *et al.* Aerobic fitness explains individual differences in the functional brain connectome of healthy young adults. *Cereb Cortex* 2018;28:3600–9.
- 96 Miles-Chan JL, Fares E-J, Berkachy R, *et al.* Standing economy: does the heterogeneity in the energy cost of posture maintenance reside in differential patterns of spontaneous weight-shifting? *Eur J Appl Physiol* 2017;117:795–807.
- 97 Gonzales MM, Tarumi T, Miles SC, *et al.* Insulin sensitivity as a mediator of the relationship between BMI and working memory-related brain activation. *Obesity* 2010;18:2131–7.
- 98 Ryan JP, Karim HT, Aizenstein HJ, *et al.* Insulin sensitivity predicts brain network connectivity following a meal. *Neuroimage* 2018;171:268–76.
- 99 Niemi GM, Skinner SK, Walk AM, *et al.* Oral glucose tolerance is associated with neuroelectric indices of attention among adults with overweight and obesity. *Obesity* 2018;26:1550–7.
- 100 Sherzai AZ, Shaheen M, Yu JJ, *et al.* Insulin resistance and cognitive test performance in elderly adults: National health and nutrition examination survey (NHANES). *J Neurol Sci* 2018;388:97–102.
- 101 Martin K, Porritt K, Aromataris E. Effectiveness of interventions to control screen use and children's sleep, cognitive and behavioral outcomes. *JBI Database System Rev Implement Rep* 2018;16:1338–45.
- 102 Kostyrka-Allchorne K, Cooper NR, Simpson A. The relationship between television exposure and children's cognition and behaviour: A systematic review. *Developmental Review* 2017;44:19–58.
- 103 Poitras V, Tremblay M. Sedentary behaviour and brain structure, brain function, and cognition in children and youth: a systematic review of reviews and randomized controlled trials.
- 104 Lyons EJ, Tate DF, Ward DS, *et al.* Energy expenditure and enjoyment during video game play: differences by game type. *Med Sci Sports Exerc* 2011;43:1987–93.
- 105 Miyachi M, Yamamoto K, Ohkawara K, *et al.* Mets in adults while playing active video games: a metabolic chamber study. *Med Sci Sports Exerc* 2010;42:1149–53.
- 106 Blackburn NE, Wilson JJ, McMullan II, *et al.* The effectiveness and complexity of interventions targeting sedentary behaviour across the lifespan: a systematic review and meta-analysis. *Int J Behav Nutr Phys Act* 2020;17:53.
- 107 Gazzaniga MS, Ivry RB, Mangun GR. *Cognitive neuroscience. The biology of mind.* New York, London: WW Norton & Company, 2008.
- 108 Lezak MD. *Neuropsychological assessment.* Oxford: Oxford University Press, 2004.
- 109 Higgins JP, Thomas J, Chandler J. Chapter 5, Collecting data. In: *Cochrane Handbook for Systematic Reviews of Interventions [Internet]*. Hoboken, NJ: Wiley, 2019: 109–41. <https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604>
- 110 Higgins JP, Thomas J, Chandler J. Chapter 1, Starting a review. In: *Cochrane Handbook for Systematic Reviews of Interventions [Internet]*. Hoboken, NJ: Wiley, 2019: 1–12. <https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604>
- 111 Thomas BH, Ciliska D, Dobbins M, *et al.* A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs* 2004;1:176–84.
- 112 Singh AS, Saliassi E, van den Berg V, *et al.* Effects of physical activity interventions on cognitive and academic performance in children and adolescents: a novel combination of a systematic review and recommendations from an expert panel. *Br J Sports Med* 2019;53:640–7.
- 113 Higgins JP, Thomas J, Chandler J. Chapter 9, Summarizing study characteristics and preparing for synthesis. In: *Cochrane Handbook for Systematic Reviews of Interventions [Internet]*. Hoboken, NJ: Wiley, 2019: 229–40. <https://onlinelibrary.wiley.com/doi/book/10.1002/9781119536604>
- 114 Hallgren M, Dunstan DW, Owen N. Passive versus mentally active sedentary behaviors and depression. *Exerc Sport Sci Rev* 2020;48:20–7.
- 115 Taylor WC. Understanding variations in the health consequences of sedentary behavior: a taxonomy of social interaction, novelty, choice, and cognition. *J Aging Phys Act* 2022;30:153–61.
- 116 Kikuchi H, Inoue S, Sugiyama T, *et al.* Distinct associations of different sedentary behaviors with health-related attributes among older adults. *Prev Med* 2014;67:335–9.
- 117 Hadgraft NT, Winkler E, Climie RE, *et al.* Effects of sedentary behaviour interventions on biomarkers of cardiometabolic risk in adults: systematic review with meta-analyses. *Br J Sports Med* 2021;55:144–54.
- 118 Kesse-Guyot E, Charreire H, Andreeva VA, *et al.* Cross-sectional and longitudinal associations of different sedentary behaviors with cognitive performance in older adults. *PLoS One* 2012;7:e47831.
- 119 Penning A, Okely AD, Trost SG, *et al.* Acute effects of reducing sitting time in adolescents: a randomized cross-over study. *BMC Public Health* 2017;17:657.
- 120 Zderic TW, Hamilton MT. Physical inactivity amplifies the sensitivity of skeletal muscle to the lipid-induced downregulation of lipoprotein lipase activity. *J Appl Physiol* 2006;100:249–57.
- 121 Rodriguez-Ayllon M, Derks IPM, van den Dries MA, *et al.* Associations of physical activity and screen time with white matter microstructure in children from the general population. *Neuroimage* 2020;205:116258.
- 122 Rodriguez-Ayllon M, Esteban-Cornejo I, Verdejo-Román J, *et al.* Physical activity, sedentary behavior, and white matter microstructure in children with overweight or obesity. *Med Sci Sports Exerc* 2020;52:1218–26.
- 123 Zavala-Crichton JP, Esteban-Cornejo I, Solis-Urra P, *et al.* Association of sedentary behavior with brain structure and intelligence in children with overweight or obesity: the ActiveBrains project. *JCM* 2020;9:1101.
- 124 Spartano NL, Davis-Plourde KL, Himali JJ, *et al.* Association of Accelerometer-Measured Light-intensity physical activity with brain volume: the Framingham heart study. *JAMA Netw Open* 2019;2:e192745.
- 125 Migueles JH, Cadenas-Sanchez C, Esteban-Cornejo I, *et al.* Associations of objectively-assessed physical activity and sedentary time with hippocampal gray matter volume in children with overweight/obesity. *J Clin Med* 2020;9:1080.
- 126 Angevaren M, Aufdemkampe G, Verhaar HJJ, *et al.* Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* 2008:CD005381.
- 127 Ludysa S, Gerber M, Pühse U, *et al.* Systematic review and meta-analysis investigating moderators of long-term effects of exercise on cognition in healthy individuals. *Nat Hum Behav* 2020;4:603–12.