Neuroscience and Biobehavioral Reviews 140 (2022) 104802

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Sedentary behaviour and brain health in middle-aged and older adults: A systematic review

Carlijn M. Maasakkers [a], Ralf W.J. Weijs [b], Claudia Dekkers [a], Paul A. Gardiner [c,d,e], Romy Ottens [a], Marcel G.M. Olde Rikkert [f], René J.F. Melis [a], Dick H.J. Thijssen [b,g,1], Jurgen A.H.R. Claassen [f,*,1]

[a] Department of Geriatrics/Radboud Alzheimer Center, Radboud Institute for Health Sciences, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6500 HB Nijmegen, the Netherlands
[b] Department of Physiology, Radboud Institute for Health Sciences, Radboud University Medical Center, Philips van Leydenlaan 15, 6500 HB Nijmegen, the Netherlands
[c] Centre for Health Services Research, Faculty of Medicine, The University of Queensland, 34 Cornwall Street, 4102 Brisbane, Australia
[d] School of Kinesiology, The University of Western Ontario, 1151 Richmond Street, N6A 3K7 London, Canada
[e] School of Health and Medical Sciences, University of Southern Queensland, Ipswich 4305 Australia
[f] Department of Geriatrics/Radboud Alzheimer Center, Donders Institute for Brain Cognition and Behaviour, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6500 HB Nijmegen, the Netherlands
[g] Research Institute for Sport and Exercise Science, Liverpool John Moores University, Byrom Street, L3 3AF Liverpool, United Kingdom

ARTICLE INFO

Keywords:
Sedentary behaviour
Neurodegeneration
Brain health
Sitting
Dementia

ABSTRACT

Sedentary behaviour may increase the risk of dementia. Studying physiological effects of sedentary behaviour on cerebral health may provide new insights into the nature of this association. Accordingly, we reviewed if and how acute and habitual sedentary behaviour relate to brain health factors in middle-aged and older adults (≥45 years). Four databases were searched. Twenty-nine studies were included, with mainly cross-sectional designs. Nine studies examined neurotrophic factors and six studied functional brain measures, with the majority of these studies finding no associations with sedentary behaviour. The results from studies on sedentary behaviour and cerebrovascular measures were inconclusive. There was a tentative association between habitual sedentary behaviour and structural white matter health. An explanatory pathway for this effect might relate to the immediate vascular effects of sitting, such as elevation of blood pressure. Nevertheless, due to the foremost cross-sectional nature of the available evidence, reverse causality could also be a possible explanation. More prospective studies are needed to understand the potential of sedentary behaviour as a target for brain health.

1. Introduction

Physical inactivity is one of the twelve modifiable risk factors that together might explain 40% of the global dementia cases, according to the Lancet Commission (Livingston et al., 2020). In the absence of pharmaceutical treatments for dementia, focus on altering these modifiable risk factors through lifestyle changes has become increasingly important (Norton et al., 2014). The impact of physical inactivity on the risk of dementia is in part related to the neuroprotective effects of exercise (Chieffi, 2017; Rashid, 2020). Exercise increases cerebral blood flow (CBF) and neurotrophic factors, which have a positive impact on angiogenesis and neurogenesis (Rashid et al., 2020). These effects translate to beneficial effects on structural brain measures associated with cognitive function (Chieffi et al., 2017). However, exercise is not always feasible for older adults due to physical limitations. Independent from exercise, physical inactivity also entails the fact that most people spend a substantial part of their day in sedentary activities (Brownson et al., 2005). Sedentary behaviour (SB) is known to have multiple detrimental cardiovascular and metabolic effects (Carter et al., 2017), which are not completely reversed by exercise (Knaeps et al., 2018; Patterson et al., 2018). Interestingly, many of these cardiovascular and metabolic effects of SB, such as hypertension, in turn have been identified as vascular risk factors for dementia (Claassen, 2015).

In light of this rationale, excessive amounts of SB might be a risk

* Correspondence to: Department of Geriatrics (route 696), Geert Grooteplein Zuid 10, 6525 GA, Nijmegen or P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.
E-mail address: Jurgen.Claassen@radboudumc.nl (J.A.H.R. Claassen).
[1] Both authors share senior-authorship.

https://doi.org/10.1016/j.neubiorev.2022.104802
Received 10 March 2021; Received in revised form 23 July 2022; Accepted 26 July 2022
Available online 28 July 2022

factor for dementia and cognitive decline via its cardiovascular effects. If proven true, this would open up possibilities to target sitting as a feasible way to intervene in efforts to prevent cognitive decline. However, before starting intervention programmes that aim to reduce sitting to prevent or slow down the progression of dementia, more evidence is needed to link SB and cognitive function. Recent epidemiological studies were unable to demonstrate an association between SB and cognitive decline (Maasakkers, 2020a; Olanrewaju, 2020), possibly due to the long time needed for SB to result in cognitive decline. Therefore, studying more proximal physiological effects of SB on the brain may provide novel insights. Moreover, several studies specifically focused on healthy young individuals, whilst it takes decades before these individuals may experience the potential detrimental effects of SB. Therefore, it seems more relevant to examine if these potential physiological manifestations in the brain as a consequence of a sedentary lifestyle are already present in middle-aged and older adults. Focusing on these age groups, and exploring the potential relation with cognitive decline, is therefore clinically relevant. With this field still in its infancy, studies have only recently started to investigate associations between SB and the brain. Summarising the evidence currently available in the literature will inform how to move this field forward. Therefore, we aimed to systematically review if and how acute and habitual SB are associated with brain health in middle-aged and older adults. By summarising these studies we will get a first impression if there is a physiological rationale for an association between SB and dementia burden.

2. Method

2.1. Search strategy

This systematic review was registered in PROSPERO (CRD42020192851). PubMed, Embase, PsycINFO, and Web of Science were searched on June 19, 2020, followed by an updated search on April 26, 2022. The search strategy comprised three components: sedentary behaviour, brain health, and middle-aged (45–64 years) and older adults (≥65 years). With the attention in the SB-field only having shifted to the brain in the past few years, we expected a compact amount of evidence. Accordingly, we decided to use the inclusive term of brain health to gather a broad overview of all available studies on physiological measures of brain health. This was done by including general terms, such as 'cerebral' or 'brain', as well as more specific terms, e.g., 'plasticity', 'BDNF', or 'atrophy'. The detailed search strategy can be found in Supplement 1. Furthermore, a manual search in reference lists and citations of included articles and relevant reviews was carried out. Duplicate articles were automatically removed using Endnote citation manager (Endnote X9, Clarivate Analytics, Philadelphia, USA). A manual screening for duplicates based on title was conducted as an additional control.

2.2. Study selection

Two reviewers (initial search, CD and CM; search update, RW and a medical student) independently screened titles and abstracts for suitability, with decisions being recorded in Rayyan (Rayyan, Qatar Computing Research Institute, Doha, Qatar) (Ouzzani et al., 2016). In case of disagreement between the two reviewers, a third reviewer (RM) was consulted to resolve different viewpoints. Remaining articles were screened full-text for eligibility. Articles were included if they were English articles that were published in a peer-reviewed journal. Conference abstracts, reviews and meta-analyses were excluded. Only studies with participants with a mean age of ≥ 45 years were included. Articles were excluded if the study population was characterised by one of the following conditions: neurological diseases, cognitive impairment or dementia, psychiatric disorders, substance abuse disorders, learning disorders, a history of traumatic brain injury, or inflammatory diseases. Studies had to operationalise the exposure variable as either acute sitting (i.e. observed) in experimental lab investigations or as a measure of habitual sedentary time in observational and intervention studies. For experimental studies, uninterrupted sitting needed to be compared to an interrupted sitting condition. The observational studies needed to include an association with a physiological brain health factor as an outcome. This means other measures such as pure cognitive function tests were excluded.

2.3. Data extraction

Review data was extracted from the included articles with a predesigned table by CD and independently checked by CM or RW. Information that was extracted included sample characteristics, information on the SB indicator, brain health measures, and main findings.

Study quality and risk of bias were independently assessed *in duplo* with the QualSyst Tool by CD and CM or RW. The QualSyst tool, with a specific version for quantitative studies, is applicable to both observational and experimental study designs (Kmet et al., 2004), including fourteen items concerning among others participant recruitment, exposure administration, and confounder correction. Items can be scored 'yes' (2), 'partial' (1), 'no' (0), and 'NA'. Subsequently, a sum score is calculated that is divided by the maximum score possible resulting in a score ranging from 0 to 1 for each study, with 1 representing the highest quality score and indicating lowest risk of bias.

3. Results

3.1. Study selection and characteristics

The literature searches yielded 7026 articles after duplicate removal, of which the full text of 115 articles were screened. Twenty-nine studies met the inclusion criteria (see Supplement 2 for PRISMA flow chart). Based on the outcome measures of the included studies, we categorised them into four subcategories: 1) Neurotrophic factors and biomolecules, 2) Cerebrovascular health, 3) Structural brain measures, and 4) Functional brain measures. Six studies involved an experimental randomised cross-over trial on the acute effects of 3–8 h of uninterrupted sitting compared to interrupted sitting (Table 1) (Hartman, 2021; Heiland, 2021; Maasakkers, 2020b; Wennberg, 2016; Wheeler, 2019, 2020). One of these studies additionally included a longitudinal component as part of an intervention study aimed at reducing sitting time (Hartman et al., 2021). Taking this study into account, three of the twenty-four observational studies used longitudinal data (Arnardottir, 2016; Burzynska, 2017; Hartman, 2021), while the other twenty-one studies performed cross-sectional analyses. Findings from these studies on associations between (changes in) habitual SB and brain health are summarised in Table 2, categorised by outcome measure (note that four studies (Burzynska, 2015; Engeroff, 2018; Launer, 2015; Maasakkers, 2021) are listed multiple times as they reported outcomes across multiple categories). Sample sizes varied from 12 to 67 for experimental studies, and 24 to 2,109 for observational studies. Mean age ranged between 46 (9) and 79 (4). In the observational studies, SB was evaluated by self-report (n = 5, (Launer et al., 2015); Bronas et al. (2019); Paxton et al. (2014); Siddarth et al., 2018; Spartano et al., 2019), or with devices (ActiGraph n = 10, ActivPAL n = 3, Actical n = 2, GENEActiv n = 2, Active style Pro n = 1, Xiaomi Mi Band n = 1). Due to the broad range of outcome measures, we discuss the results in a narrative manner.

3.2. Neurotrophic factors and biomolecules

Neurotrophic factors and other biomolecules (e.g., brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and amyloid β-42 (Aβ42)) were the main outcome of two experimental studies (Wennberg, 2016; Wheeler, 2020) and seven studies involving cross-sectional observational analyses (Engeroff, 2018; Judice, 2021; Law, 2018; Paxton, 2014; Spartano, 2017, 2019, 2022). To measure

Table 1
Included experimental studies on acute cerebral effects of sitting.

Study	N total (% female)	Mean age (SD)	Intervention arms	Outcome measure (instrument used)	Main results
Neurotrophic factors and biomolecules					
Engeroff et al., 2018	67 (52%)	67 (7)	● 8 hrs sitting ● Exercise bout + 6.5 hrs sitting ● Exercise bout + 6.5 hrs interrupted sitting with every 30 min 3 min walking	BDNF area under the curve (ELISA on blood samples)	Sitting < Exercise + sitting Sitting < Exercise + interrupted sitting Exercise + sitting = Exercise + interrupted sitting
Wennberg et al. (2016)	19 (47%)	60 (8)	● 5 hrs sitting ● 5 hrs interrupted sitting with every 30 min 3 min walking	BDNF (assay on blood samples) Cortisol (assay on blood samples) Catechols[a] (HPLC with CD on blood samples)	No difference in temporal changes by condition No difference in temporal changes by condition No difference in temporal changes by condition
Cerebrovascular health					
Ekelund et al., 2019[b]	12 (17%)	70 (7)	● 8 hrs sitting ● Exercise bout + 6.5 hrs sitting ● Exercise bout + 6.5 hrs interrupted sitting with every 30 min 3 min walking	CBFV temporal pattern (TCD in MCA) CBFV day average (TCD in MCA)	Sitting ↓ vs both Exercise + sitting ↑ and Exercise + interrupted sitting ↑ Exercise + sitting > Sitting Exercise + sitting > Exercise + interrupted sitting
Maasakkers et al. (2020b)	22 (41%)	78 (5)	● 3 hrs sitting ● 3 hrs interrupted sitting with every 30 min 2 min walking Both 2x with 1x high and 1x low mental activity	CBFV (TCD in MCA) Cerebral autoregulation (TCD in MCA + Finapres) Cerebral vasomotor reactivity (TCD in MCA) Cerebral resistance (TCD in MCA + Finapres)	No effect over time or between conditions Over time VLF phase ↑, no effect between conditions No effect LF phase and gain over time or between conditions No effect over time or between conditions Over time ↑, no effect between conditions
Hartman et al. (2021)	24 (63%)[c]	65 (5)	● 3 hrs sitting ● 3 hrs interrupted sitting with every 30 min 2 min walking	CBFV during rest (TCD in MCA) Cerebrovascular conductance index during rest (TCD in MCA + Finapres) Cerebral vasomotor reactivity (TCD in MCA) Cerebral autoregulation (TCD in MCA + Finapres)	No effect over time or between conditions No effect over time or between conditions No effect over time or between conditions No effect over time or between conditions
Giurgiu et al., 2020	13 (38%)	51 (5)	● 3 hrs sitting with every 30 min 3 min seated social interactions ● 3 hrs interrupted sitting with every 30 min 3 min walking ● 3 hrs interrupted sitting with every 30 min 3 min simple resistance activities	Changes in whole, left and right prefrontal (de) oxygenated hemoglobin (NIRS) by 1-, 2- and 3-back cognitive task-related activation	No effect over time in the uninterrupted (social) sitting condition and no time-by-condition interactions

Abbreviations: BDNF=brain-derived neurotrophic factor, CBFV=cerebral blood flow velocity, CD=coulometric detection, ELISA=enzyme-linked immunosorbent assay, HPLC=high-performance liquid chromatography, MCA=middle cerebral artery, N=number, NIRS=near-infrared spectroscopy, LF=low-frequency, SD=standard deviation, TCD=transcranial doppler, VLF=very low frequency.
[a] Norepinephrine, dihydroxyphenylglycol, epinephrine, dihydroxyphenylalanine, dopamine, dihydroxyphenylglycol/norepinephrine.
[b] Substudy of the same randomised cross-over trial of Wheeler et al, 2019 (Ekelund et al., 2019).
[c] Cerebrovascular measurements were performed in 23 participants.

these outcomes, all studies used immunoassays on blood samples or cerebrospinal fluid. One study additionally used high-performance liquid chromatography. BDNF and IGF-1 are growth factors that are beneficial for the brain due to their link with long-term memory (Bekinschtein et al., 2008), as well as neuro- and angiogenesis (Torres-Aleman, 2010). The two experimental studies evaluated BDNF levels before and after 5 and 8 hrs of (un)interrupted sitting, but found no differences between conditions (Wennberg, 2016; Wheeler, 2020). However, 30 min of moderate intensity walking acutely increased BDNF levels (Wheeler et al., 2020), a finding in line with studies confirming exercise is able to increase BDNF levels (Szuhany et al., 2015), primarily by upregulating hippocampal mRNA expression (Oliff et al., 1998). Related to the observational studies, no association between BDNF and habitual SB was seen in three observational studies (Judice, 2021; Spartano, 2019, 2022), combining analyses that involved 3579 participants with a mean age ranging from 47 (9) to 60 (10) years. Another cross-sectional study with 50 participants aged 75 (7) found an inverse correlation (Engeroff et al., 2018).

IGF-1 is known to increase after exercise (Spartano et al., 2019), which may mediate some of the beneficial effects of physical activity on the brain (Voss et al., 2014). None of the three cross-sectional studies included in this review found an association between IGF-1 and habitual SB (Paxton, 2014; Spartano, 2017, 2019).

One study investigated Alzheimer's Disease (AD) biomarkers. Higher levels of SB were associated with lower cerebrospinal fluid Aβ42 levels, but were not associated with other AD biomarkers (Law et al., 2018). These lower cerebrospinal fluid Aβ42 levels indicate greater brain parenchymal amyloid burden and are already observed in the pre-clinical phase of AD (Andreasen et al., 2003). Their presence in this group might be explained by the fact that, even though they were cognitively healthy, this study included participants at risk for AD (Law et al., 2018). This suggests that in that study, pre-clinical AD was associated with increased SB.

3.3. Cerebrovascular health

Studies focusing on cerebrovascular health used transcranial Doppler (n = 4) or arterial spin labelling MRI (n = 4) to measure cerebrovascular perfusion outcomes, or have used near-infrared spectroscopy (n = 2) to measure prefrontal oxygenation.

Four experimental studies examined the acute impact of 3–8 hrs of uninterrupted sitting on cerebrovascular perfusion (Hartman, 2021; Maasakkers, 2020b; Wheeler, 2019) or prefrontal oxygenation (Heiland et al., 2021). Since sitting is associated with impaired blood flow and vascular function in the lower extremities (Carter et al., 2017), the hypothesis was that similarly negative effects may be present in the

Table 2
Included observational studies on cerebral effects of habitual sitting.

Study	N total (% female)	Mean age (SD)	SB measurement[a]	Outcome measure (instrument used)	Covariate adjustment	Main results
Neurotrophic factors and biomolecules						
Law et al., 2018	85 (61%)	64 (5)	ActiGraph GT3X+ (%/day)	Alzheimer's Disease biomarkers (Immuno assays on CSF)	1. Age, sex, APOE ε4-status, time interval, assay batch 2. (1) + moderate PA	1. Positive association SB and Aβ42 1. No association SB and total tau, phosphorylated tau, total tau/Aβ42, or phosphorylated tau/Aβ42 2. No association SB and any CSF biomarker
Paxton et al. (2014)	755 (100%)	61[b] [50-79]	Single-item questionnaire (categorised into quartiles Q1-Q4)	IGF-1 (ELISA on blood sample) IGFBP-3 (ELISA on blood sample)	Age, education, occupation, race, PA, estrogen use, hypertension, physical functioning, BMI, waist circumference, smoking, alcohol consumption, total daily calories	IGF-1 not different between quartiles SB IGFBP-3 not different between quartiles SB
Spartano et al., 2017[c]	2109 (54%)	46 (9)	Actical (%/day)	IGF-1 (ELISA on blood sample)	1. age, sex, BMI, hypertension, CVD, smoking, cohort, season, residence place, overnight wear 2. (1) + MVPA	1 + 2. No association SB and IGF-1
Spartano et al., 2019	1730 (45%)	60 (10)	Single-item questionnaire	IGF-1, VEGF, BDNF (ELISA on blood sample)	1. Age, sex 2. (1) + smoking, BMI, cholesterol, triglycerides, lipid medication, APOE- ε4	1 + 2. No association SB and IGF-1, VEGF, or BDNF
Engeroff et al., 2018	50 (n.k.)	75 (7)	ActiGraph GT1M	BDNF (ELISA on blood sample)		Negative correlation SB and BDNF
Spartano et al., 2022	1769 (51%)	47 (9)	Actical (%/day)	BDNF (ELISA on blood sample)	1. Age, sex, platelet count, smoking, depression. 2. (1) + BMI, hypertension, diabetes, CVD.	1 + 2. No association SB and BDNF
Judice et al., 2021	80 (48%)	58 (8)	Actigraph GT3X+	BDNF (ELISA on blood sample)	1. Age, sex, time of diabetes diagnosis, fasting glucose levels 2. (1) + MVPA 3. (2) + cardiorespiratory fitness	1 + 2 + 3. No association SB and BDNF
Cerebrovascular health						
Launer et al., 2015	680 (52%)	50 (4)	Single-item questionnaire	Grey matter CBF (pCASL MRI)	1. Age, sex, race 2. (1) + education, smoking, BMI, blood pressure, diabetes	1 + 2. No association SB and grey matter CBF
Zlatar et al. (2014)	33 (67%)	69 (9)	ActiGraph GT1M	Left and right hippocampal CBF (ASL MRI)	1. Age, genetic risk, SB*genetic risk 1 + 2. (1) + wear time	1 + 2. No association SB and left hippocampal CBF in APOE ε4 noncarriers 1 + 2. Positive association SB and left hippocampal CBF in APOE ε4 carriers 1. No association SB and right hippocampal CBF
Zlatar et al., 2019	52 (58%)	72 (5)	ActiGraph GT3X+ or GT3X-BT	Frontal and medial temporal CBF (pCASL MRI)	Age, sex, scanner used/type, wear time, MVPA	Negative association SB and CBF frontal ROI. Significant clusters: Right anterior middle frontal gyrus, left and right, paracentral lobule, right posterior middle frontal gyrus No association SB and CBF hippocampal/parahippocampal ROI
Hartman et al., 2021	24 (63%)[d]	65 (5)	ActivPAL3 micro	Resting CBFV and cerebrovascular conductance index before and after a 16-wk reduced sitting intervention (TCD in MCA + Finapres)		Negative correlation SB change and change in CBFV and cerebrovascular conductance index
Maasakkers et al., 2021	38 (55%) and 48 (54%)[e]	70 (5) and 74 (6)[e]	GENEActiv	Grey matter CBF (ASL MRI) Prefrontal tissue saturation index during rest, and after orthostatic challenge (NIRS)	1. Age, sex, education 2. (1) + smoking, alcohol use, BMI, cardiovascular conditions, use of medication for hypertension, depression 3. (2) + MVPA	1 + 2 + 3. Grey matter CBF not different between high and low sedentary group 1 + 2 + 3. Prefrontal tissue saturation index during rest, and after orthostatic challenge not different between high and low sedentary group
Structural brain measures						
Arnardottir et al., 2016	352 (66%)	79 (4)	ActiGraph GT3X *f*	Grey matter volume 5-yr ago, current, and 5-yr change (MRI) WM volume 5-yr ago, current, and 5-yr change (MRI)	1. Age, sex 2. (1) + brain infarcts, follow-up, education, PA, BMI, depression, MAP, diabetes, smoking	1 + 2. No association grey matter 5-yr ago, current, or change over 5-yr and current SB 1 + 2. No association WM 5-yr ago and current SB 1 + 2. Negative association current WM and current SB 1 + 2. Negative association WM change over 5-yr and current SB

(*continued on next page*)

Table 2 (*continued*)

Study	N total (% female)	Mean age (SD)	SB measurement[a]	Outcome measure (instrument used)	Covariate adjustment	Main results
Engeroff et al., 2018	50 (n.k.)	75 (7)	ActiGraph GT1M	Left and right hippocampal volume (qMRI)		No association SB and left or right hippocampal volume
Siddarth et al., 2018	35 (71%)	60 (8)	Single-item from IPAQ-E	Total and regional[g] MTL thickness (MRI)	1. Age 2. Age, sex, BMI, education	1. Negative association SB and total MTL thickness 1. Negative association SB and ERC thickness 1. Negative association SB and PHC thickness 1. Negative association SB and SUB thickness 1. No association SB and CA1, CA23DG, FUS, or PRC 2. No association SB and total MTL thickness
Launer et al., 2015	680 (52%)	50 (4)	Single-item questionnaire	Total brain volume (MRI)	1. Age, sex, race 2. (1) + education, smoking, BMI, blood pressure, diabetes	1. No association continuous SB and total brain volume 1 + 2. Total brain volume 75th percentile < 25th percentile SB
				Abnormal WM volume (FLAIR MRI)		1. No association continuous SB and abnormal WM volume 2. Abnormal WM volume 75th percentile < 25th percentile SB
				WM microstructural integrity (DTI MRI)		1. Negative association continuous SB and WM FA 1. WM FA 75th percentile < 25th percentile SB 2. No association percentile SB and WM FA
Bronas et al. (2019)	94 (51%)	68 (7)	Nine-item SBQ & SBQ-S	WM hyperintensity volume (MRI)	Age, sex, education, FRSP-10, eGFR	Positive association SB and WM hyperintensity volume
Burzynska et al. (2014)	88 (68%)	65 (4)	ActiGraph GT3X	WM hyperintensity volume (MRI) Regional[h] WM microstructural integrity (DTI MRI)	1. Age, sex 2. (1) + wear time 3. (1) + CRF 4. (1) + MVPA	1. No association SB and WM hyperintensity volume 1. Negatively partial correlation SB and parahippocampal FA 1. No association SB and other regional FA 2. No association SB and parahippocampal FA 3 + 4. SB explains variance parahippocampal FA
Burzynska et al. (2015)	100 (66%)	65 (4)	ActiGraph GT3X	WM microstructural integrity (DTI MRI)		No association SB and global FA
Burzynska et al. (2017)[i]	174 (69%)	65 (5)	ActiGraph GT3X or GT1M	Microstructural integrity of 20 WM tracts over 6-month period (DTI MRI)	Age	Negative correlation baseline SB and 6-month change FA in cc2 Negative correlation baseline SB and 6-month change FA in prefrontal WM No association baseline SB and 6-month change other WM tracts
Bergman et al. (2020)	40 (n.k.) and 39 (n.k.)[j]	46 (4) and 57 (3)[j]	ActivPAL3 (%/day)	Hippocampal volume (MRI)	Age, sex, intracranial volume	No association SB and hippocampal volume in younger group Negative association SB and hippocampal volume in older group
Maasakkers et al., 2021	38 (55%) and 48 (54%)[e]	70 (5) and 74 (6)[e]	GENEActiv	Grey matter volume, WM volume, hippocampal volume, hippocampal subfield[k] volumes and cortical thickness	1. Age, sex, education, estimated total intracranial volume (only for variables on volumes) 2. (1) + smoking, alcohol use, BMI, cardiovascular conditions, use of medication for hypertension, depression 3. (2) + MVPA	1 + 2 + 3. Grey matter volume, WM volume, hippocampal volume, subiculum volume, presubiculum volume, parasubiculum volume, GC-ML-DG volume, CA3 volume, CA4 volume, fimbria volume, HATA volume, and cortical thickness not different between high and low sedentary group 1 + 2. Lower CA1 volume and lower molecular layer HP volumes in high sedentary group 3. CA1 volume and molecular layer HP volume not different between high and low sedentary group 1 + 2 + 3. Lower tail volume in high sedentary group
				WM hyperintensities (MRI)		1 + 3. WM hyperintensities not different between high and low sedentary group 2. More WM hyperintensities in high sedentary group

(*continued on next page*)

Table 2 (*continued*)

Study	N total (% female)	Mean age (SD)	SB measurement[a]	Outcome measure (instrument used)	Covariate adjustment	Main results
Machida et al. (2021)	485 (53%)	73 (6)	Active style Pro HJA-750 C	Left and right hippocampal volume (MRI)	1. unadjusted 2. Age, sex, intracranial volume 3. (2) + education 4. (3) + BMI, smoking, alcohol use 5. (4) + use of medication for hypertension, dyslipidemia, and diabetes	1. Positive association SB and left hippocampal volume 2 + 3 + 4 + 5. No association SB and left hippocampal volume 1 + 2 + 3 + 4 + 5. No association SB and right hippocampal volume
Vergoossen et al., 2021	1715 (48%)	60 (8)	ActivPAL3	Total brain and WM volume (MRI)	1. Age, sex, education, MRI lag time, wake time, intracranial volume 2. (1) + diabetes 3. (2) + BMI, systolic blood pressure, total-to-HDL-cholesterol ratio, smoking status, alcohol use, history of cardiovascular disease, use of antihypertensive medication, use of lipid-modifying medication	1. Negative association SB and total brain volume 2 + 3. No association SB and total brain volume 1 + 2 + 3. No association SB and WM volume
Functional brain measures						
Burzynska et al. (2015)	100 (66%)	65 (4)	ActiGraph GT3X	Neural activity (rs-fMRI with BOLD contrast)	Age, sex	No association SB and grey matter SD_{BOLD}
Dougherty et al. (2017)	93 (66%)	64 (6)	ActiGraph GT3X+ (%/day)	Regional glucose metabolism[α] (3D FDG PET imaging)	Age, sex, BMI, APOE ε4-status	No association SB and cerebral glucose metabolism in any region
Engeroff et al., 2018	50 (n.k.)	75 (7)	ActiGraph GT1M	Neural integrity Neuronal energy reserve + metabolism (MRS) Choline and energy metabolism (MRS)		No association SB and NAA/tCr No association SB and ATP/PCr No association SB and tCho/tCR, GPC/PCr, or PCho/PCr
Smith et al., 2021	34 (44)	70 (5)	GENEActiv (%/day)	Neuroplasticity: MEP amplitudes following cTBS (EMG)	Age	No association SB and neuroplasticity
Domingos et al. (2021)	104 (56%)	68 (3)	Xiaomi Mi Band 2	Functional connectivity (rs-fMRI)	age, sex, MMSE, GDS	Negative association SB and functional connectivity, specifically in superior gyrus, frontal middle gyrus, medial frontal gyrus, occipital inferior gyrus, cingulate gyrus, and parahippocampal gyrus
Vergoossen et al., 2021	1715 (48%)	60 (8)	ActivPAL3	Whole brain and regional[m] node degree (dMRI)	1. Age, sex, education, MRI lag time, wake time 2. (1) + diabetes 3. (2) + BMI, systolic blood pressure, total-to-HDL-cholesterol ratio, smoking status, alcohol use, history of cardiovascular disease, use of antihypertensive medication, use of lipid-modifying medication	1. Negative association SB and whole brain node degree 2 + 3. No association SB and whole brain node degree 1. Negative association SB and basal ganglia node degree 2 + 3. No association SB and basal ganglia node degree 1 + 2 + 3. No association SB and frontal lobe, temporal lobe, parietal lobe, occipital lobe or primary motor cortex node degree

[a]Sedentary behaviour was operationalised as hours/min per day/week unless stated otherwise.
[b]Median age [range].
[c]IGF-1 measured six years before Actical measurement.
[d]Cerebrovascular measurements were performed in 23 participants.
[e]High (sitting >8 hrs/day) and low (sitting ≤8 hrs/day) sedentary group, respectively.
[f]GT3X measurement approximately five years after first MRI assessment.
[g]Regions are CA1, CA23DG, fusiform gyrus (FUS), perirhinal-(PRC), entorhinal-(ERC), parahippocampal cortex (PHC), and subiculum (SUB).
[h]Five regions are anterior corpus callosum, anterior cingulum, superior longitudinal fasciculi, paraphippocampal white matter, and temporal lobe white matter.
[i]Follow-up of 6-months is mean over four intervention groups (active control, dance, walking, walking+nutrition).
[j]Younger (age ≤51 years) and older group (age >51 years), respectively.
[k]Regions are tail, subiculum, CA1, presubiculum, parasubiculum, molecular layer HP, GC-ML-DG, CA3, CA4, fimbria, and HATA.
[l]Six regions are left and right inferior temporal gyri, left and right angular gyri, posterior cingulate, and bilateral hippocampus.
[m]Regions are frontal lobe, temporal lobe, parietal lobe, occipital lobe, basal ganglia and primary motor cortex.

Abbreviations: APOE=apolipoprotein E, ASL=arterial spin labelling, ATP=adenosine triphosphate, BDNF=brain-derived neurotrophic factor, BMI = body mass index, BOLD=blood oxygenation level dependent, CBF=cerebral blood flow, CRF=cardiorespiratory fitness, CSF=cerebrospinal fluid, CVD=cardiovascular disease, DTI=diffusion tensor imaging, eGFR=estimated glomerular filtration rate, ef=effect size, ELISA=enzyme-linked immunosorbent assay, FA=fractional anisotropy, FDG PET=fluor-18-deoxyglucose positron emission tomography, FLAIR=fluid attenuated inversion recovery, FRSP-10 =Framingham stroke risk-10-year prediction score, GPC=glycerophosphocholine, IGF-1 =insulin-like growth factor-1, IGFBP-1 =IGF-binding protein 1, IPAQ-E = international physical activity questionnaire to elderly, MAP=mean arterial pressure, MMSE=Mini-Mental State Examination, MTL=medial temporal lobe, MRI=magnetic resonance imaging, MRS=magnetic resonance spectroscopy, MVPA=moderate-to-vigorous PA, N = number, NAA=N-acetyl-aspartate, n.k.=not known, PA=physical activity, pCASL=pseudo-continuous ASL, PCr=phosphocreatine, PCho=phosphocholine, pr=partial correlation, qMRI=quantitative MRI, r = correlation coefficient, ROI=region of interest, SB=sedentary behaviour, SBQ = SB questionnaire, SD=standard deviation, SD_{BOLD}=moment-to-moment variability in the BOLD signal, tCr=total creatine, tCho=total choline, VEGF=vascular endothelial growth factor, WM=white matter.

cerebrovascular system (Carter et al., 2018). Indeed, in older adults, 3 hrs of sitting increased cerebrovascular resistance in the study by Maasakkers et al (Maasakkers et al., 2020b). (conductance is the inverse of resistance), but CBF remained stable, and cerebral autoregulation was unaffected. Of note, 3 hrs uninterrupted sitting had the same effect on cerebrovascular resistance as 3 hrs sitting that was interrupted by short bouts of walking (Maasakkers et al., 2020b). Theoretically, increases in cerebrovascular resistance (or decreases in cerebrovascular conductance) may be a result of preserved autoregulation, in an attempt to maintain CBF despite increased blood pressure levels resulting from a three-hour sitting period, either interrupted and uninterrupted. Wheeler et al. noted a decline in CBF velocity of approximately 10 cm/s compared to baseline after 8 hrs of sitting (Wheeler et al., 2019). However, no correction for changes in $PaCO_2$ could be made, while CO_2 has a vasodilatory effect and can disturb the extrapolation of CBF velocity to CBF that is based on a constant vessel diameter. In a recent study, Hartman et al. examined changes in cerebrovascular perfusion during 3-h sitting before and after a 16-wk "reduce sitting"-intervention (Hartman et al., 2021). Whilst they confirm the decrease in cerebrovascular conductance index following sitting, they also found that the 16-wk intervention, that effectively reduced total sitting time by 1 h/day in a subgroup, resulted in increased cerebrovascular conductance index and CBF velocity. Taken together, this suggests that decreases in CBF (velocity) are possible following prolonged bouts of sitting. Regarding cognitive task-related prefrontal oxygenation, the immediate effects of uninterrupted sitting were non-significant, and were comparable to interrupted sitting conditions (Heiland et al., 2021).

Four cross-sectional observational studies examined the association between CBF and habitual SB (Launer, 2015; Maasakkers, 2021; Zlatar, 2014, 2019). Although no differences in total grey matter CBF were found between sedentary and non-sedentary individuals by Maasakkers et al (Maasakkers et al., 2021). Zlatar et al. demonstrated a negative association between SB and CBF in specific regions of the frontal lobe (Zlatar et al., 2019). No association was found for SB and CBF of the (para)hippocampal region of interest, however this was also not the case for all other types of physical activities (e.g., vigorous physical activity). The authors therefore propose that the frontal lobe may be more sensitive to free-living daily activities, compared to the hippocampus which might be more responsive to exercise interventions (Zlatar et al., 2019). Another explanation could relate to the fact that the hippocampus is a predominately grey-matter structure (Sullivan et al., 1995), since the study by Launer et al., 2015 found SB not to be associated with grey matter CBF. If sedentary behaviour indeed has strong inter-regional effects on perfusion of the brain, it is important to realise that measures of global cerebral blood flow may not be preferred to detect and understand the relation between sedentary behaviour and brain health. Measures of global cerebral blood flow may underestimate or even mask a potential impact of sedentary behaviour with specific brain regions. Lastly, one study investigated hippocampal blood flow in older adults at risk for AD (Zlatar et al., 2014). Nine older adults, all carriers of the apolipoprotein (APOE) ε4 allele and therefore at increased risk of developing AD, were compared to 24 non-ε4 carriers. Although right hippocampal CBF was not associated with SB, this study found that higher volumes of SB were associated with higher left hippocampal CBF in APOE ε4 carriers (Zlatar et al., 2014). These higher CBF levels were interpreted as an early compensatory mechanism, given the normal cognitive function levels of the participants (Zlatar et al., 2014).

3.4. Structural brain measures

SB has been most frequently studied in relation to structural brain measures, e.g., cerebral volume and cortical thickness (Arnardottir, 2016; Bergman, 2020; Engeroff, 2018; Launer, 2015; Maasakkers, 2021; Machida, 2021; Siddarth, 2018; Vergoossen, 2021), as well as white matter (WM) hyperintensities and its microstructural integrity (Bronas, 2019; Burzynska, 2014, 2015, 2017; Launer, 2015; Maasakkers, 2021), all measured using MRI. Cerebral atrophy is one of the pathological markers of AD and dementia, hence the focus of several studies on the relation between SB and volumetric analyses. One cross-sectional study showed that total brain volume in the 75th percentile of SB was significantly lower compared to the 25th percentile of SB (Launer et al., 2015). In line with this, a negative association was found for total and specific regional medial temporal lobe thickness with self-reported sitting time in another cross-sectional study (Siddarth et al., 2018). Vergoossen et al. found that the negative association with total brain volume did not remain significant after adjustment for additional confounders (Vergoossen et al., 2021). Our research group recently reported comparable cortical thickness when comparing sedentary with non-sedentary individuals (Maasakkers et al., 2021) In contrast, Arnardottir et al. reported a negative cross-sectional association with WM volume (Arnardottir et al., 2016), although another study found no association between SB and WM volume (Vergoossen et al., 2021). Moreover, in our recent study (Maasakkers et al., 2021), we found no difference in WM volume between a sedentary and non-sedentary group. The latter study also found no group differences in grey matter or hippocampal volume, which is in line with findings from other studies that generally reported the absence of an association between SB and grey matter (Arnardottir et al., 2016) or hippocampal volume (Engeroff, 2018; Machida, 2021). When looking at hippocampal subfields, a marked lower hippocampal tail volume was found in the sedentary group (Maasakkers et al., 2021). Similarly, another study also found no association between SB and hippocampal volume in a relatively young group (mean age 46 years), however, a negative association was demonstrated in a somewhat older group (mean age 57 years) (Bergman et al., 2020). Longitudinally, a change in WM volume measured over five years was negatively associated with SB levels at the end of that five-year period (Arnardottir et al., 2016). This means that SB would not (only) be a risk factor for atrophy, but that a bidirectional association could be present in which WM atrophy leads to higher levels of SB.

WM disruptions are often seen in age-related cognitive decline (Burzynska et al., 2014). WM microstructural integrity can be evaluated using DTI MRI to measure fractional anisotropy, which reflects among others fiber integrity. When this WM microstructural integrity decreases, this is associated with cognitive decline. Cross-sectionally, global and parahippocampal WM microstructural integrity was lower in participants with more habitual SB (Burzynska, 2014; Launer, 2015). Burzynska et al. (2017) investigated the effects of a six-month lifestyle intervention on WM integrity. Despite the intervention, WM integrity declined in most areas for all groups. The decline in prefrontal WM over six months was worse for participants with higher levels of baseline SB (Burzynska et al., 2017). Another cross-sectional study found no association between habitual SB and global WM microstructural integrity (Burzynska et al., 2015).

A different aspect of WM damage related to cognitive decline are WM hyperintensities. One study in 88 older adults found no association between WM hyperintensities and SB (Burzynska et al., 2014). Launer et al. (2015) found no association between abnormal WM volume and continuous self-reported SB in 680 middle-aged adults either. However, after adjusting for confounders they did find that abnormal WM volume was higher for participants in the 75th percentile of SB compared to the lowest 25th percentile (Launer et al., 2015). When adjusting for covariates, Maasakkers et al. demonstrated more WM hyperintensities in sedentary adults compared to non-sedentary peers (Maasakkers et al., 2021). Lastly, another cross-sectional study found a positive association between SB (measured with a SB questionnaire) and WM hyperintensities in older adults (Bronas et al., 2019).

3.5. Functional brain measures

With different techniques, i.e. blood oxygen level-dependent MRI, functional MRI, magnetic resonance spectroscopy, fluorodeoxyglucose positron emission tomography and electromyography, specific functions

of the brain can be captured and explored in relation to SB. Our search yielded six studies including different functional brain measures. Burzynska et al. measured oxygenation dependent signals with fMRI, that reflect neural activity, which were not affected by SB (Burzynska et al., 2015). Cerebral glucose metabolism, which predicts cognitive decline when decreased, was not related to SB either (Dougherty et al., 2017). Regarding neuronal networks, one study demonstrated negative associations between SB and functional connectivity in specific gyri (Domingos et al., 2021). Vergoossen et al. demonstrated that whole brain or regional node degrees were not associated with SB when adjusting for confounders that particularly relate to cardiovascular health (Vergoossen et al., 2021). Lastly, two studies demonstrated that SB was not associated with measures for quantifying neuroplasticity (Engeroff, 2018; Smith, 2021).

3.6. Quality appraisal of included studies

An overview of the detailed quality scores per study can be found in Supplement 3. Level of agreement for the independent *in duplo* quality appraisals was 84%. Overall, studies scored high with scores ranging between 0.81 and 1.00. Submaximal scores were for example given on the items of limited confounder correction and validity of the exposure measures (i.e. self-reported SB). However, it has to be stressed that most studies into habitual SB were cross-sectional, which is not taken into account in this measure.

4. Discussion

With recent epidemiological analyses unable to confirm an association between SB and cognitive decline, we focussed on more proximal outcome measures of brain health, to investigate the association between SB and dementia. For that aim we systematically reviewed if and how acute and habitual SB are associated with physiological brain health factors in middle-aged and older adults. Twenty-nine studies were included in this review, with mainly cross-sectional designs. First, no indications were found that SB is associated with neurotrophic factors such as BDNF and IGF-1. Second, findings on the impact of acute and habitual SB on cerebrovascular measures were mixed. Third, although not completely unambiguously, several studies indicate that there is an association between SB and structural WM health. Lastly, most studies that looked at brain function found no alterations by habitual SB.

If SB is causally related to dementia, a physiological mechanism needs to be present via which this behaviour affects the brain. We will therefore now discuss these relationships for each biomarker that was studied. In contrast to studies which investigated effects of exercise on neuroendocrine markers, our results do not indicate that neurotrophic factors are involved in a pathway for SB. Possibly, a physical activity threshold is required for the release of BDNF, as e.g. ten minutes of moderate exercise was not enough to increase BDNF concentrations (Huang et al., 2014). This may explain why SB is not sufficient to alter these levels of BDNF.

The other pathway that was studied with regard to acute SB were the cerebrovascular outcomes. Nine studies investigated the relationship between SB and cerebrovascular health. Some immediate changes were seen in cerebrovascular resistance and CBF after acute bouts of uninterrupted sitting, although no effects on cerebral autoregulation were found. Observational results on habitual SB were mixed with a potential regional effect of SB on CBF. However, it was not possible to differentiate if regional differences in CBF reflect differences in brain activity/metabolism, or vascular changes. Studies on structural measures were also not univocal, however they tentatively point towards an association between SB and WM health. One hypothesis for this association is a pathway via cardiovascular and metabolic effects. SB is associated with cardiovascular disease risk (Carter et al., 2017). Increases in blood pressure, insulin resistance, and blood lipids are all examples of these effects. At the same time, these risk factors have a negative impact on WM health, which in turn might increase the risk of dementia (Maillard et al., 2015). Other structural measures, including grey matter, were not associated with SB. We speculate that the reason for this finding could relate to the fact that grey matter might be less sensitive to vascular risks (Mitchell et al., 2011). The cortex has a richer supply of blood vessels, and a much higher baseline CBF compared to white matter that is perfused by terminal penetrating arterioles (Rosen et al., 1991). With the hippocampus being predominately composed of grey matter (Sullivan et al., 1995), the main absence of both structural (Arnardottir, 2016; Bergman, 2020; Engeroff, 2018; Maasakkers, 2021; Machida, 2021) and cerebrovascular (Launer, 2015; Maasakkers, 2021; Zlatar, 2014, 2019) effects in the hippocampal and grey matter areas might be explained. As these WM disruptions are related to cognitive decline (Burzynska et al., 2014), this region-specific sensitivity for both the cerebrovascular and structural outcome measures needs further exploration. A second hypothesis to explain the association between SB and WM health is reverse causality. Years before cognitive decline sets in, and before AD can be clinically diagnosed, neurodegenerative changes are already present (Risacher and Saykin, 2013). The atrophy and WM hyperintensities studied here, but also the reduced cerebrospinal fluid levels of Aβ42, are good examples, as these changes are already seen in the pre-symptomatic stages of AD (Risacher and Saykin, 2013). This underlying neurodegenerative pathology can be responsible for apathy and loss of initiative (Robert et al., 2009). In turn this might explain increased levels of SB in dementia patients (Hartman et al., 2018). So, although previous literature corroborates the potential indirect pathway of SB affecting cardiovascular risk factors (Carter et al., 2017), in turn leading to brain abnormalities (Claassen, 2015), this reverse causality cannot be disregarded with the current evidence available.

The evidence to date does not indicate that SB affects brain function, but this was only investigated in six studies that looked at different functional outcomes such as functional connectivity, resting state networks or metabolism. This is congruent with the absence of effects on grey matter, which has a dominant role in metabolism and functional networks. However, white matter lesions could also be expected to affect connectivity. Speculatively, there may be a delay between the initiation of white matter lesions (axonal damage) until their effect on neuronal function or connectivity.

For most brain health factors a limited amount of studies have been conducted and mainly in a cross-sectional way. Of the twenty-nine studies included in this review, only six were experimental study designs and three longitudinal analyses. The high quality scores given to our included studies, should in that sense be interpreted with caution as observational studies are not downgraded using this scoring system in a way as they are in the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluations) (Guyatt et al., 2011). Therefore, careful consideration should be applied to claims of a causal nature.

4.1. Limitations

A main limitation of our systematic review is that included studies covered a wide variety of outcome measures across different categories on physiological brain health, also using different measurement techniques and study designs. Due to this high level of heterogeneity, we were unable to aggregate findings from (a subset of) included studies into a quantitative analysis to provide strong conclusive evidence on associations between SB and measures of physiological brain health. However, our qualitatively described overview of findings highlight current research gaps. The fact that we have studied a rapidly emerging and new research field should be acknowledged. The oldest studies included in our review originate from 2014, whilst the majority (i.e. 19/29, 66%) of studies were published in the past four years, including 8 papers in 2021 alone (i.e. 28% of all output).

Another limitation is that most measurement techniques only

indirectly measure brain health. However, several of these surrogate markers are related to clinical manifestations.

4.2. Future perspectives

Next to the move from cross-sectional research towards longitudinal causal evidence, certain measurement issues need to be addressed to move this field forward. Part of these recommendations were already made in 2014 by Voss et al (Voss et al., 2014)., e.g. the measurement of SB with accelerometer devices. Preferably with the ActivPAL that is able to distinguish between postures. At the same time, different types of SB, such as watching TV or studying for an exam, might have other effects on the brain due to their diverse cognitive activity (Gur, 1982; Voss, 2014). Furthermore, most studies have used a continuous measure of SB, while SB might only become detrimental after eight hours (Ekelund et al., 2019), and the duration and type of breaking up the sitting bout are important as well (Voss et al., 2014). New technologies combining accelerometers with mobile apps seem promising to overcome practical challenges related to these limitations (Giurgiu et al., 2020). Moreover, if SB has an indirect effect on the brain via its cardiovascular effects, we might be looking at the effect of this single risk factor in a too isolated way knowing that risk factors can interact with each other (Rose, 1991). A lifestyle approach where we look at the combined effect of multiple risk factors on brain health measures might therefore be more suitable. Lastly, due to this hypothesised indirect pathway via vascular function, cognitive tests sensitive to vascular cognitive impairments, such as the executive functioning Trail Making Test, should be considered in future long-term follow up studies on SB's effects on cognitive decline.

With regard to the prevention of cognitive decline, a review from Falk et al. published in 2017 (Falck et al., 2017) set out recommendations for SB, based on existing policy recommendations and available evidence. The authors proposed to avoid SB wherever possible, to limit discretionary SB to < 2 h/day, to break up sitting after 30 min of uninterrupted sitting and to increase light-intensity activity to > 2 h/day while substituting time spent in SB. Based on our overview of available studies, we believe that identifying SB as a target for dementia prevention is still premature. However, given the cardiovascular effects of SB, targeting sitting may be beneficial for improving general health. In addition to the recommendations provided by Falck et al., we highlight a recent study included in our review that successfully reduced SB with 1 h/day within individuals who followed a "reduce sitting"-intervention (Hartman et al., 2021). Importantly, such interventions unlikely can be used interchangeably between (clinical) populations, and require close co-creation with the relevant end-users. Another remark is that there seems no linear relationship between SB and brain health, hence detrimental effects of SB may only be present when spending significant amounts of time in SB. We propose to use cut-off values (e.g. <9.5 h/day), that seem feasible targets, even in highly sedentary individuals. Moreover, these cut-off values are also feasible through interventions, especially since reducing SB with relatively small numbers (e.g. 1–2 h/day) may be sufficient to yield significal beneficial effects. At the same time, it is important to keep in mind that if the effect of SB works via a more indirect pathway of general health, its effect on the brain and dementia will be characterised by a large delay. The cardiovascular effects of SB do not immediately lead to brain abnormalities, neither do these in turn acutely cause dementia. Therefore, intervention strategies will need to be successful for a long time before effects on the brain will become measurable. Simultaneously, the timing of an intervention at late-life might not be as effective as an intervention at mid-life. Mid-life hypertension is known to influence the effect late-life blood pressure has on the brain (Muller et al., 2014). If this timing effect also holds for SB, it is not surprising that no strong effects were found in the included cross-sectional studies looking at late-life SB levels. These concerns need to be investigated before SB can be used as one of the targets in a lifestyle prevention strategy.

5. Conclusion

This systematic review provided an overview of the available studies on SB and brain health in middle-aged and older adults. The area has not been widely studied, whilst most studies have been performed in recent years. This highlights that this field is rapidly evolving, likely leading to the publication of several new studies in the upcoming years. Still, the evidence to date does not indicate that SB is associated with neurotrophic factors or functional brain measures. However, there is tentative evidence that structural deviations in WM health are associated with habitual SB. An explanatory pathway for this effect might relate to the vascular effects of SB. Nevertheless, due to the foremost cross-sectional nature of the included studies, a reverse association is also possible. More prospective studies on multiple brain health factors with appropriate SB measures are therefore needed to judge the potential of SB as a target in a multifactorial lifestyle prevention strategy for dementia.

Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104802.

References

Andreasen, N., et al., 2003. Cerebrospinal fluid levels of total-tau, phospho-tau and Aβ42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. Acta Neurol. Scand. 107, 47–51.
Arnardottir, N.Y., 2016. Association of change in brain structure to objectively measured physical activity and sedentary behavior in older adults: age, gene/environment susceptibility-Reykjavik study. Behav. Brain Res. 296, 118–124.
Bekinschtein, P., et al., 2008. BDNF is essential to promote persistence of long-term memory storage. Proc. Natl. Acad. Sci. 105 (7), 2711–2716.
Bergman, F., et al., 2020. Walking time is associated with hippocampal volume in overweight and obese office workers. Front. Hum. Neurosci. 14, 11.
Bronas, U.G., et al., 2019. Sedentary time and white matter hyperintensity volume in older adults. Med. Sci. Sports Exerc. 51 (8), 1613.
Brownson, R.C., Boehmer, T.K., Luke, D.A., 2005. Declining rates of physical activity in the United States: what are the contributors? Annu. Rev. Public Health 26, 421–443.
Burzynska, A.Z., et al., 2014. Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. PLoS One 9 (9).
Burzynska, A.Z., et al., 2015. Physical activity is linked to greater moment-to-moment variability in spontaneous brain activity in older adults. PLoS One 10 (8), e0134819.
Burzynska, A.Z., et al., 2017. White matter integrity declined over 6-months, but dance intervention improved integrity of the fornix of older adults. Front. Aging Neurosci. 9, 59.
Carter, S., et al., 2017. Sedentary behavior and cardiovascular disease risk: mediating mechanisms. Exerc. Sport Sci. Rev. 45 (2), 80–86.
Carter, S.E., et al., 2018. Regular walking breaks prevent the decline in cerebral blood flow associated with prolonged sitting. J. Appl. Physiol. 125 (3), 790–798.
Chieffi, S., et al., 2017. Neuroprotective effects of physical activity: evidence from human and animal studies. Front. Neurol. 8, 188.
Claassen, J.A., 2015. New cardiovascular targets to prevent late onset Alzheimer disease. Eur. J. Pharmacol. 763, 131–134.
Domingos, C., et al., 2021. Free-living physical activity measured with a wearable device is associated with larger hippocampus volume and greater functional connectivity in healthy older adults: an observational, cross-sectional study in Northern Portugal. Front. Aging Neurosci. 13, 14.
Dougherty, R.J., et al., 2017. Moderate physical activity is associated with cerebral glucose metabolism in adults at risk for Alzheimer's disease. J. Alzheimer's Dis. 58 (4), 1089–1097.
Ekelund, U., 2019. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. BMJ 366, l4570.
Engeroff, T., 2018. Is objectively assessed sedentary behavior, physical activity and cardiorespiratory fitness linked to brain plasticity outcomes in old age? Neuroscience 388, 384–392.
Falck, R.S., Davis, J.C., Liu-Ambrose, T., 2017. What is the association between sedentary behaviour and cognitive function? A systematic review. Br. J. Sports Med. 51 (10), 800–811.
Giurgiu, M., 2020. Accuracy of sedentary behavior–triggered ecological momentary assessment for collecting contextual information: development and feasibility study. JMIR mHealth uHealth 8 (9), e17852.

Gur, R.C., 1982. Sex and handedness differences in cerebral blood flow during rest and cognitive activity. Science 217 (4560), 659–661.
Guyatt, G., 2011. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J. Clin. Epidemiol. 64 (4), 383–394.
Hartman, Y.A., 2018. Dementia patients are more sedentary and less physically active than age-and sex-matched cognitively healthy older adults. Dement. Geriatr. Cogn. Disord. 46 (1–2), 81–89.
Hartman, Y.A.W., 2021. Long-term and acute benefits of reduced sitting on vascular flow and function. Med Sci. Sports Exerc 53 (2), 341–350.
Heiland, E.G., 2021. Frequent, short physical activity breaks reduce prefrontal cortex activation but preserve working memory in middle-aged adults: ABBaH study. Front. Hum. Neurosci. 15, 14.
Huang, T., et al., 2014. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. Scand. J. Med. Sci. Sports 24 (1), 1–10.
Judice, P.B., 2021. Sedentary patterns are associated with BDNF in patients with type 2 diabetes mellitus. Eur. J. Appl. Physiol. 121 (3), 871–879.
Kmet, L.M., Cook, L.S., Lee, R.C., 2004. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. Alberta Heritage Foundation for Medical Research, Edmonton.
Knaeps, S., 2018. Ten-year change in sedentary behaviour, moderate-to-vigorous physical activity, cardiorespiratory fitness and cardiometabolic risk: independent associations and mediation analysis. Br. J. Sports Med. 52 (16), 1063–1068.
Launer, L.J., 2015. Vascular factors and multiple measures of early brain health: CARDIA brain MRI study. PLoS One 10 (3).
Law, L.L., 2018. Moderate intensity physical activity associates with CSF biomarkers in a cohort at risk for Alzheimer's disease. Alzheimer's Dement. Diagn. Assess. Dis. Monit. 10 (1), 188–195.
Livingston, G., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396 (10248), 413–446.
Maasakkers, C.M., 2020a. The association of sedentary behaviour and cognitive function in people without dementia: a coordinated analysis across five cohort studies from COSMIC. Sports Med. 50 (2), 403–413.
Maasakkers, C.M., 2020b. The short-term effects of sedentary behaviour on cerebral hemodynamics and cognitive performance in older adults: a cross-over design on the potential impact of mental and/or physical activity. Alzheimer's Res. Ther. 12 (1), 1–11.
Maasakkers, C.M., 2021. Hemodynamic and structural brain measures in high and low sedentary older adults. J. Cereb. Blood Flow. Metab. 41 (10), 2607–2616.
Machida, M., 2021. Objectively measured intensity-specific physical activity and hippocampal volume among community-dwelling older adults. J. Epidemiol.
Maillard, P., et al., 2015. Cooccurrence of vascular risk factors and late-life white-matter integrity changes. Neurobiol. Aging 36 (4), 1670–1677.
Mitchell, G.F., et al., 2011. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain 134 (11), 3398–3407.
Muller, M., 2014. Joint effect of mid-and late-life blood pressure on the brain: the AGES-Reykjavik study. Neurology 82 (24), 2187–2195.
Norton, S., 2014. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 13 (8), 788–794.
Olanrewaju, O., 2020. Sedentary behaviours, cognitive function, and possible mechanisms in older adults: a systematic review. Aging Clin. Exp. Res. 32 (6), 1–16.
Oliff, H.S., 1998. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. Mol. Brain Res. 61 (1–2), 147–153.
Ouzzani, M., 2016. Rayyan—a web and mobile app for systematic reviews. Syst. Rev. 5 (1), 210.
Patterson, R., et al., 2018. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. European journal of epidemiology 33 (9), 811–829.
Paxton, R.J., et al., 2014. Associations between time spent sitting and cancer-related biomarkers in postmenopausal women: an exploration of effect modifiers. Cancer Causes Control 25 (11), 1427–1437.
Rashid, M.H., 2020. The neuroprotective effects of exercise on cognitive decline: a preventive approach to Alzheimer disease. Cureus 12 (2).
Risacher, S.L., Saykin, A.J., 2013. Neuroimaging biomarkers of neurodegenerative diseases and dementia. Seminars in Neurology. Thieme Medical Publishers.
Robert, P., et al., 2009. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur. Psychiatry 24 (2), 98–104.
Rose, G., 1991. Ancel keys lecture. Circulation 84 (3), 1405–1409.
Rosen, B.R., 1991. Contrast agents and cerebral hemodynamics. Magn. Reson. Med. 19 (2), 285–292.
Siddarth, P., 2018. Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. PLoS One 13 (4).
Smith, A.E., 2021. Daily activities are associated with non-invasive measures of neuroplasticity in older adults. Clin. Neurophysiol. 132 (4), 984–992.
Spartano, N.L., 2017. Associations of objective physical activity with insulin sensitivity and circulating adipokine profile: the Framingham Heart Study. Clin. Obes. 7 (2), 59–69.
Spartano, N.L., 2019. Self-reported physical activity and relations to growth and neurotrophic factors in diabetes mellitus: the Framingham Offspring Study. J. Diabetes Res. 2019.
Spartano, N.L., 2022. Accelerometer-measured, habitual physical activity and circulating brain-derived neurotrophic factor: a cross-sectional study. J. Alzheimers Dis. 85 (2), 805–814.
Sullivan, E.V., 1995. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. Neurobiol. Aging 16 (4), 591–606.
Szuhany, K.L., Bugatti, M., Otto, M.W., 2015. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. J. Psychiatr. Res. 60, 56–64.
Torres-Aleman, I., 2010. Toward a comprehensive neurobiology of IGF-I. Dev. Neurobiol. 70 (5), 384–396.
Vergoossen, L.W.M., 2021. Association of physical activity and sedentary time with structural brain networks-the Maastricht Study. Geroscience 43 (1), 239–252.
Voss, M.W., et al., 2014. 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. 7 (1), 9–24.
Wennberg, P., 2016. Acute effects of breaking up prolonged sitting on fatigue and cognition: a pilot study. BMJ Open 6 (2), e009630.
Wheeler, M.J., 2019. Morning exercise mitigates the impact of prolonged sitting on cerebral blood flow in older adults. J. Appl. Physiol. (1985) 126 (4), 1049–1055.
Wheeler, M.J., 2020. 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. 54 (13), 776–781.
Zlatar, Z.Z., et al., 2014. Increased hippocampal blood flow in sedentary older adults at genetic risk for Alzheimer's disease. J. Alzheimer's Dis. 41 (3), 809–817.
Zlatar, Z.Z., 2019. Dose-dependent association of accelerometer-measured physical activity and sedentary time with brain perfusion in aging. Exp. Gerontol. 125, 110679.

Appendix

Supplement 1 – Detailed search strategy

Pubmed

(Sedentary Behavior[MeSH] OR sitting position[MeSH] OR sedentary[tiab] OR sitting[tiab])
AND (Aged[MeSH] OR middle aged[MeSH] OR older adult[tiab] OR older adults[tiab] OR elderly[tiab] OR elders[tiab] OR older men[tiab] OR older women[tiab] OR older people[tiab] OR geriatric[tiab] OR geriatrics[tiab] OR senior[tiab] OR seniors[tiab] OR older population[tiab] OR old people[tiab] OR older-age[tiab] OR old age[tiab] OR mid-age[tiab] OR middle-age[tiab] OR middle-aged[tiab] OR adult[tiab] OR adults[tiab])
AND (Brain[MeSH] OR brain[tiab] OR cerebral[tiab] OR neur*[tiab] OR cephalic[tiab] OR grey matter[tiab] OR gray matter[tiab] OR white matter[tiab] OR hippocamp*[tiab] OR parahippocampal[tiab] OR temporal lobe[tiab] OR prefrontal cortex[tiab] OR ventricles[tiab] OR limbic[tiab] OR amygdala[tiab] OR cortical thickness[tiab] OR cerebrum[tiab] OR cerebrovascular circulation[MeSH] OR cerebrovascular[tiab] OR perfusion[tiab] OR CBF[tiab] OR angiogenesis[tiab] OR blood oxygenation[tiab] OR hypoperfusion[tiab] OR oxygen extraction[tiab] OR autoregulation[tiab] OR CO2 reactivity[tiab] OR vasomotor reactivity[tiab] OR carbon dioxide reactivity[tiab] OR arteriogenesis[tiab] OR vascular endothelium[tiab] OR hyperperfusion[tiab] OR Neurogenesis[MeSH] OR neuronal plasticity [MeSH] OR plasticity[tiab] OR BDNF[tiab] OR growth factor*[tiab] OR atrophy[tiab] OR hyperintensit*[tiab] OR HPA axis[tiab] OR amyloid[tiab] OR tau[tiab] OR neural activ*[tiab] OR default mode network[tiab] OR frontal executive network[tiab] OR connectivity[tiab])
NOT (rat[ti] OR rats[ti] OR mice[ti])

Embase

(Sedentary lifestyle/ OR Sedentary time/ OR sitting/ OR sedentary.ti,ab OR sitting.ti,ab)
AND (Aged/ OR middle aged/ OR older adult.ti,ab OR older adults.ti,ab OR elderly.ti,ab OR elders.ti,ab OR older men.ti,ab OR older women.ti,ab OR older people.ti,ab OR geriatric.ti,ab OR geriatrics.ti,ab OR senior.ti,ab OR seniors.ti,ab OR older population.ti,ab OR old people.ti,ab OR older-age.ti,ab OR old age.ti,ab OR mid-age.ti,ab OR middle-age.ti,ab OR middle-aged.ti,ab OR adult.ti,ab OR adults.ti,ab)
AND (Exp brain/ OR brain atrophy/ OR brain function/ OR brain.ti,ab OR cerebral.ti,ab OR neur*.ti,ab OR cephalic.ti,ab OR grey matter.ti,ab OR gray matter.ti,ab OR white matter.ti,ab OR hippocamp*.ti,ab OR parahippocampal.ti,ab OR temporal lobe.ti,ab OR prefrontal cortex.ti,ab OR ventricles.ti,ab OR limbic.ti,ab OR amygdala.ti,ab OR cortical thickness.ti,ab OR cerebrum.ti,ab OR Exp Brain blood flow/ OR Exp brain circulation/ OR cerebrovascular.ti,ab OR perfusion.ti,ab OR CBF.ti,ab OR angiogenesis.ti,ab OR blood oxygenation.ti,ab OR hypoperfusion.ti,ab OR oxygen extraction.ti,ab OR autoregulation.ti,ab OR CO2 reactivity.ti,ab OR vasomotor reactivity.ti,ab OR carbon dioxide reactivity.ti,ab OR arteriogenesis.ti,ab OR vascular endothelium.ti,ab OR hyperperfusion.ti,ab OR Nervous system development/ OR nerve cell plasticity/ OR plasticity.ti,ab OR BDNF.ti,ab OR growth factor*.ti,ab OR atrophy.ti,ab OR hyperintensit*.ti,ab OR HPA axis.ti,ab OR amyloid.ti,ab OR tau.ti,ab OR neural activ*.ti,ab OR default mode network.ti,ab OR frontal executive network.ti,ab OR connectivity.ti,ab)
NOT (rat.ti OR rats.ti OR mice.ti)

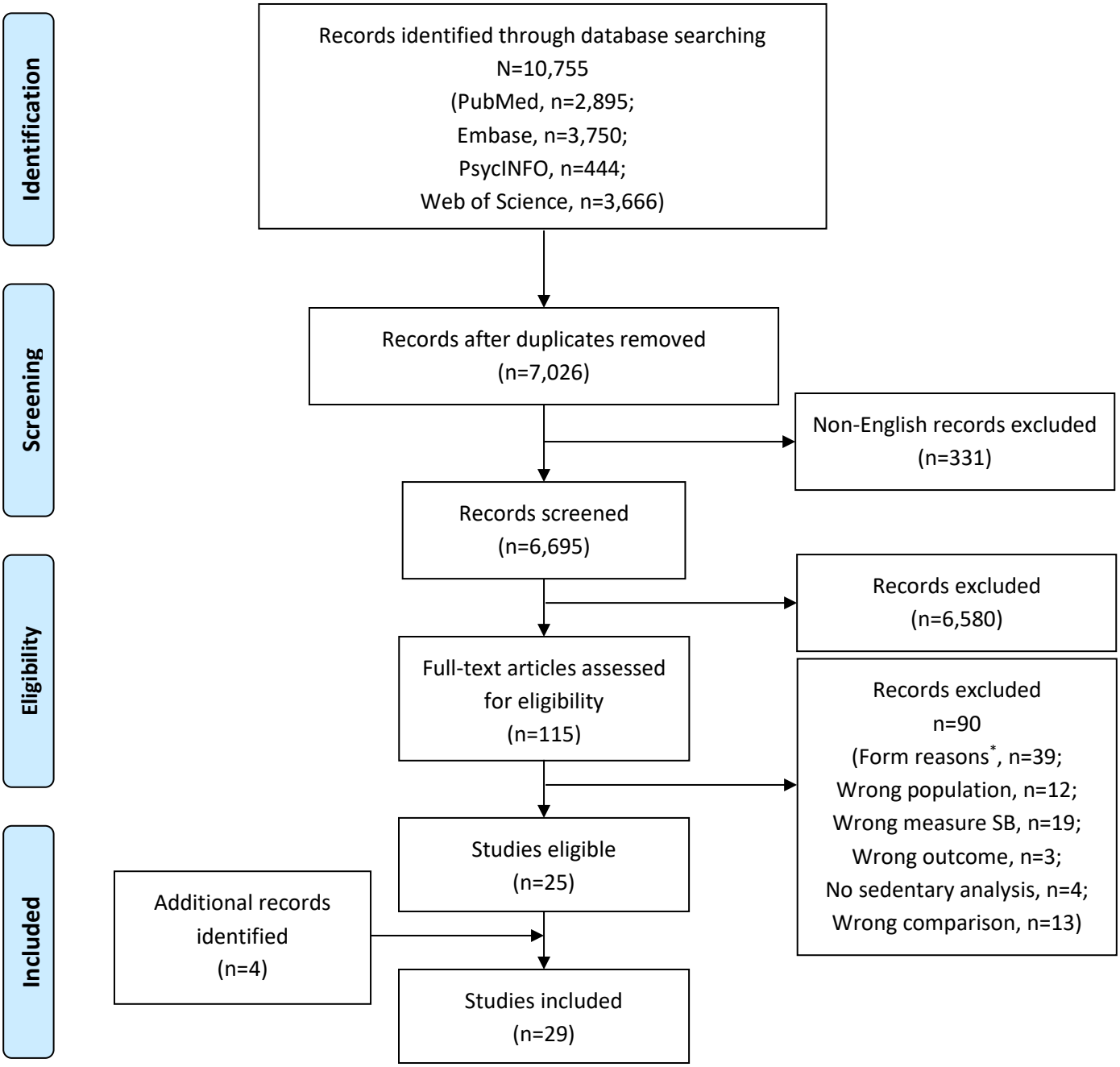
PsycINFO

(Sedentary behavior/ OR sedentary.tw. OR sitting.tw.)
AND (older adult.tw. OR older adults.tw. OR elderly.tw. OR elders.tw. OR older men.tw. OR older women.tw. OR older people.tw. OR geriatric.tw. OR geriatrics.tw. OR senior.tw. OR seniors.tw. OR older population.tw. OR old people.tw. OR older-age.tw. OR old age.tw. OR mid-age.tw. OR middle-age.tw. OR middle-aged.tw. OR adult.tw. OR adults.tw.)
AND (Exp brain/ OR cerebral atrophy/ OR brain.tw. OR cerebral.tw. OR neur*.tw. OR cephalic.tw. OR grey matter.tw. OR gray matter.tw. OR white matter.tw. OR hippocamp*.tw. OR parahippocampal.tw. OR temporal lobe.tw. OR prefrontal cortex.tw. OR ventricles.tw. OR limbic.tw. OR amygdala.tw. OR cortical thickness.tw. OR cerebrum.tw. OR Cerebral blood flow/ OR cerebrovascular.tw. OR perfusion.tw. OR CBF.tw. OR angiogenesis.tw. OR blood oxygenation.tw. OR hypoperfusion.tw. OR oxygen extraction.tw. OR autoregulation.tw. OR CO2 reactivity.tw. OR vasomotor reactivity.tw. OR carbon dioxide reactivity.tw. OR arteriogenesis.tw. OR vascular endothelium.tw. OR hyperperfusion.tw. OR plasticity.tw. OR BDNF.tw. OR growth factor*.tw. OR atrophy.tw. OR hyperintensit*.tw. OR HPA axis.tw. OR amyloid.tw. OR tau.tw. OR neural activ*.tw. OR default mode network.tw. OR frontal executive network.tw. OR connectivity.tw.)
NOT (rat.ti. OR rats.ti. OR mice.ti.)

Web of science

(TS=(sedentary OR sitting))
AND (TS=(older adult OR older adults OR elderly OR elders OR older men OR older women OR older people OR geriatric OR geriatrics OR senior OR seniors OR older population OR old people OR older-age OR old age OR mid-age OR middle-age OR middle-aged OR older age OR old-age OR mid age OR middle age OR middle aged OR adult OR adults))
AND (TS=(Brain OR cerebral OR neur* OR cephalic OR grey matter OR gray matter OR white matter OR hippocamp* OR parahippocampal OR temporal lobe OR prefrontal cortex OR ventricles OR limbic OR amygdala OR cortical thickness OR cerebrum OR cerebrovascular OR perfusion OR CBF OR angiogenesis OR blood oxygenation OR hypoperfusion OR oxygen extraction OR autoregulation OR CO2 reactivity OR vasomotor reactivity OR carbon dioxide reactivity OR arteriogenesis OR vascular endothelium OR hyperperfusion OR Neurogenesis OR plasticity OR BDNF OR growth factor* OR atrophy OR hyperintensit* OR HPA axis OR amyloid OR tau OR neural activ* OR default mode network OR frontal executive network OR connectivity))
NOT (TI=(rat OR rats OR mice))

Supplement 2 – PRISMA Flow chart



**Form reasons: wrong publication type, n=22; reviews, n=14; unavailability of full-text, n=2; foreign language, n=1.*

Supplement 3 – QualSyst scoring of included studies

	Arnardottir et al. (2016)	Bergman et al. (2020)	Bronas et al. (2019)	Burzynska et al. (2014)	Burzynska et al. (2015)	Burzynska et al. (2017)	Domingos et al. (2021)	Doughertya et al. (2017)	Engeroff et al. (2018)	Hartman et al. (2021)	Heiland et al. (2021)	Judice et al. (2021)	Launer et al. (2014)	Law et al. (2018)	Maasakkers et al. (2020)	Maasakkers et al. (2021)	Machida et al. (2021)	Paxton et al. (2014)	Siddarth et al. (2018)	Smith et al. (2021)	Spartano et al (2017)	Spartano et al. (2019)	Spartano et al. (2022)	Vergoossen et al. (2021)	Wennberg et al. (2016)	Wheeler et al. (2019)	Wheeler et al. (2020)	Zlatar et al. (2014)	Zlatar et al. (2019)
1. Question or objective	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2. Design	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2	2	1	2
3. Method of subject selection	2	2	2	1	1	1	2	1	2	2	2	2	2	2	1	2	2	2	2	1	1	2	2	2	2	2	2	2	2
4. Subject characteristics	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
5. Random allocation	NA	1	NA	NA	NA	2	NA	NA	NA	1	1	NA	NA	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	2	2	NA	NA
6. Blinding of investigators	NA	0	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	2	2	NA	NA
7. Blinding of subjects	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8. Outcome/exposure measure	2	2	1	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	1	2	2	1	2	2	2	2	2	2	2
9. Sample size	2	1	2	2	2	2	2	2	1	2	1	2	2	2	1	2	1	2	2	1	2	2	2	2	1	2	2	2	2
10. Analysis	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
11. Estimate of variance	2	2	2	1	2	2	0	1	2	2	2	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
12. Controlled for confounding	2	2	2	1	1	1	2	2	2	2	2	2	2	1	2	2	2	2	1	1	2	2	2	2	2	2	2	1	1
13. Results reported in detail	2	2	2	1	1	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
14. Results support conclusions	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total sum	22	22	20	18	19	22	19	19	20	23	22	20	19	21	21	22	21	21	19	19	20	21	22	22	23	26	26	20	21
Total possible sum	22	26	22	22	22	26	22	22	22	24	24	22	22	22	26	22	22	22	22	22	22	22	22	22	26	26	26	22	22
Summary score	**1.00**	**0.85**	**0.91**	**0.82**	**0.86**	**0.85**	**0.86**	**0.86**	**0.91**	**0.96**	**0.92**	**0.91**	**0.86**	**0.95**	**0.81**	**1.00**	**0.95**	**0.95**	**0.86**	**0.86**	**0.91**	**0.95**	**1.00**	**1.00**	**0.88**	**1.00**	**1.00**	**0.91**	**0.95**

Items can be scored 'yes' (2), 'partial' (1), 'no' (0), and 'NA'.