Sedentary behaviours, cognitive function and possible mechanisms in older adults - A systematic review.

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Abstract (215/250)

Background: Physical activity can improve cognitive function of older adults, but the influence of sedentary behaviour on cognition is less clear. This systematic review investigated associations between sedentary behaviour and cognitive function in older adults without dementia, and possible mechanisms involved.

Methods: Major databases were searched for studies in English between 01/01/1999 and 31/10/2019. The systematic review followed COSMOS-E guideline and a pre-registered protocol (CRD42019122229). Risk of bias was assessed using NICE Quality appraisal checklist. Findings were narratively synthesized and presented.

Findings: Eighteen studies comprised of Thirteen cross-sectional and five longitudinal analyses (n= 40,228). Evidence suggested varied associations between varied sedentary behaviours and cognitive function in older adults. 50% of study analyses did not control for physical activity. 3/18 studies demonstrated associations between higher sedentary levels and lower levels of brain biomarkers, while 1/18 showed auto-regulatory effect in the left hippocampus. Conducting a meta-analysis was not justifiable due to considerable methodological, participant, outcome and exposure heterogeneity.

Conclusion: There is a lack of clarity about the overall and independent association between sedentary behaviour and cognition in older age. Underlying mechanisms are similar to physical activity and probably multi-modal. More studies with robust designs and methodology are needed to confirm effect of sedentary behaviour on cognition.

Key words: Sedentary behaviours, older adults, cognition, review, meta-analysis

Key points

- Independent association between sedentary behaviors and cognition in older people is unclear;
- There is considerable heterogeneity in available studies;
- Mechanisms explaining association are similar to physical activity and probably multi-modal;
- Future intervention studies are needed to confirm causal associations and effect.

1 Introduction

Aside from ageing, physical inactivity, defined as attaining less than recommended physical activity levels is one of the largest attributable risk factor of incident dementia (Norton et al., 2014; Piercy et al., 2018). The American Society of Sports Medicine recommends that older people engage in150 minutes and 75 minutes of moderate and vigorous intensity activities per week respectively(Piercy et al., 2018). While achieving higher physical activity levels across the life-course is associated with healthy ageing (Daskalopoulou et al., 2017), it may be challenging in later life due to barriers such as entrenched behaviours, health status, isolation and poor access to amenities(Olanrewaju et al., 2016). In addition to physical in/activity, there is growing interest in the potential deleterious impact of sedentary behavior on health outcomes.

Sedentary behaviour (SB) refers to any waking behaviour characterized by an energy expenditure of ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture(Tremblay et al., 2017). The prevalence of sedentary behaviour is high in older adults and appears to increase with age (Harvey et al., 2013), co-morbidities (Fleig et al., 2016) and cognitive decline (Nemoto et al., 2018). A systematic review found that almost 60% of older adults world-wide reported sitting for more than four hours per day and when device-measured, 67% of the older population were sedentary for more than 8.5 hours in their waking day (Harvey et al., 2013). A separate study, which objectively assessed twenty-four-hour movement and non-movement behaviours among community dwelling older people using a multi-sensor activity monitor found that 30.7% of their total daily time was engaged in sedentary behaviours. Findings from a meta-analysis suggested higher levels of sedentary behavior are associated with all-cause mortality, cardiovascular disease mortality, cardiovascular disease incidence, cancer mortality, and type 2 diabetes incidence, possibly independent of physical activity levels (Biswas and Alter, 2015).

A more recent meta-analysis indicated a log-linear association between a cut-off of nine hours of daily sedentary time and all-cause mortality in adults aged 18-64 years(Ku et al., 2018). However, the relationship of sedentary behaviour with the cognitive health of older adults is less clear and inconclusive. The first systematic review on this topic searched literature between 1, January 1990 and 6, February 2016, included and evaluated eight observational studies (Falck et al., 2017a). Its findings suggested that sedentary behaviour was negatively associated with cognitive decline in adults aged 40 years and over.

Further, this review highlighted several issues such as sample size, context of sedentary behaviours, quality of included primary studies reviewed, and poor evidence on long term associations.

In addition to the need for an updated review, we have identified several gaps within literature regarding the relationship between sedentary behavior and cognitive function in older adults including lack of clarity about associations in the older age; associations by sedentary behavior context; magnitude of associations and potential mechanisms which underpin the associations. This review proposes to further the existing body of knowledge by (1) conducting a comprehensive review of the evidence investigating the associations between types of sedentary behaviours and cognitive function in older adults (65years+) (2) review possible physiological mechanisms that may underlie the associations (3) perform a meta-analysis of estimates from included studies.

2 Methods

This review protocol was registered on PROSPERO (CRD42019122229) and reviews follow COSMOS-E guideline (Dekkers et al., 2019).

2.1 Types of Studies

We searched for quantitative studies including but not limited to randomized controlled trials (RCTs); controlled clinical trials (CCTs); controlled before and after studies (CBAs); interrupted time series (ITS); quasi-experimental; cohort, case-control and cross-sectional studies. Only human studies were considered. Primary studies published between 01/01/1999 and 31/10/2019 in English were included. Studies that solely focused on qualitative methods and reporting only qualitative data were excluded.

2.2 Participants / Population

Studies were included if participants had a mean age of 65+ and lived in the community. Studies with participants diagnosed with dementia were excluded.

2.3 Exposure

We used the Sedentary Behaviour Research Network consensus terminology, which includes and defines sedentary behavior as any waking behavior characterized by <= 1.5 metabolic equivalents (METs) in sitting, lying or reclining posture (Tremblay et al., 2017). We loosely pre-defined study exposure to capture a wide range of objectively (device

measured) and self -reported sedentary behaviours in sitting, lying, or recline position. We reported on possible physiological mechanisms that may mediate and /or influence the effects of sedentary behaviours on cognition such as oxidative stress, glucose metabolism and neuroplasticity.

2.4 Comparators / Control

Studies with any comparator or no comparator.

2.5 Primary outcomes

Primary outcomes included measures of effects and / or associations with any domain of cognitive function, capacity, reserve, decline as measured by any appropriate and validated tool including cognitive tests, and relevant brain imaging.

2.6 Secondary outcomes

We reported associations between sedentary behaviours and neuro-biomarkers with known associations with and /or surrogates of cognitive function in human studies.

2.7 Searches

We used a wide range of search terms covering the following concepts and domains including ageing and older people; sedentary behaviours, physical activity, cognitive function, inactivity, cognition, physiology, pathology, and relevant neuro-biomarkers. Please see appendix for full details of our search protocol as registered on PROSPERO. Databases searched between 01/01/1999 and 31/10/2019 included: MEDLINE, EMBASE, PsycINFO, CINAHL, Social Science Index, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment (HTA). Reference lists of previous reviews included studies, York CRD databases. Websites were searched for grey literature (e.g. WHO, Google scholar).

2.8 Data extraction, selection and coding

Titles and abstracts were screened independently by two reviewers (OO, SS). Differences between reviewers' results were resolved by discussion and when necessary in consultation with a third reviewer (LS). If after discussion, there was still doubt about the relevance of a study for the review it was retained. Full paper copies were obtained for all reviews identified by the title/abstract screening. Full paper screening was conducted independently by two people (OO, SS). We extracted data on study design; age; exposures, characteristics of study participants, outcome measures and results.

2.9 Quality assessment and Risk of Bias

Risk of bias and quality were assessed using NICE Quality appraisal checklist for quantitative studies reporting correlations and associations, based on the appraisal step of the 'Graphical appraisal tool for epidemiological studies (GATE)' (NICE, 2014). For each study, we awarded an overall quality grading for internal validity (IV) and a separate one for external validity (EV) as follows:

- (++) All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.
- (+) Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or adequately described, the conclusions are unlikely to alter.
- (-) Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

All our studies were fully, and double quality assessed. Any discrepancy between reviewers was resolved by discussion.

2.10 Data Synthesis

Findings were narratively synthesized and presented. A meta-analysis was considered, but significant methodological heterogeneity precluded a meaningful meta-analysis. We explored heterogeneity by mapping variation in study designs and characteristics based on mode of sedentary behaviour measurement (self-reported versus device-measured).

3 Results (overall)

The overall search yielded 9109 records after 451 duplicates were removed. Eighteen studies on sedentary behavior associations and mechanisms met the inclusion criteria(Bronas et al., 2019; Çukić et al., 2018; Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Engeroff et al., 2018; Falck et al., 2017b; Fancourt and Steptoe, 2019; Garcia-Hermoso et al., 2018; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Ku et al., 2017; Kurita et al., 2018; Maasakkers et al., 2019; Nemoto et al., 2018; Steinberg et al., 2015; Vance et al., 2005; Wanigatunga et al., 2018; Zlatar et al., 2019, 2014) . Countries of study were USA (N=7), Canada (N=1), UK (N=2), Europe (N=3), Chile (N=1), Japan (N=3) and Taiwan (N=1). The study identification flowchart is shown in Fig. 1. A summary of the included reviews, descriptive characteristics and effect estimates are

presented in Table 1. Total number of participants was 40,228, with mean ages between 65-83 years. Our search did not yield any primary intervention study.

Thirteen cross-sectional (Bronas et al., 2019; Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Engeroff et al., 2018; Falck et al., 2017b; Garcia-Hermoso et al., 2018; Kurita et al., 2018; Nemoto et al., 2018; Steinberg et al., 2015; Vance et al., 2005; Wanigatunga et al., 2018; Zlatar et al., 2019, 2014) and five longitudinal or follow-up studies (Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Ku et al., 2017; Maasakkers et al., 2019) or analyses were included. Three studies (Falck et al., 2017b; Nemoto et al., 2018; Zlatar et al., 2019) reported findings from primary studies while the rest were secondary analysis of existing data from cohort and randomized trials. 3/18 studies reported both positive and negative associations between multiple sedentary behavior exposures and cognition, while the rest reported single associations. 6/18 and 9/18 studies reported positive and negative associations between sedentary behaviours and cognitive function respectively.

Sedentary behaviour types and how these were measured varied across studies. Sedentary behaviour levels were measured using various accelerometer or inclinometer(Engeroff et al., 2018; Falck et al., 2017b; Ku et al., 2017; Wanigatunga et al., 2018; Zlatar et al., 2019, 2014), while the rest of the studies reported self-reported measured sedentary behaviours using validated and non-validated questionnaires. Five studies reported TV watching (Da Ronch et al., 2015; Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014; Maasakkers et al., 2019; Nemoto et al., 2018), Two studies reported sitting time (Garcia-Hermoso et al., 2018; Maasakkers et al., 2019); two studies reported computer /internet use (Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012) and one study reported reading (Nemoto et al., 2018). One study grouped a number of sedentary exposures and termed them ‘Cognitive Activities in Sitting Position’(Kurita et al., 2018). These included reading books or newspapers; writing a diary or letters without using a mobile or smart phone; solving crossword puzzles; playing board games; using a computer, including internet use; and maintaining housekeeping records.

All studies used regression models that adjusted for commonly used socio-economic factors associated with activity levels such as age, gender, ethnicity, marital status, education and occupation. Outcomes of cognitive domains varied across studies. In addition to outcomes of global cognition (Mini-Mental Scale Examination, Alzheimer’s disease Assessment scale-Cognition, CogState computerized battery), other domains

measured included memory (immediate and delayed recall, Benton Visual Retention test), perceptual organization and planning (Rey-Osterrieth Complex figure (Rey-O), executive function (Trail Making test), semantic fluency, processing speed (immediate word recall, Wechsler Adult Intelligence Scale-III Digit Symbol Coding (WAISC-DSC)), and neurological biomarkers (BDNF serum levels, cerebral blood flow, White Matter hyper-intensity volume).

Fig 1: PRISMA Flow diagram

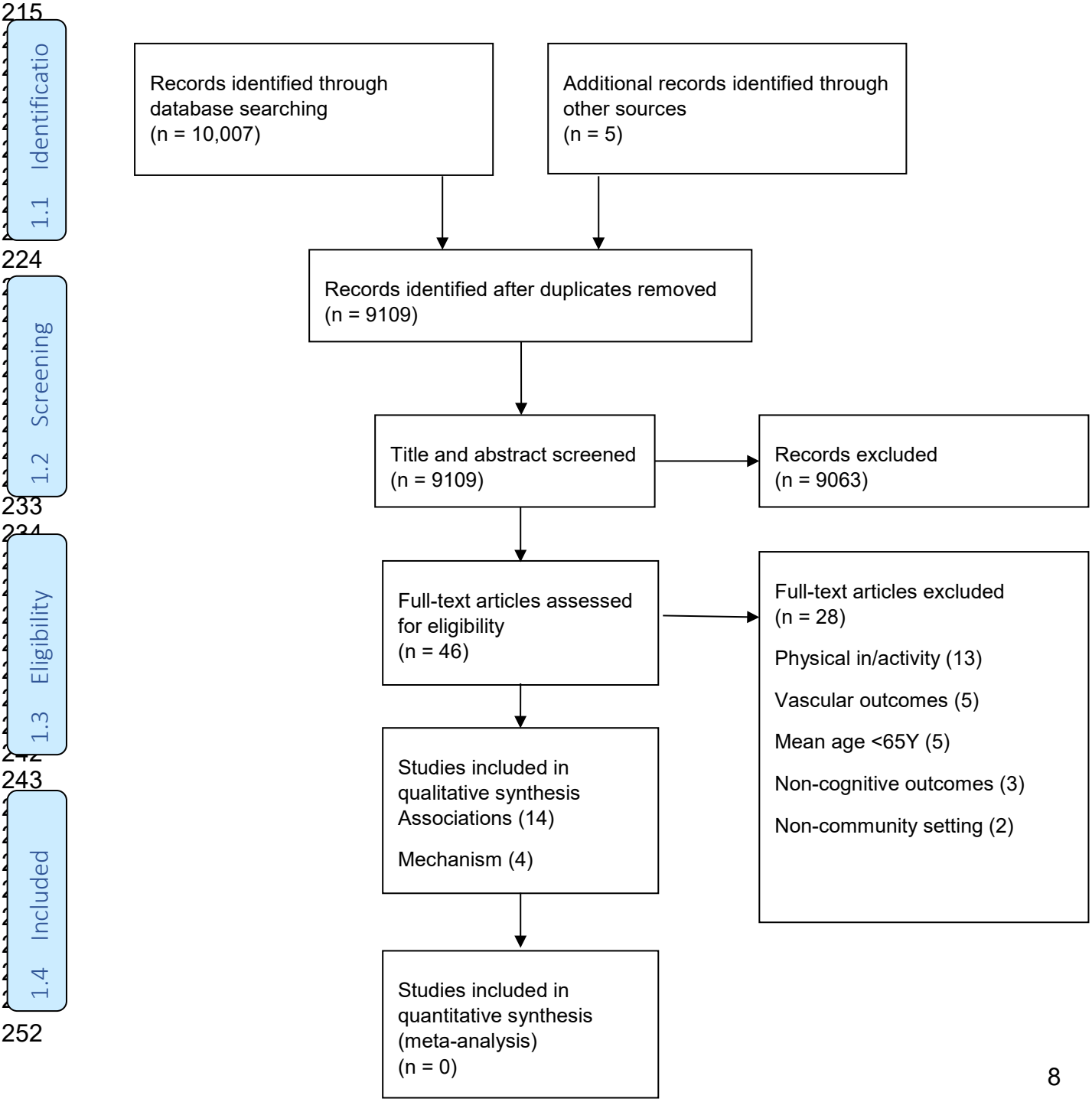

Table 1: Included reviews and study characteristics

Name	N	Age (years)	Exposure	Design	*Outcome measure* / Direction of Association	Effect estimate / size	co-variates adjusted	Study quality (Internal / External validity)
Bronas 2019	121	60+ (Mean age: 68.3Y)	Sedentary behavior measured using SB questionnaire (SBQ)	Secondary analysis of cross-sectional data	*WMH volumes using MRI:* Positive association with WMH volumes. Association was stronger at lower levels of kidney function, as measured by eGFR.	Unadjusted estimates (b=0.012, P=0.002, 95%CI: 0.004-0.02); Adjusted (b = 0.013; P < 0.001; 95% CI, 0.006–0.020)	Age, sex education, FSRP-10 and eGFR,	IV (-) EV(++)
Da Ronch, 2015	1383	Mean 72.5 Range (65-84) 47.6%% female	Time spent watching TV in the past week (self-reported)	Cross-sectional analysis of MentDis_ICF6+ study	*MMSE score:* Negative association	B co-efficient (-0.105; CI: -38.7,13.5) P<0.001	gender, age, study centre, years of education, living status, level of functioning, no. of medical diagnosis and PA	IV (-) EV(++)
Edwards, 2017	2472	Mean 69.9 Range (60-85) 55.3% female	Time spent in past (self-reported) 30 days SED (+5hours/day versus <1hour/day)	Cross-sectional analysis of NHANES data	*Digital Symbol Substitution test (DSST):* Negative association for the highest SED levels (+5H/day) and in model not controlled for MVPA	B co-efficient (-2.5; CI: -5.1, -0.2) P=0.07	age, gender, race-ethnicity smoking, BMI, MVPA	IV (+) EV(++)
Falck, 2017	150	Mean 71.1 Age 55+ 67.1% female	% SED time (accelerometer)	Cross-sectional study	*ADAS-COG Plus:* Negative association	B co-efficient (.007) P=0.089	age, sex and education	IV (-) EV(++)
Fancourt, 2019	3590	Mean 67.1 Age 50+ 56.3% female	>3.5 hours/day of TV (self-reported)	Cohort 6Y FU (secondary analysis of ELSA)	*Verbal memory:* Negative association	B co-efficient (-0.13; CI: -0.2, -0.06) P<0.001	baseline cognition, sex, age, education, employment, retirement, wealth, social support, depression, self-reported health, smoking, alcohol, long standing and chronic conditions, PA, mobility problems, reading daily newspaper, internet use	IV (+) EV(++)
					Semantic fluency: No association	B co-efficient (-0.13; CI:-0.27,-0.02) P<0.082		
Garcia-Hermoso, 2018	989	Mean 74.1 Age 65+ 69% female	Total time spent sitting / day (self-reported)	Cross-sectional analysis of Chilean Health Survey data	*MMSE scores:* Negative association for highest SED levels +4H/day of sitting	B co-efficient (-0.063) P<0.001	age, sex, BMI, education and lone living, alcohol, drugs use, tobacco intake, depression	IV (+) EV(+)
Hamer, 2014	6359	Mean 64.9 Age 50+ 54.8% female	Average daily time watching TV (<2 hours, 2-4 hours, 4-6 hours/day) (self-reported)	Cohort 2Y FU (secondary analysis of ELSA)	*Change in composite global cognitive scores derived from standardized memory and verbal fluency:* Negative association	B co-efficient (0.2; CI: 0.07, 0.33). Reference is '>6 hours'.	Age, sex, smoking, physical activity, alcohol, social class, disability, chronic illness, body mass index, baseline CES-D score, and mutually for each sedentary behaviour.	IV (-) EV(++)
			Use internet (Yes/No)		Positive association	B co-efficient (-0.87; CI: -0.99, -0.76). Reference level is 'Yes'		

Table 1: Included reviews and study characteristics (continued)

Name	N	Age (years)	Exposure	Design	*Outcome measure* /Direction of association	Effect estimate / size	co-variates adjusted	Study quality (Internal / External validity)
Kesse-Guyot, 2012	2179	Mean 65.6 Range (52-67), 45% female	Time spent in computer use (self-reported/ minutes/day)	Cohort 6Y FU (cross-sectional analysis of SU.VI.MAX 2 cohort)	*Verbal memory:* Positive association	MD (highest tertile) 1.86; CI: 0.95, 2.77. P<0.0001	age, gender, supplementary group education, occupational categories, retirement, tobacco use, BMI, CES-D, general health, History of CVD, diabetes, hypertension, leisure-time PA, SED (TV, reading, computer)	IV (-) EV(++)
Ku, 2017	274	Mean 74.5 Age 65+ 54.4% female	+11 hours/day in SED (accelerometer)	Cohort 2Y FU (secondary analysis)	*Cognitive ability (AD8):* Negative association for highest SED levels +11H/day of sitting	Rate ratios (2.1; CI: 1.19, 3.72) P=0.008	Baseline cognition, sex, age, accelerometer wear time, education, marital status, income, smoking, co-morbidities, depressive symptoms, MVPA, ADLs.	IV (+) EV(+)
Kurita, 2018	5300	Mean 75 Age 65+ 52% female	No. of cognitive activities in sitting (CAS) >1/week (self-reported)	Cross-sectional analysis of National Center for Geriatrics and Gerontology-Study of Geriatric Syndrome	*Prevalence of CI, defined by low scores in two or more of the tests in the National Center for Geriatrics and Gerontology - Functional Assessment Tool:* Positive association /reduced odds of CI	odds ratio (0.61; CI: 0.55,0.68) P<0.001	age, sex, education, chronic diseases, GDS, MVPA and sitting time	IV (+) EV(++)
Maasakkers 2019	10,450	Mean age (66.7-75.1Y	Various Self-reported TV; sitting time/weekday/weekend; sitting time at work/home/driving car; accelerometer.	Secondary analysis of five cohort studies (HELIAD, PATH, SALSA,SGS,SLAS2)	*Global cognition (MMSE /3MS):* No association	HELIAD (B=0.028, 95%CI: -.21, .077, P=0.26) SALSA (B=-0.011, 95%CI: -.058,.037, P=0.66) SGS (B=-0.001, 95%CI: -.01,0.007, P=0.73) SLAS (B=-0.011, 95%CI: -.027,.004, P=0.16) PATH (B=0.001, 95%CI:-.021,.022, P=0.96)	Age, gender, ethnicity, education, income, BMI, morbidity count, perceived health, alcohol consumption, smoking status, marital status, living status, depression, sleep quality, blood pressure, and PA.	IV (+) EV(++)
Nemoto, 2018	5328	65+ 54.5% female	Time spent watching TV (>=3 hours/day) in last 7 days (self-reported)	Cross-sectional study (survey)	*Subjective cognitive complaints:* Negative association / increased odds of SCC	odds ratio (1.09; CI: 0.9, 1.32) P=0.36	Age, sex, education residential status, self-reported health, alcohol, smoking, medical history, loss-event experience, stress and depression.	IV (-) EV(+)
			Time spent reading books / newspapers (>=30mins/day) in last 7 days (self-reported)		Positive association/reduced odds of SCC	Odds ratio (0.47; CI: 0.39,0.57) P<0.01		

Name	N	Age (years)	Exposure	Design	*Outcome measure* / Direction of association	Effect estimate / size	co-variates adjusted	Study quality (Internal / External validity)
Steinberg, 2015	125	Mean age 77 Age 65+ 66% female	Weekly SED (hours) (self-reported)	Cross-sectional analysis of baseline data from longitudinal study	*Executive Function (CogState computerized cognitive test composite scores):* Negative association	B co-efficient (0.006; CI:.001,.111) P<0.01	age, sex, race and education	IV (-) EV(+)
Vance, 2005	158	Mean 75 47.5% female	Total time spent SED / time at rest in 1 week (minutes) (self-reported)	Cross-sectional analysis of baseline data	*BVRT:* Positive association	correlation co-efficient (0.16) P<0.05	Social isolation and depression.	IV (-) EV(+)
Wanigatunga 2018	1275	Mean 79 Range (70-89) 67% female	Objectively measured sedentary levels as in % time spent in +1 min, +30min, +60min bouts	Cross-sectional analysis of LIFE study	*Working memory [Wechsler Adult Intelligence Scale-III Digit Symbol Coding (DSC):* Negative association for highest SED levels. High % of +1min bout length.	Unstandardized B co-efficient (-2.03; SE (0.85)	self-reported age, sex, race/ethnicity, education, income, marital status, BMI, smoking status, sleep quality, perceived stress, comorbidity	IV (+) EV(+)
Engeroff 2018	50	Mean 75 Age 65+ % female (unspecified)	Sedentary (accelerometer)	Cross-sectional analysis of SMART study	*BDNF serum levels:* Negative association	correlation co-efficient (-0.347) P<0.05	Unadjusted	IV (-) EV(++)
Zlatar 2014	33	Mean (APOE-4: 71; non-APOE4: 68) Range (52-81) 68.5% female	Sedentary (accelerometer - 7 days consecutive)	Cross-sectional analysis of longitudinal study	*Left hippocampal blood flow:* Positive association/ regulatory compensation. Significant in APOE carriers only.	B co-efficient (0.74; P=0.002); Non-APOE carriers (0.096, P=0.61)	age, PA, APOE carrier,	IV (-) EV(+)
Zlatar 2019	52	mean age(72 +/-5Y)	Sedentary (accelerometer - 7 days consecutive)	Cross-sectional study	*Executive and memory composite scores; CBF using MRI:* No significant association with cognitive function scores. Negative association between sedentary time and CBF in medial and lateral frontal regions.	R middle frontal (B=-0.10, SE=0.02, P<0.01); L&R paracentral lobule (B-0.08, SE=0.03, P<0.01);	Age, sex, scanner, scan-type, MVPA, accelerometer wear time	IV (-) EV(+)

TV (television), MentDis_ICF6+ (Mental Disorder prevalence study in 65+ years in Europe), MMSE (Mini-Mental State Examination, B (Beta), PA (Physical activity), SED (sedentary), NHANES (National Health and Nutrition Examination Survey), BMI (Body Mass Index), MVPA (Moderate to Vigorous Physical Activity), ADAS-COG plus (Alzheimer's Disease Assessment Scale-Cognition plus), ELSA (English Longitudinal Study of Ageing), FU (Follow-up), CES-D (Centre for Epidemiologic Studies-Depression scale), CVD (Cerebrovascular disease), MD (Mean Deviation), SU.VI.MAX 2 (The Supplementation en Vitamines et Mineraux Antioxydants), AD8 (Alzheimer's Disease dementia screening interview), ADL (Activities of Daily living), GDS (Geriatric Depression Scale), BVRT(Benton Visual Retention Test), LIFE (Lifestyle Interventions and Independence for Elderly), SE (Standard Error), SMART, BDNF (Brain-Derived Neurotrophic Factor), APOE (Apolipoprotein), HELIAD (Hellenic Longitudinal Investigation of Ageing and Diet), PATH (Personality and Total Health Through Life Project), SALSA (Sacramento Area Latino Study on Aging), SGS (Sasaguri Genkimon Study), SLAS2 (Singapore Longitudinal Ageing Studies (II)), WMH (White Matter Hyperintensity), FSRP (Framingham Stroke Risk Profile), eGFR (Estimated Glomeruli Filtration Rate), CBF (Cerebral blood flow), MRI (Magnetic Resonance Imaging), IV (Internal validity), EV (External validity)

NICE quality appraisal checklist:
(++) All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.
(+) Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
(-) Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

3.1 Risk of Bias

Included studies were assessed for risk of bias. Eleven studies were assessed to have considerable risk of bias (Bronas et al., 2019; Da Ronch et al., 2015; Falck et al., 2017b; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Nemoto et al., 2018; Steinberg et al., 2015; Vance et al., 2005; Wanigatunga et al., 2018; Zlatar et al., 2014, 2019). 40% of included studies were subject to observable variable confounding (Bronas et al., 2019; Falck et al., 2017b; Ku et al., 2017; Steinberg et al., 2015; Vance et al., 2005; Wanigatunga et al., 2018; Zlatar et al., 2014) and all studies were subject to some residual confounding. All studies with self-reported measurement of sedentary exposure were subject to some information bias (social desirability and reporting). More than 60% of studies did not report recruitment and selection methods and mostly referred to original study protocol for information (Da Ronch et al., 2015; Engeroff et al., 2018; Fancourt and Steptoe, 2019; Garcia-Hermoso et al., 2018; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Kurita et al., 2018; Vance et al., 2005; Wanigatunga et al., 2018). Further, seven studies reported missing outcome data through attrition or incomplete collection (Bronas et al., 2019; Da Ronch et al., 2015; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Maasakkers et al., 2019; Steinberg et al., 2015; Wanigatunga et al., 2018).

3.2 Heterogeneity

We explored methodological and clinical heterogeneity by mapping study characteristics such as sedentary behaviour definition, design and population characteristics across mode of sedentary behaviour measure (fig. 2-3).

Sedentary behaviours were broadly divided into device-measured (N=6, (Engeroff et al., 2018; Falck et al., 2017b; Ku et al., 2017; Wanigatunga et al., 2018; Zlatar et al., 2019, 2014)) and self-reported measured (N=12, (Bronas et al., 2019; Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Fancourt and Steptoe, 2019; Garcia-Hermoso et al., 2018; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Kurita et al., 2018; Maasakkers et al., 2019; Steinberg et al., 2015; Vance et al., 2005; Volkers et al., 2011)). Device-measured sedentary behaviours were obtained via hip-worn (N=5, (Engeroff et al., 2018; Ku et al., 2017; Wanigatunga et al., 2018; Zlatar et al., 2019, 2014)) and wrist-worn (N=1, (Falck et al., 2017b)) accelerometer. All accelerometer readings were monitored continuously for seven days and data were only valid where minimum daily wear time was ten hours. However, acceptable wear time per week varied between three to five days per week. Self-reported sedentary behaviour levels were broadly categorised into those

measured using non-validated (N=5, (Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014; Nemoto et al., 2018)) and widely used validated questionnaires (N=6, Global Physical Activity Questionnaire (GPAQ) (Garcia-Hermoso et al., 2018), Modifiable Activity Questionnaire (MAQ) (Kesse-Guyot et al., 2012), International Physical Activity Questionnaire (IPAQ) (Kurita et al., 2018), The Community Health Activity Program for Seniors (CHAMPS) (Steinberg et al., 2015), Sedentary Behaviour Questionnaire (SBQ) (Bronas et al., 2019) and Physical Activity Questionnaire (PAQ) (Vance et al., 2005). One study reported multiple measures of sedentary behaviour which included various self-reported and accelerometer-derived measures.

Non-validated, self-reported questionnaires measured sedentary behaviour participation in terms of hours per day in past week (N=3, (Da Ronch et al., 2015; Hamer and Stamatakis, 2014; Nemoto et al., 2018)); and average hours per day (N=1, (Fancourt and Steptoe, 2019)); time spent in SB over thirty days (N=1, (Edwards and Loprinzi, 2017)). There was heterogeneity in country of study: America (N=9), Europe (N=3), Japan (N=3), Taiwan (N=1), UK (N=2). The number of studies varied in terms of study design, duration of follow-up and outcome estimates reported (Figure 3). Studies with device-measured sedentary behaviours reported fewer positive associations (N=1,(Zlatar et al., 2014)).

Ten studies controlled for physical activity in at least one of the regressions models reported (Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Ku et al., 2017; Kurita et al., 2018; Maasakkers et al., 2019; Zlatar et al., 2019, 2014). 4/10 studies controlled for device-measured physical activity: 150+ minutes/week of moderate to vigorous physical activity (Ku et al., 2017), hours/day of MVPA (Maasakkers et al., 2019) and accelerometer measured physical activity (Zlatar et al., 2019, 2014) (light< 1952 counts/min, moderate 1952-5725 counts/min, vigorous>5725 counts/min). 6/10 studies controlled for self-reported measured physical activity (Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Kurita et al., 2018). Three of the aforementioned studies measured physical activity by validated questionnaires namely International Physical Activity Questionnaire (Da Ronch et al., 2015; Kurita et al., 2018) and Modifiable Activity Questionnaire (Kesse-Guyot et al., 2012), while the rest used non-validated self-reported questionnaires.

Fig 2: Heterogeneity: Diversity in sedentary behaviour definition categorized by mode of SB measure

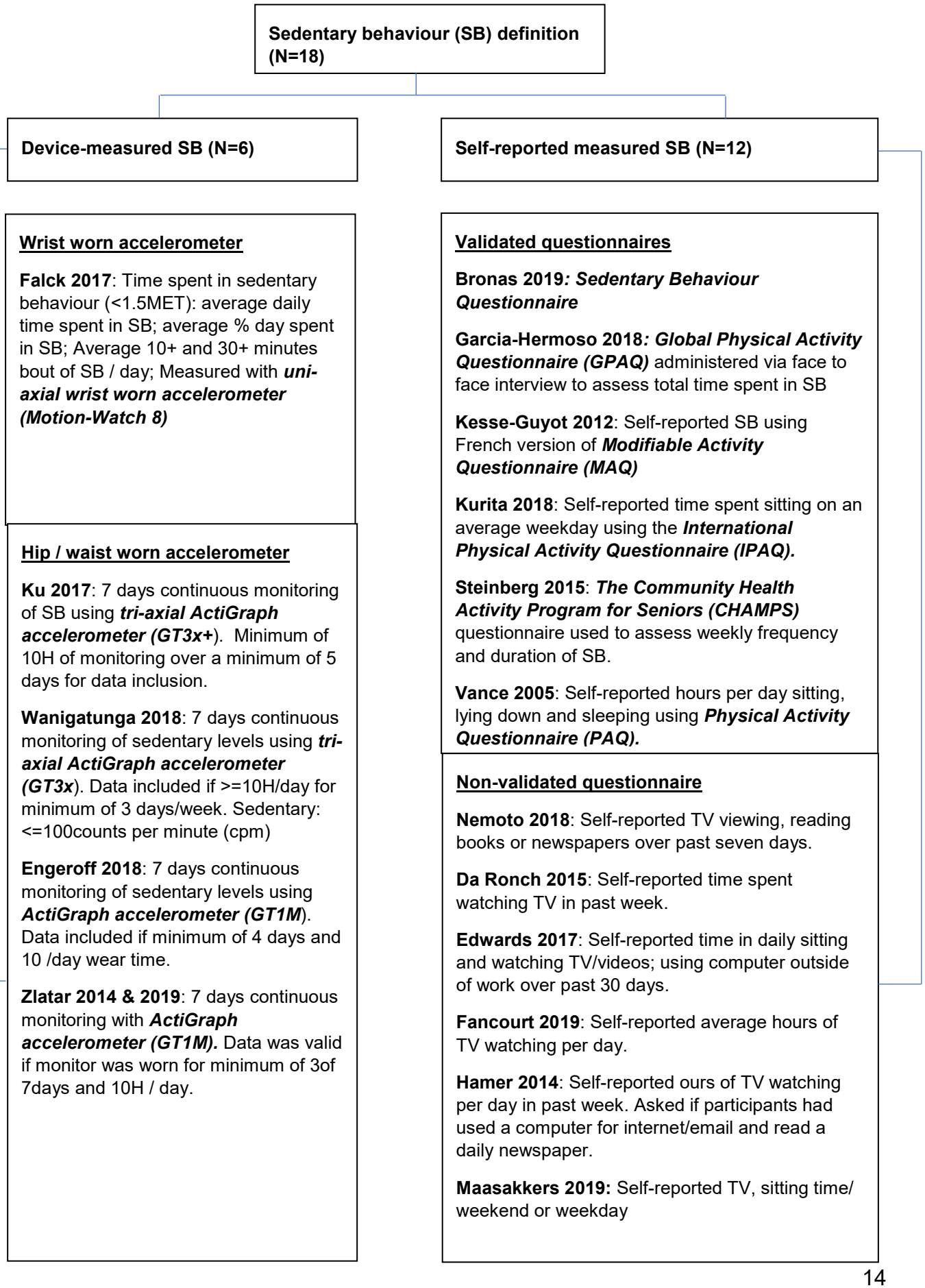

Fig 3: Heterogeneity: Diversity in study design, methods and characteristics categorized by mode of SB measure

Sedentary behaviour (SB) definition (N=18)

Device-measured SB (N=6)		**Self-reported SB (N=12)**
USA/Americas (n=4) Japan (n=1) Taiwan (n=1)	**Country**	USA / America (n=5) Europe (n=3) Japan (n=2) UK (=2)
Cross-sectional (5) Longitudinal (1)	**Study design**	Cross-sectional (n=8) Longitudinal (n=4)
<=5 years (n=1)	**Duration of follow-up**	<=5 years (n=1) 6-10 years (n=3)
Controlled for PA (n=3) No PA in regression (n=3)	**Regression models**	Controlled for PA (n=7) No PA in regression (n=5)
Beta coefficient (n=4) Correlation co-efficient (n=2)	**Effect Estimate**	Beta co-efficient (n=8) Mean Deviation (n=1) Odds Ratio (n=2) Correlation co-efficient (n=1)

Sedentary behaviour (SB); Physical activity (PA); United Kingdom (UK)

3.3 Associations between sedentary behaviours and cognition

Fourteen studies examined associations between cognition and sedentary behaviours (Da Ronch et al., 2015; Edwards and Loprinzi, 2018; Falck et al., 2017b; Fancourt and Steptoe, 2019; Garcia-Hermoso et al., 2018; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Ku et al., 2017; Kurita et al., 2018; Maasakkers et al., 2019; Nemoto et al., 2018; Steinberg et al., 2015; Vance et al., 2005; Wanigatunga et al., 2018). Risk of bias was present (-) in 8/14 studies (Da Ronch et al., 2015; Falck et al., 2017b; Hamer and Stamatakis, 2014; Kesse-Guyot et al., 2012; Nemoto et al., 2018; Steinberg et al., 2015; Vance et al., 2005; Wanigatunga et al., 2018) such that it would have compromised or altered reported findings (Appendix A). Television viewing was consistently reported as been associated with poorer cognitive function (Da Ronch et al., 2015; Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014). Although Fancourt et al (Fancourt and Steptoe, 2019), found negative association between television viewing and verbal memory (B=-0.13, 95%CI:-0.2,-0.06, P<0.001), the same study found no association with semantic fluency (B=-0.13 95%CI:-0.27,-0.02, P=0.082).

7/14 and 3/14 studies reported either negative (Da Ronch et al., 2015; Edwards and Loprinzi, 2017; Falck et al., 2017b; Garcia-Hermoso et al., 2018; Ku et al., 2017; Steinberg et al., 2015; Wanigatunga et al., 2018) or positive (Kesse-Guyot et al., 2012; Kurita et al., 2018; Vance et al., 2005) associations between sedentary behaviours and cognitive function respectively. Three reported both positive and negative associations (Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014; Nemoto et al., 2018). 1/14 studies, which analysed data from 10,450 older adults without dementia reported no cross-sectional and longitudinal association between total sedentary time and lower global cognition (P>0.05) (Maasakkers et al., 2019).

6/7 studies, which reported negative associations were statistically significant in highest levels of sedentary activities only (Edwards and Loprinzi, 2017; Garcia-Hermoso et al., 2018; Ku et al., 2017; Wanigatunga et al., 2018) or when regression models were uncontrolled for physical activity (Falck et al., 2017b; Steinberg et al., 2015). For instance, in Edwards' study, over five hours of sedentary behaviour was associated with Digital Symbol Substitution test (DSST) scores (B=-3.1, 95%CI: -5.8, -0.4, P=0.02) in a model uncontrolled for physical activity (PA). When adjusted for PA, the estimate was attenuated with reduced significance (B=-2.5; 95%CI: -5.1-0.2; P=0.07).

While Falck and colleagues (2017) reported significant associations between higher sedentary bout length (+30mins/day) and poorer cognition (B=0.061, P=0.016), Wanigatunga et al study (2018) found no association with prolonged sedentary bouts: +30, +60mins/day (unstandardized B=-2.03; SE: 0.85). One study (Falck et al., 2017b) explored the influence of Mild Cognitive Impairment (MCI) status on negative associations found between sedentary time and cognition. They reported that MCI status did not differentiate associations between sedentary behaviour and cognitive function. Positive associations were mainly reported in studies with exposure to reading (Nemoto et al., 2018), computer (Kesse-Guyot et al., 2012), internet use (Hamer and Stamatakis, 2014), and cognitive activities performed in sitting (Kurita et al., 2018). Vance et al reported positive association between total time spent in sedentary behaviours and visual memory and attention (B=0.16, P>0.05).

3.4 Possible mechanisms underlying associations

Four human studies explored potential mechanisms (Bronas et al., 2019; Engeroff et al., 2018; Zlatar et al., 2019, 2014). Three studies (Bronas et al., 2019; Zlatar et al., 2019, 2014) reported cross-sectional analyses of existing healthy /normal ageing studies, while Engeroff and colleagues(18, N=50) analysed baseline data from a randomised controlled trial. Zlatar and colleagues investigated the role of Apolipo-protein-E carriers, a genetic risk for developing AD in the relationship between hippocampal cerebral blood flow (mL/100g tissue/min) and device-measured sedentary levels (Zlatar et al., 2014). Average sedentary time among the participants was eight hours /day. They found that left hippocampal cerebral blood flow increased with prolonged sedentary levels in Apolipoprotein-E-carriers (APOE) (B=0.74, p = .002) compared with non-APOE carriers (B=0.096, P=0.61). However, the study did not reveal any association between cerebral blood flow and memory performance.

In a more recent study, Zlatar and colleagues explored the dose-response relationship between accelerometer measured sedentary time on frontal and medial temporal cerebral flow and its associations with cognitive function in older persons(Zlatar et al., 2019). Average sedentary time among participants was nine hours /day. The study demonstrated negative associations between average daily sedentary time and cerebral blood flow in right anterior middle frontal gyrus (B=-0.10, SE=0.02, P<0.01); left and right paracentral lobule (B=-0.08, SE=0.03, P<0.01); and right posterior middle frontal gyrus (B=-0.11,

SE=0.02, P<0.01). In a similar fashion with their previous study, there were no correlations between sedentary time, cerebral blood flow and executive or memory function.

Bronas and colleagues investigated the role of estimated Glomeruli Filtration Rate (eGFR) in the relationship between sedentary time and White Matter Hyperintensity (WMH) in older adults without dementia and chronic kidney disease. Average sedentary time in participants was 64.7 hours per week. Both unadjusted (b=0.012, 95%CI: .004-.020, P=0.002) and adjusted models (b=0.013, 95%CI: .006-0.02, P<0.001) showed that higher total sedentary time was associated with larger WMH volumes (Bronas et al., 2019). Engeroff and associates reported associations between brain plasticity outcomes including brain derived neurotrophic factors (BDNF), magnetic resonance spectroscopy (MRS)-based markers, and hippocampal volume (Engeroff et al., 2018). Average sedentary time in participants was ten hours / day. Negative associations (r=-0.347, P<0.05) were reported between time spent in sedentariness measured as activity count of less than 100 / minute and BDNF in healthy older adults. Brain metabolism measured by glycerophosphocholine to phosphocreatine (GPc/PCr) and adenosine triphosphate to phosphocreatine (ATP/PCr) ratios were not related to sedentary levels (<100 counts/minute). Finally, hippocampal volume, measured as ratio to total intracranial volume was also not related to sedentariness (<100 counts/minute)(Engeroff et al., 2018).

4 Discussion

Contrary to findings in a systematic review by Falck and colleagues, which suggested that sedentary behaviours were associated with lower cognitive performance in adults 40 years and over, our review found varied and inconclusive evidence on the direction of associations between sedentary behaviours and cognitive function in older adults (Falck et al., 2017a). Falck and colleagues included eight studies, while this review evaluated eighteen studies, including four studies from Falck et al review. Like our review, Falck and colleagues included studies with any measured sedentary behaviour including validated and non-validated self-reported instruments and accelerometer assessed. Their review included all adult participants, 40 years and over including those living with dementia and cognitive problems. Our study focused on the older population and excluded people living with dementia. Unlike Falck et al study, we explored possible physiological mechanism to explain associations between cognition and sedentary behaviours.

We did not find any intervention study that met our review's pre-specified criteria. We were unable to conduct a meta-analysis to determine the magnitude of association due to significant heterogeneity among studies. Studies varied considerably in terms of design, exposure, outcome, and effect estimate measures. There was also significant risk of bias in studies reviewed notably selection, information, confounding, report and social desirability biases. For example, Hamer et al (Hamer and Stamatakis, 2014) reported 10% attrition rate and significant missing data. As a result, effect size reported may have been overestimated because analyses were performed on residual data of younger and more active participants. Studies were predominantly cross sectional; hence results were subject to reverse-causality. Associations between television viewing and poorer cognitive levels were consistently reported in both longitudinal and cross-sectional study analyses (Da Ronch et al., 2015; Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014). However, Nemoto et al study (Nemoto et al., 2018) results were not statistically significant (OR 1.09; CI: 0.9, 1.32, P=0.36) due to the under-representation of older Japanese participants that watched television. Although, Fancourt et al (Fancourt and Steptoe, 2019) reported some association between TV watching and verbal memory, there was no relation with semantic fluency. Half of the studies reviewed did not adjust for physical activity in their regression models.

Our findings indicate a possible influence of physical activity on the inverse relationships between sedentary behaviour and cognitive function reported in some of the studies reviewed. 4/7 studies, which reported negative regression /correlation co-efficient estimates and controlled for physical activity in their analyses were only statistically significant in highest sedentary levels ranging from 4-11 hours/ day (Edwards and Loprinzi, 2017; Garcia-Hermoso et al., 2018; Ku et al., 2017; Wanigatunga et al., 2018). However, one of these studies were subject to some confounding and attrition bias (Wanigatunga et al., 2018). Wanigatunga and colleagues reported statistically significant associations between device-measured sedentary levels and working memory only in participants engaged in high percentage sedentary time (>=1-min bout:167-511 minutes / day) not in low (29-249 minutes/day) or medium (123-306 minutes/day) percentage sedentary time (Wanigatunga et al., 2018). Further, 2/7 studies with negative regression co-efficient estimates reported models, which did not control for physical activity (Falck et al., 2017b; Steinberg et al., 2015). The remaining study (1/7), which reported negative regression estimates and controlled for physical activity limited its category of television

viewing to a maximum value of 3H or more. This may have limited power of analyses by not accurately reflecting true extent of sedentary behaviour (Da Ronch et al., 2015).

Studies have mooted that sedentary activities (reading, computer, puzzle) through cognitive stimulation may contribute positively to cognitive health (Kesse-Guyot et al., 2012; Kurita et al., 2018; Nemoto et al., 2018). While the present review found some evidence to support this assertion, the studies included all assumed that the behaviours were performed in passive positions such as sitting or recline and did not explain the context surrounding these behaviours. For example, reading, internet and computer use may be performed in standing, which may result in over-estimation of effect confounded by light to moderate physical activity level (Palmer et al., 2019). Further, studies that explored this concept of sedentary cognitive activities have involved participants who were wealthy, healthy, highly active thereby subjecting results to further bias. For example, 46% of participants in Nemoto et al study had participated in over 150 minutes per week of moderate-to-vigorous exercise (Nemoto et al., 2018). Only 6.4% of participants in a separate study with similar findings had any form of cognitive impairment (Kurita et al., 2018). Perhaps, older adults that participate in these types of activities can tolerate higher cognitive demand /loading and therefore have better cognitive ability. While this concept is interesting, it needs further exploration.

The largest study (N=10,450) to date to have investigated the relationship between sedentary behaviour and cognitive function in a secondary analyses of five cohorts and included in our review, neither found a cross-sectional nor longitudinal association between total sedentary time and global cognition in older people (Maasakkers et al., 2019). However, one of the cohorts analysed in this study showed positive association ($B=0.118$, $P<0.001$), which was strongest in older people who participated in high physical activity.

4.1 Possible Mechanisms

Voss et al (Voss et al., 2014) postulated mechanisms responsible for the associations between sedentary behaviours and cognition could occur at the cellular and systemic level. These include hippocampal neurogenesis; modulation of endogenous growth factors, vascular, neuro-endocrine and inflammation (oxidative stress). Engeroff and associates (Engeroff et al., 2018) indicated negative association between brain derived neurotrophic factor (BDNF) and sedentary level. However, this study did not find any association with brain volume. Conversely, a recent cross-sectional analysis found that

higher sedentary time was associated with greater White Matter Hyperintensity volume, biomarker associated with increased risk of cognitive decline (Bronas et al., 2019). Similarly a separate study (Siddarth et al., 2018) demonstrated some association between hours of sitting per day and total medial temporal lobe thickness in a mixed population of middle aged and older adults.

In a similar mechanism to physical activity, sedentary behaviours, may influence cerebrovascular remodelling through angiogenesis or further adaptations of the arterial vasculature(Voss et al., 2014). Physical activity exerts an auto regulatory influence on global cerebral blood flow (CBF) by keeping it constant (Hoffman et al., 1981; Ogoh and Ainslie, 2009). Zlatar et al study found a similar auto-regulatory effect of prolonged sedentariness on left hippocampal CBF in Apolipoprotein-E carriers, a risk factor for Alzheimer's disease (Zlatar et al., 2014). In a separate and recent study, Zlatar and colleagues demonstrated a dose-response relationship between sedentary time and cerebral blood flow in the lateral and medial frontal lobes (Zlatar et al., 2019).

A limitation of this review is that 11/18 studies had considerable risk of bias, with the possibility of incorrect estimation of true effects / association. However, this does not entirely mean that studies were poorly conducted and low in overall quality. For instance, 15/18 studies were secondary analyses of existing data / studies and it may have been impractical for the authors to mitigate against biases such as selection, missing data and unmeasured residual confounding. This review focuses on studies published in English. Two studies reported secondary analyses of data collected from different waves (two and six-year follow up) of the English Longitudinal Study of Ageing and possibly reported duplicate data on participants (Fancourt and Steptoe, 2019; Hamer and Stamatakis, 2014). An included study may have measured sleeping time along with other sedentary behaviours as this was included in the Physical Activity Questionnaire used (Vance et al., 2005). Although this study was aimed at the older adult population (65+ years) and reported mean age across studies was 65+ years, the actual range of participants may have included data on middle age adults (50+) in some of the analyses. A further limitation is that 12/18 studies self-reported sedentary behaviours using validated and non-validate outcome measures. This is because majority of survey / cohort studies use self-report as a measurement of sedentary behaviour (Harvey et al., 2013). There is evidence that self-reported sedentary behaviours are often under-estimated in older adults (Harvey et al., 2015). However, self-reported measures may be important to understanding the contexts

surrounding sedentary behaviours. To our knowledge, this is the first systematic review to investigate this topic specifically in the older adult population. This review explores design heterogeneity and possible mechanism that may underlie associations between sedentary behaviour and cognitive function in older adults.

5 Conclusion

In an increasingly ageing population with barriers to accessing physical activity and increasing sedentary levels, displacing sedentary behaviour might be a complementary strategy towards better cognitive health in the older population. Although, our review found some evidence of varied associations between sedentary behaviours and cognitive function in older adults, there isn't conclusive evidence for the overall direction of relationship independent of physical activity. Our review found evidence of the moderating or attenuating effects of physical activity on the associations found between sedentary behaviours and cognition in older adults. Selected studies had design limitations and considerable risk of bias.

Like physical activity, sedentary behaviours appeared to elicit cerebral auto-regulatory effect by increasing blood flow in parts of the hippocampus in Apolipoprotein-E-carriers, a risk factor for developing Alzheimer's disease. Conversely, higher sedentary time was associated with deficient bio-marker levels sometimes associated with poorer brain health such as reduced cerebral blood flow in the frontal lobe, reduced brain derived neurotrophic factors, and greater White Matter Hyperintensity volume. Our findings do not support targeting sedentary behaviours in order to promote cognitive health in older people.

5.1 Future study implication

Future research should aim to address gaps including, underlying bio-mechanism, dose-response, and long-term associations. Intervention studies with robust designs are needed to ascertain true effect of sedentary behaviour on cognition. Longitudinal studies are desirable, but more should include device-measured sedentary time and properly control for physical activity among other co-variates in their regression analyses. While device-measured sedentary behaviour is highly desirable, self-reported measures should not be entirely excluded from future studies and should be used as adjunct to device-measures in order to understand the context around the exposure. Missing data from attrition and unavailable data should also be accounted and controlled for in regression analyses. Future reviews need to explore both animal and human studies to further understand potential mechanisms that may explain the role of sedentary behaviour on cognitive health. Finally, some consistency is needed among researchers in this field to standardise measures of exposure and outcomes used in future studies, starting with adopting the

consensus paper on sedentary behaviours definitions by the Sedentary Behaviour Research Network(Tremblay et al., 2017).

6 Declaration

6.1 Compliance with ethical standards

Not applicable. Systematic review.

6.2 Funding

This review was supported by the Cambridgeshire and Peterborough NHS Foundation Trust.

6.3 Conflict of Interest

The authors declare that they have no competing interests.

6.4 Ethical approval

Not applicable

6.5 Informed consent

Not applicable

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Appendices

Appendix A: NICE Quality appraisal checklist: quantitative studies reporting correlations and associations

Study	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	3.1	3.2	3.3	3.4	3.5	4.1	4.2	4.3	4.4	5.1 (IV)	5.2 (EV)
Bronas 2019	+	+	++	+	++	NA	-	++	+	+	NA	NA	NA	NR	++	++	++	-	++
DaRonch 2015	++	+	++	++	++	NA	+	++	++	+	NA	NA	NA	NR	++	++	++	-	++
Edwards 2017	++	+	++	++	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	+	++
Falck 2017	++	++	++	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	-	++
Fancourt 2019	++	+	+	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	+	++
Garcia-Hermoso 2018	++	+	+	++	++	NA	+	-	++	++	NA	NA	NA	NR	++	++	+	+	+
Hamer 2014	+	+	+	+	++	NA	+	++	+	+	NA	NA	+	NR	++	++	++	-	++
Kesse-Guyot 2012	+	+	+	+	++	NA	+	++	++	+	NA	NA	++	NR	++	++	++	-	++
Ku 2017	++	++	++	++	++	NA	+	+	++	++	NA	NA	+	++	++	++	++	+	+
Kurita 2018	++	+	+	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	+	++
Maasakkers 2019	++	+	+	+	++	NA	++	++	++	+	NA	NA	NA	NR	++	++	++	+	++
Nemoto 2018	++	+	+	-	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	-	+
Steinberg 2015	++	++	++	+	++	NA	+	++	++	++	NA	NA	NA	NR	+	++	++	-	+
Vance 2005	++	+	+	-	++	NA	-	++	++	++	NA	NA	NA	NR	++	++	+	-	+
Wanigatunga 2018	+	+	+	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	+	+	+
Engeroff 2018	+	+	+	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	-	++
Zlatar 2014	++	+	+	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	-	+
Zlatar 2019	++	+	+	+	++	NA	+	++	++	++	NA	NA	NA	NR	++	++	++	-	+

(++) All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.

(+) Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.

(-) Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Internal Validity (IV); External Validity (EV); not reported (NR); not applicable (NA)

Appendix B: Search Strategy

1. exp sedentary lifestyle/ or sedentary.mp.

2. sedentar*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

3. sedentary behaviour.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

4. sedentary activity.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

5. sedentary lifestyle.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

6. sitting.mp. or sitting/

7. supine position.mp. or supine position/

8. recline.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

9. television viewing.mp. or television/ or television viewing/

10. computer time.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

11. desk bound.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

12. physical inactivity.mp. or exp physical inactivity/

13. cogniti*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

14. cognitive function.mp. or exp cognition/

15. cognitive ability.mp.

16. memory test.mp. or memory test/

17. Neuropsychological test.mp. or neuropsychological test/

18. cognitive reserve.mp. or cognitive reserve/

19. biomarkers.mp. or biological marker/

20. biology/ or biology.mp.

21. neuropathology.mp. or neuropathology/

22. genetic.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

23. mechanism.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

24. old$.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

25. older people.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

26. ageing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

27. aging/ep [Epidemiology]

28. older adult.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

29. older population.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

30. seniors.mp. or elderly care/

31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

32. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

33. 24 or 25 or 26 or 27 or 28 or 29 or 30

34. 31 and 32 and 33

35. limit 34 to (English language and yr="1999 -Current" and (aged <65+ years>))