Objectively assessed physical activity and sedentary behavior and global cognitive function in older adults: a systematic review

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\textbf{ARTICLE INFO}

\textbf{Keywords:}
Aged
sedentary behavior
motor activity
accelerometry
cognition

\textbf{ABSTRACT}

\textbf{Background:} Both physical activity (PA) and sedentary behavior (SB) are important factors for healthy ageing. This systematic review aimed to determine the association of objectively assessed (instrumented) PA and SB with global cognitive function in older adults.

\textbf{Methods:} PubMed, Embase, the Cochrane Library (via Wiley), CINAHL, PsychINFO, and SPORTDiscus (via EBSCO) were searched from inception to June 21, 2020 for articles that described associations of objectively assessed PA/SB with global cognitive function in older adults aged 60 years and older. Results were synthesized using an effect direction heat map and albatross plots portrayed estimated effect sizes (standardized regression coefficients (\(\beta\)s)), which were summarized in boxplots.

\textbf{Results:} In total, 45 articles were included representing a total of 15,817 older adults (mean/median age ranged from 65 to 88 years; 49.5% female). Longitudinal studies (n = 7) showed that higher moderate-to-vigorous and light PA (MVPA and LPA, respectively) and lower SB were associated with better global cognitive function.

\textbf{Conclusions:} Higher PA and lower SB are associated with better global cognitive function in older adults. The greatest estimated effect sizes were found for moderate-to-vigorous and TPA, suggesting that greater duration of any PA, and high intensity PA could be most beneficial for global cognitive function.
1. Introduction

Physical activity (PA) reduces the risk of age-related diseases such as cardiovascular disease, type II diabetes mellitus (Wahid et al., 2016), and Alzheimer’s disease (Stephen et al., 2017) and is pivotal for healthy ageing. Older adults are therefore recommended to perform 150 minutes a week of moderate-to-vigorous PA (Garber et al., 2011). However, many older adults spend at least ten hours a day in sedentary behavior (SB) (Ardovittir et al., 2013; Arndottir et al., 2017; Fitzgerald et al., 2015; Ortlieb et al., 2014), which is known to be associated with cognitive function. Systematic reviews, including predominantly sub-national prospective register of systematic reviews, with registration of age (ABM). The following information was extracted: first author, publication year, country, cohort, study design and follow-up (if applicable), characteristics of study cohort (population selection), sample size, age (in years), sex (number and percentage of females), objective PA and SB measuring instrument (accelerometer or pedometer), device name, wearing location of the device, number of monitor days, mean device wear time, minimum wearing duration to define a valid day (in hours per day), number of valid days required for analysis, reported measures of PA and SB and their definition, PA and SB score, tool and definition used for the global cognitive function assessment, the score of global cognitive function, adjustment model(s), statistical test(s) used to study the association of interest, effect size(s) with 95% confidence interval(s) (CI) or standard error(s) (SE), and significance level(s) (p-value).

2. Methods

2.1. Information sources and search strategy

The protocol of this review was registered in PROSPERO International prospective register of systematic reviews, with registration number CRD42018103910. The electronic databases PubMed, Embase, the Cochrane Library (via Wiley), CINAHL, PsychINFO, and SPORTDiscus (via EBSCO) were searched from inception to June 21st, 2020 for articles describing associations of objectively measured PA and SB with any health outcome in older adults using the following search terms: ‘active or inactive lifestyle’, ‘motor activity’, and ‘people over 60 years of age’. The full search strategy is provided in Appendix A. Endnote (Version X8.2 Clarivate Analytics, Philadelphia, USA) and Rayyan QCRI (Ouzzani et al., 2016) were used to organize and manage articles that specifically reported associations of PA and SB with global cognitive function.

2.2. Inclusion criteria

Full-text articles published in English or Dutch were considered eligible if the following criteria were met: 1) observational or experimental study, 2) mean or median age of cohort greater than or equal to 60 years, 3) PA and SB were measured objectively (using an instrument i.e. an accelerometer or pedometer), 4) a measure of global cognitive function defined as Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Modified Mini-Mental State (3MS) Test (Teng and Chui, 1987), Six Item Screener (SIS) (Callahan et al., 2002), Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Skinner et al., 2012), Ascertain Dementia 8-Item Questionnaire (AD8) (Galvin et al., 2005), or any other validated assessment tool explicitly described as evaluating global cognitive function was reported, and 5) PA and SB were studied in relation to global cognitive function. Intervention studies were included if the association at baseline was reported or if data from the control group data could be used.

2.3. Article selection

Title and abstract screening and the subsequent screening of full-text articles were performed by two independent assessors (LDA and AGMR) and discrepancies regarding inclusion and exclusion judgments were settled by another assessor (EMR). References of included articles were checked for additional eligible articles.

2.4. Data extraction

Two independent assessors (LDA, AGMR or KAR) completed data extraction and disagreements were resolved by an additional assessor (ABM). The following information was extracted: first author, publication year, country, cohort, study design and follow-up (if applicable), characteristics of study cohort (population selection), sample size, age (in years), sex (number and percentage of females), objective PA and SB measuring instrument (accelerometer or pedometer), device name, wearing location of the device, number of monitor days, mean device wear time, minimum wearing duration to define a valid day (in hours per day), number of valid days required for analysis, reported measures of PA and SB and their definition, PA and SB score, tool and definition used for the global cognitive function assessment, the score of global cognitive function, adjustment model(s), statistical test(s) used to study the association of interest, effect size(s) with 95% confidence interval(s) (CI) or standard error(s) (SE), and significance level(s) (p-value).

2.5. Quality assessment

Each article was assessed for study quality and risk of bias by two assessors (LDA and AGMR) using modified versions of the Newcastle-Ottawa Scale (NOS) for cross-sectional and longitudinal studies (Wells et al., 2000), tailored to this systematic review; presented in Appendix B. Articles were assessed based on the following domains: 1) selection: representativeness of study cohort and ascertainment of exposure, 2) comparability: adjustment model and statistical test, and 3) outcome: assessment of the outcome and, in case of a longitudinal study design, adequacy to follow-up. The median of total stars (points) was set as the cut-off to discriminate between high and low quality (i.e., low and high risk of bias), defined as ≥4 or <4 out of 7 and ≥5 or <5 out of 9 stars for cross-sectional and longitudinal studies, respectively.

2.6. Statistical analysis

Associations of PA and SB with global cognitive function were selected according to the following hierarchy of adjustment: 1) age and sex, 2) age and sex, and other factors, 3) age or sex, and other factors, 4) neither age nor sex, other factors only, and 5) unadjusted. When multiple statistical analyses were used to describe the association of interest, the following order was considered: 1) adjusted linear regression, 2) adjusted logistic regression, 3) partial correlation, 4) unadjusted linear regression, including Pearson’s and Spearman’s correlation, 5) ANOVA, and 6) Mann-Whitney test, student’s t-test, or chi-squared test.

When the same measure of PA or SB was reported in different units the following continuous measures were preferred: step counts (#/day), activity counts (#/day), and duration of PA (total PA, TPA; moderate to vigorous PA, MVPA; and light PA, LPA) and SB (unit of time/day). Intensity measures included energy expenditure (EE) and metabolic equivalent of task (MET). Frequency and accumulation of PA and SB, respectively, were characterized as the number and duration of bouts, as...
well as (long) breaks in sedentary time (BST). Where p-values were not reported or reported using cut-off (e.g., reported as < 0.05), p-values were calculated using different methods. For linear regression, the upper and lower limit of the 95% confidence interval (CI) were used to calculate the standard error (SE), SE = (upper limit - lower limit of 95% CI)/(2*1.96), which was then used to obtain the absolute (abs) z-statistic (z) value, $z = \text{abs}(\text{regression coefficient/SE})$ to acquire the calculated p-value (p(calc)), $p(\text{calc}) = \exp((-0.717*z) - (0.416*z^2))$. Where ratio measured calculations were applied for except that the upper and lower limit of the 95% CI as well as the regression coefficient were first transformed into logarithms using natural log (ln) (Altman and Bland, 2011). For correlations, the sample size (n) and coefficients (including Pearson’s R, Spearman’s Rho) were used to obtain the t-statistic (t), $t = \sqrt{n} \cdot \frac{\text{mean}}{\text{sd}}$, which was compared to a two-sided t-distribution using Microsoft Excel’s T.VERD.2 T function to work out p(calc). Where mean scores were compared between groups, the means and standard deviations (sd) were used to acquire t via $(\text{mean}_1-\text{mean}_2)/\sqrt{\left((\text{sd}_1^2/\text{n}_1)+(\text{sd}_2^2/\text{n}_2)\right)}$, which was compared to a two-sided t-distribution using the above-mentioned function in Microsoft Excel (unpublished observations, 2020) (Ramsay et al., 2021). Associations for which the p-value could not be calculated were conservatively estimated as $>0.25$ (for non-significant associations) or $0.01 \leq p < 0.05$ (for significant associations) and included in the effect direction heat map but excluded from the albatross plots, as further described below.

2.7. Data visualization

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al., 2009) and Synthesis Without Meta-analysis (SWIM) (Campbell et al., 2020) guidelines, results on the associations of PA and SB with global cognitive function were synthesized using an effect direction heat map (qualitative overview) and albatross plots (quantification of estimated effect sizes).

2.8. Effect direction heat map

All associations of PA and SB with global cognitive function were ordered by sample size. The observed effect direction was derived from whether higher PA and lower SB were associated with better (positive effect) or worse (negative effect) global cognitive function, which was signified by an upwards or downwards triangle, respectively (Thomson and Thomas, 2013). Statistical significance level was indicated using a color scheme: p < 0.001 (dark blue filled triangle), 0.001 ≤ p < 0.01 (blue filled triangle), 0.01 ≤ p < 0.05 (light blue filled triangle), 0.05 ≤ p < 0.1 (light grey empty triangle), 0.1 ≤ p < 0.25 (grey empty triangle), and p ≥ 0.25 (dark grey empty triangle).

2.9. Albatross plots

Albatross plots present the estimated magnitude of reported associations (effect sizes) as a function of their sample size against two-sided p-values, stratified by the observed effect direction. More specifically, data (effect sizes) as a function of their sample size against two-sided p-values were superimposed onto the plot for reference to evaluate standardized regression coefficient at $\beta = 0.1$, $\beta = 0.2$, and $\beta = 0.3$. Albatross plots were generated using the Stata Statistical Software: Release 16.0 (StataCorp LLC, College Station, Texas, United States) for each measure of PA or SB with global cognitive function if that measure was reported in greater than or equal to five articles. Subgroup analyses were performed to assess the influence of population selection (general versus disease population), and adjustments (adjusted versus unadjusted associations) on estimated $f$s.

Boxplots were generated to summarize estimated $f$s, but due to the number of included articles longitudinal studies were depicted individually in contrast to cross-sectional studies. Boxplots were made using Plotly (Plotly Technologies Inc., Montreal, Quebec, Canada) to recapitulate the obtained $\beta$ coefficients.

3. Results

3.1. Article selection

The search resulted in 18,086 articles of which 9,660 articles remained after removal of duplicates. A total of 1,025 articles were independently screened for full-text, resulting in 45 articles (Alosco et al., 2012; Amagasa et al., 2020; Barnes et al., 2008; Brown et al., 2012; Cavalcante et al., 2018; Cerff et al., 2017; Chen et al., 2020; Eggermont and Scherder, 2009; Elhakeem et al., 2019; English et al., 2016; Falck et al., 2017; Fulcher et al., 2014; Hartman et al., 2018; Hausdorff et al., 2018; Iso-Markku et al., 2018; Ivata et al., 2013; Kimura et al., 2013; Koolhuijsen et al., 2019; Ku et al., 2017; Kuhlmei et al., 2013; Kurose et al., 2019; Liguori et al., 2020; Loprinzi et al., 2018; Lu et al., 2018; Manas et al., 2020; Mantri et al., 2019; Marmeleira et al., 2017; Moyle et al., 2017; Rantalainen et al., 2020; Razjouyan et al., 2020; Siddarth et al., 2018; Smagula et al., 2020; Stubbs et al., 2017; Suzuki et al., 2020; Taylor et al., 2019; Terashi et al., 2019; Thapa et al., 2020; Ume et al., 2018; Varma and Watts, 2017; Wondergem et al., 2020; Wondergem et al., 2019; Wu et al., 2020; Zhu et al., 2017) included in this review. An overview of the full article selection process can be found in Fig. 1.

3.2. Article characteristics

Table 1 shows the characteristics of seven longitudinal (Chen et al., 2020; Xu et al., 2017; Manas et al., 2020; Smagula et al., 2020; Stubbs et al., 2017; Wondergem et al., 2020; Zhu et al., 2017) and 38 cross-sectional (Alosco et al., 2012; Amagasa et al., 2020; Barnes et al., 2008; Brown et al., 2012; Cavalcante et al., 2018; Cerff et al., 2017; Eggermont and Scherder, 2009; Elhakeem et al., 2019; English et al., 2016; Falck et al., 2017; Fulcher et al., 2014; Hartman et al., 2018; Hausdorff et al., 2018; Iso-Markku et al., 2018; Ivata et al., 2013; Kimura et al., 2013; Koolhuijsen et al., 2019; Kuhlmei et al., 2013; Kurose et al., 2019; Liguori et al., 2020; Loprinzi et al., 2018; Lu et al., 2018; Mantri et al., 2019; Marmeleira et al., 2017; Moyle et al., 2017; Rantalainen et al., 2020; Razjouyan et al., 2020; Siddarth et al., 2018; Suzuki et al., 2020; Taylor et al., 2019; Terashi et al., 2019; Thapa et al., 2020; Ume et al., 2018; Varma and Watts, 2017; Wondergem et al., 2020; Wondergem et al., 2019; Wu et al., 2020), articles, which represent 7122 (mean or median age ranged from 65 to 86 years; 39.3% female) and 8685 (mean or median age ranged from 63.4 to 88 years; 54.7% female) older adults, respectively. Follow-up time for longitudinal studies ranged from five weeks to three years. Some populations of cohorts were selected based on participants with specific disease characteristics (population selection): heart failure (Alosco et al., 2012; Fulcher et al., 2014), cardiovascular disease (Kurose et al., 2019), peripheral artery disease (Cavalcante et al., 2018), stroke (English et al., 2016; Wondergem et al., 2020; Wondergem et al., 2019), Parkinson’s disease (Cerff et al., 2017; Kuhlmei et al., 2013; Loprinzi et al., 2018; Mantri et al., 2019; Terashi et al., 2019; Van Uem et al., 2018) dementia (Eggermont and Scherder, 2008; Moyle et al., 2017; Taylor et al., 2019), and Alzheimer’s disease (Liguori et al., 2020). All other articles were conducted in a general population of older adults. (Amagasa et al., 2020; Barnes et al., 2008; Brown et al., 2012; Chen et al., 2020; Elhakeem et al., 2019; Falck et al., 2017; Hartman et al., 2018).
2018; Hausdorff et al., 2018; Iso-Markku et al., 2018; Iwata et al., 2013; Kimura et al., 2013; Koohsari et al., 2019; Lu et al., 2018; Manas et al., 2020; Rantalainen et al., 2020; Suzuki et al., 2020; Thapa et al., 2020; Umegaki et al., 2018; van Alphen et al., 2016; Varma and Watts, 2017; Wu et al., 2020; Zhu et al., 2017)

Three study cohorts included nursing home residents (Eggermont and Scherder, 2008; Kuhlmei et al., 2013; Marmeleira et al., 2017).

4. Physical activity and sedentary behavior measures

All studies made use of accelerometers to objectively measure PA and SB. PA measures comprised of the following measures: number of steps (or time spent walking), (Alosco et al., 2012; Cerff et al., 2017; Chen et al., 2020; Fulcher et al., 2014; Hausdorff et al., 2018; Iso-Markku et al., 2018; Kurose et al., 2019; Mantri et al., 2019; Marmeleira et al., 2017; Moyle et al., 2017; Razjouyan et al., 2020; Siddarth et al., 2018; Taylor et al., 2019; van Uem et al., 2018), activity counts (or accelerations) (Barnes et al., 2008; Brown et al., 2012; Cerff et al., 2017; Eggermont and Scherder, 2008; Elhaakeem et al., 2019; Hartman et al., 2018; Kuhlmei et al., 2013; Liguori et al., 2020; Lu et al., 2018; Marmeleira et al., 2017; Rantalainen et al., 2020; Smagula et al., 2020; Terashi et al., 2019; van Alphen et al., 2016), and duration of TPA (Cavalcante et al., 2018; Cerff et al., 2017; Eggermont and Scherder, 2008; Iwata et al., 2013; Marmeleira et al., 2017; van Uem et al., 2018; Wu et al., 2020), MVPA (or vigorous PA (VPA) or moderate PA (MPA) individually), (Amagasa et al., 2020; Cavalcante et al., 2018; Cerff et al., 2017; English et al., 2016; Falck et al., 2017; Fulcher et al., 2014; Hartman et al., 2018; Iso-Markku et al., 2018; Kimura et al., 2013; Koohsari et al., 2019; Loprinzi et al., 2018; Manas et al., 2020; Marmeleira et al., 2017; Rantalainen et al., 2020, Razjouyan et al., 2020, Stubbs et al., 2017; Suzuki et al., 2020; Thapa et al., 2020; Umegaki et al., 2018, Varma and Watts, 2017; Wondergem et al., 2020; Wondergem et al., 2019; Wu et al., 2020; Zhu et al., 2017), and LPA (Amagasa et al., 2020; Cavalcante et al., 2018; Cerff et al., 2017; Hartman et al., 2018; Iso-Markku et al., 2018; Koohsari et al., 2019; Marmeleira et al., 2017; Razjouyan et al., 2020, Stubbs et al., 2017; Suzuki et al., 2020; Umegaki et al., 2018, Varma and Watts, 2017; Wondergem et al., 2020; Wondergem et al., 2019; Wu et al., 2020; Zhu et al., 2017). SB was measured in all studies as SB duration (or time spent lying) (Amagasa et al., 2020; Cerff et al., 2017; English et al., 2016; Falck et al., 2017; Hartman et al., 2018; Iso-Markku et al., 2018; Kimura et al., 2013; Koohsari et al., 2019; Loprinzi et al., 2018; Manas et al., 2020; Marmeleira et al., 2017; Rantalainen et al., 2020, Razjouyan et al., 2020, Stubbs et al., 2017; Suzuki et al., 2020; Thapa et al., 2020; Umegaki et al., 2018, Varma and Watts, 2017; Wondergem et al., 2020; Wondergem et al., 2019; Wu et al., 2020; Zhu et al., 2017). Intensity measures included energy expenditure (EE) (Cerff et al., 2017; Kurose et al., 2019; Moyle et al., 2017; Stubbs et al., 2017; van Uem et al., 2018) and metabolic equivalent of task (MET) (Iso-Markku et al., 2018; Moyle et al., 2017). Frequency and accumulation of PA and SB, respectively, were characterized as the
| Author year | Country | Cohort | Study design | Population | Sample size (n) | Age, in years | Female, n (%) |
|-------------|---------|--------|--------------|------------|----------------|---------------|---------------|
| Alosco 2012 | US      | N/A    | Cross-sectional | Heart failure | 96 (active: 21; limited in PA: 44; sedentary: 31) | 69.81 ± 8.79 (N/R) | 35 (36.5) (N/R) |
| Barnes 2008 | US      | SOF    | Cross-sectional | Community-dwelling w/ long-term care | 511 | 73.4 ± 5.6 | 271 (53.0) |
| Brown 2012  | AU      | AIBL   | Cross-sectional | Community-dwelling | 2736 (Q1 to Q4: 684) | Q1: 84.1 ± 3.9; Q2: 83.7 ± 3.5; Q3: 83.2 ± 3.6; Q4: 82.6 ± 3.5 | 100 |
| Dementi 2018 | AU      | N/A    | Cross-sectional | Symptomatic peripheral artery disease | 130 | 67 ± 8 | 117 (54) |
| Cerff 2017  | DE, NL, | N/A    | Cross-sectional | Parkinson’s disease (mild to moderate) | 48 (NC: 17; MCI: 22; dementia: 9) | In median (range), NC: 71 (44 to 80); MCI: 68 (57 to 78); dementia: 72 (67 to 75) | NC: 7 (41); MCI: 5 (23); dementia: 0 |
| Chen 2020   | TW, GB, | N/A    | Longitudinal | Community-dwelling | 273 | 65-69 years: n = 70; 70-79 years: n = 146; 80+: n = 58 (based on total n = 274) | 149 (54.4) (based on total n = 274) |
| Eggermont 2008 | NL | N/A    | Cross-sectional | Nursing home residents w/ dementia or cognitive deterioration | 76 | 84.2 ± 5.1 | 66 (86.8) |
| Elbakeem 2019 | GB | VIBR   | Cross-sectional | Community-dwelling | 558 | 69 ± N/R | 269 (48.2) |
| English 2016 | AU | N/A    | Cross-sectional | Stroke | (46 to 49) | 67.2 ± 11.2 (based on total n = 50) | 17 (34) (based on n = 50) |
| Falck 2017   | CA      | N/A    | Cross-sectional | Community-dwelling | 150 | 71.11 ± 7.22 | 101 (67.10) |
| Fulcher 2014 | US      | N/A    | Cross-sectional | Heart failure | 93 | 68.48 ± 9.48 | 31 (33.7) |
| Hartman 2018 | IL, US, | N/A    | Cross-sectional | Community-dwelling dementia patients and control subjects | 94 (dementia: 45; control subjects: 49) | Dementia: 79.6 ± 5.9; control subjects: 80.0 ± 7.7 | Dementia: 22 (48.9); control subjects: 25 (51.0) |
| Hausdorff 2018 | IL, US, | N/A    | Cross-sectional | Mild cognitive impairment and control subjects | 136 (MCI: 36; control subjects: 100) | MCI: 77.8 ± 6.4; control subjects: 76.0 ± 6.2 | MCI: 26 (72.7); control subjects: 78 (78.0) |
| Iso-Markku 2018 | IT, FI | FTC    | Cross-sectional | Twins | 276 | 72.9 ± 1.0 | 374 (51.5) |
| Iwata 2013   | JP      | N/A    | Cross-sectional | Dementia patients and control subjects (including mild cognitive impairment) | 30 (dementia: 14; control subjects: 16) | Dementia, M: 74.2 ± N/R and F: 75.4 ± N/R; control subjects, M:72 ± N/R and F: 74.6 ± N/R | Dementia: 9 (64.3); control subjects: 5 (31.3) |
| Kimura 2013  | JP      | N/A    | Cross-sectional | Community-dwelling | 43 (brisk walking long: 22; short: 21) | Brisk walking long: 71.3 ± 3.5; short: 70.9 ± 4.1 | Brisk walking long: 9 (42.9); short: 14 (63.6) |
| Koohsari 2019 | JP | N/A    | Cross-sectional | Community-dwelling | 274 | 74.5 ± 6.1 | 149 (54.4) |
| Ku 2017      | TW, GB, | N/A    | Longitudinal | Community-dwelling | 274 | 74.5 ± 6.1 | 149 (54.4) |
| Kuhlmei 2013 | DE, GB  | N/A    | Cross-sectional | Nursing home residents w/ dementia, mild cognitive impairment, control subjects | 76 (dementia: 32; MCI: 21; control subjects: 23) | 81 ± 7 (N/R) | 66 (86.8) (N/R) |
| Kurose 2019  | JP      | N/A    | Cross-sectional | Cardiovascular disease patients in a cardiac rehabilitation program | 102 | 74.1 ± 7.4 | 38 (37.3) |
| Liguori 2020 | IT      | N/A    | Cross-sectional | Alzheimer’s disease | 18 | 71.0 ± 5.9 | 10 (55.6) |
| Loprinzi 2018 | US | N/A    | Cross-sectional | Parkinson’s disease | 23 | 68.7 ± N/R | 10 (43.5) |
| Lu 2018      | CN      | N/A    | Cross-sectional | Alzheimer’s disease, mild cognitive impairment, control subjects | 810 (AD: 182; MCI: 105; low MoCA only: 252; control subjects: 271) | AD: 80.8 ± 5.9; MCI: 83.6 ± 3.7; low MoCA only: 83.4 ± 4.0; control subjects: 81.9 ± 3.5 | AD: 121 (65.4); MCI: 51 (48.6); low MoCA only: 120 (47.6); control subjects: 104 (38.2) |
| Mañas 2020   | ES, AU, | TSHA   | Longitudinal (FU: 3.0 ± 0.8 years) | Community-dwelling | 186 (active: 60; inactive: 126) | Active: 75.32 ± 3.05; inactive: 77.29 ± 4.13 | Active: 21 (35.0); inactive: 77 (61.1) |
| Mantri 2019  | US      | N/A    | Cross-sectional | Parkinson’s disease | 30 | In median [IQR]: 70 (Terashita et al., 2017; Itaga et al., 2020 Umegaki et al., 2018van Alphen et al., 2018van Uem et al., 2018 Varma and Watts, 2017) | 2 (6.7) |
| Marmeireira 2017 | PT | N/A    | Cross-sectional | Nursing home residents w/ and w/o cognitive impairment | 38 (cognitive impairment yes: 29; no: 9) | Cognitive impairment (n = 48) yes: 83.9 ± 7.7; no (n = 22): 82.2 ± 8.8 | Cognitive impairment (n = 48) yes: 35 (72.9); no (n = 22): 12 (54.5) |
| Moyle 2017   | AU, QA, | N/A    | Cross-sectional | Dementia patients w/ long-term care | 192 | 85.5 ± 7.7 | 142 (74.0) |

Note: Table 1 Characteristics of included studies.


### Table 1 (continued)

| Author year | Country | Cohort | Study design | Population | Sample size (n) | Age, in years | Female, n (%) |
|-------------|---------|--------|--------------|------------|----------------|---------------|---------------|
| Rantalainen 2020 | FI, AU, SG | | Cross-sectional | Community-dwelling | 60 (dementia; memory complaints: 24; no memory concerns: 27) | 75 ± 10 | 129 (79) |
| Rajouyan 2020 | US | N/A | Cross-sectional | Community-dwelling | 159 | 72.7 ± 8.1 | 18 (69.2) |
| Siddarth 2018 | US | N/A | Cross-sectional | Memory complaints (w/o dementia) | 26 | 86 ± 2.6 (at MRI assessment) | 37 (53) |
| Smagula 2020 | US | Health ABC | Longitudinal (FU: 14 years) | Community-dwelling | 70 | 74.52 ± 6.12 | 149 (54.4) |
| Stubbs 2017 | GB, TW | N/A | Cross-sectional | Community-dwelling | 274 | 68.0 ± 0.9 | 68 (50.0) |
| Suzuki 2020 | JP | Arakawa 85+ | Cross-sectional | Community-dwelling | 45 | 81.4 ± 6.4 | 19 (42) |
| Taylor 2019 | AU | N/A | Cross-sectional | Community-dwelling | 136 | 76.97 ± 3.69 | 17 (32.7) |
| Terashi 2019 | JP | N/A | Cross-sectional | Parkinson’s disease | 52 | 72 ± 4.7 | 102 (60) |
| Thapa 2020 | KR | N/A | Cross-sectional | Community-dwelling | 170 | 74.52 ± 6.12 | 212 (46.4) |
| Umemaki 2018 | JP | TOPICS | Cross-sectional | Community-dwelling | 455 | 68.0 ± 0.9 | 68 (50.0) |
| Van Alphen 2016 | NL | N/A | Cross-sectional | Dementia patients and control subjects | 146 (dementia: 120; control subjects: 26) | 81.4 ± 6.4 | 19 (42) |
| Van Uem 2018 | DE, NL | N/A | Cross-sectional | Parkinson’s disease w/ and w/o dementia | 47 (dementia yes: 8; no: 39) | 72 ± 4.7 | 17 (32.7) |
| Varma 2017 | US | N/A | Cross-sectional | Dementia patients and control subjects | 92 (dementia: 39; control subjects: 53) | 73.5 ± 6.5 | 17 (32.7) |
| Wondergem 2019 | NL | RISE | Cross-sectional | Stroke | 190 (exercise: 43; movers: 87; prolongers: 60 in a sedentary group) | 73.5 ± 6.5 | 17 (32.7) |
| Wondergem 2020 | NL | N/A | Longitudinal (FU: 5 weeks) | Stroke | 140 | 67.1 ± 10.8 | 47 (33.6) |
| Wu 2020 | CN | N/A | Cross-sectional | Community-dwelling | 308 | 68.66 ± 5.37 | 177 (57.7) |
| Zhu 2017 | CN, US | REGARDS | Longitudinal (FU: 2.9 ± 1.1 years) | Community-dwelling | 6452 | 69.7 ± 8.5 | 3565 (55.3) |

Age is presented as mean ± standard deviation, median (range), or number of participants in age groups. US: United States, JP: Japan, GB: United Kingdom of Great Britain and Northern Ireland, BE: Belgium, AU: Australia, BR: Brazil, DE: Germany, NL: The Netherlands, TW: Taiwan, CN: Canada, IL: Israel, IT: Italy, FI: Finland, ES: Spain, PT: Portugal, QA: Qatar, KR: Korea. NEIGE: Neuron to Environmental Impact across Generations, SOF: Study of Osteoporotic Fractures, AIBL: Alzheimer’s Disease Cooperative Study, TSHA: Toledo Study of Healthy Aging, Health ABC: The Health, Aging and Body Composition Study, N/A: not applicable. FU: follow-up period. W/ with, w/o: without. N/R: not reported, Q: quartile, NC: non-cognitively impaired, MCI: mild cognitive impairment, AD: Alzheimer’s Disease, MoCA: Montreal Cognitive Assessment.

### 4.1. Cognitive parameters

Global cognitive function was assessed in the included studies using the following tools: Mini-Mental State Examination (MMSE), (Alonso et al., 2012; Amagasa et al., 2020; Barnes et al., 2008; Brown et al., 2012; Eggermont and Scherer, 2008; Hartman et al., 2018; Kimura et al., 2013; Koohari et al., 2019; Kurose et al., 2019; Liguori et al., 2020; Manas et al., 2020; Marmeirela et al., 2017; Rajouyan et al., 2020; Siddarth et al., 2018; Terashi et al., 2019; Thapa et al., 2020; Umemaki et al., 2018; van Alphen et al., 2016; van Uem et al., 2018); Montreal Cognitive Assessment (MoCA) (Cavalcante et al., 2018; English et al., 2016; Loprinzi et al., 2018; Lu et al., 2018; Mantri et al., 2019; Rantalainen et al., 2020; Taylor et al., 2019; Wondergem et al., 2020; Wondergem et al., 2019; Wu et al., 2020); Movement Disorder Society (MDS) Task Force Level II recommendation (Cerff et al., 2017; van Uem et al., 2018); Ascertain Dementia 8-Item Questionnaire (AD8) (Siddarth et al., 2018; Terashi et al., 2019; Thapa et al., 2020), Alzheimer’s Disease Assessment Scale Cognition Subscale (ADAS-Cog Plus) (Falcik et al., 2017), modified Mini-Mental State Examination (3MS) (Fulcher et al., 2014; Smagula et al., 2020), Clinical Dementia Rating Scale (Hausdorff et al., 2018; Varma and Watts, 2017), Telephone Interview for Cognitive Status and Telephone Assessment for Dementia (Isomarkku et al., 2018), Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (Iwata et al., 2013), DemTect Battery (Kuhlmei et al., 2013), Rowlands Universal Dementia Assessment (RUDAS) (Moyle et al., 2017), and Six Item Screener (Zhu et al., 2017) (Appendix Table C2).

### 4.2. Association of PA/SB with global cognitive function

Table 2 describes all associations between PA/SB and global cognitive function. These associations are visualized by effect directions in heatmaps in Fig. 2. Estimated βs obtained from albatross plots in Fig. 3 are compared in Fig. 4 via boxplots providing the median and number (Cerff et al., 2017; Falcik et al., 2017; Taylor et al., 2019; van Uem et al., 2018) and duration (Amagasa et al., 2020; Cerff et al., 2017; van Uem et al., 2018; Wondergem et al., 2020) of PA bouts (periods of activity) and the number (Cerff et al., 2017; Falcik et al., 2017; Hartman et al., 2018; Lu et al., 2018; van Uem et al., 2018) and duration (Cerff et al., 2017; English et al., 2016; Hartman et al., 2018; Lu et al., 2018; van Uem et al., 2018) of SB bouts as well as breaks in sedentary time (BST) (Hartman et al., 2018; Lu et al., 2018) (Appendix Table C1).
Table 2
Associations of objectively measured physical activity and sedentary behavior with cognition.

| Author year | PA/SB measure(s) | Cognition | Adjustment | Effect size (95% confidence interval) | p-value used for data syntheses |
|-------------|-----------------|-----------|------------|--------------------------------------|-------------------------------|
| Alosco 2012 | Steps (#/day) active, limited PA, sedentary | Cognitive function across PA groups | MMSE (0 to 30) | Unadjusted ANOVA F(2, 93) = 3.09 | p = 0.05 |
|            | MVPA (min/day) Impaired cognition | MMSE score below or equal to 23 out of 30 | Age and sex OR = 0.71 (0.45, 1.12) | p(calc) = 0.141 |
|            | Bouted MVPA (min/day) Impaired cognition | MMSE score below or equal to 23 out of 30 | Age and sex OR = 0.93 (0.72, 1.19) | — |
| Amagasa 2020 | Sporadic MVPA (min/day) Impaired cognition | MMSE score below or equal to 23 out of 30 | Age and sex OR = 0.85 (0.44, 1.68) | — |
|            | LPA (min/day) Impaired cognition | MMSE score below or equal to 23 out of 30 | Age and sex OR = 1.34 (0.51, 3.83) | p(calc) = 0.581 |
| Barnes 2008 | Activity counts (#/min) quartiles; Q1 = least active | Cognitive function | MMSE score below or equal to 23 out of 30 | Age and sex OR = 1.03 (0.46, 2.27) | p(calc) = 0.947 |
| Brown 2012 | Activity counts (#/day) Cognitive function | MMSE (0 to 30) | Age, sex, education years, APOE e4 allele carriage, body mass index, and cardiovascular disease β = 0.04 (N/R); p ≥ 0.05 | p(N/R) ≥ 0.25 |
|            | TPA (min/day) Cognitive function | MoCA (0 to 30) | Age, sex, education status, and disease severity B = 0.003 (-0.004, 0.010); SE = 0.003 | p = 0.393 |
| Cavalcante 2018 | MVPA (min/day) Cognitive function | MoCA (0 to 30) | Age, sex, education status, and disease severity B = 0.740 (-0.282, 1.761); SE = 0.516 | p = 0.154 |
|            | LPA (min/day) Cognitive function | MoCA (0 to 30) | Age, sex, education status, and disease severity B = 0.004 (-0.005, 0.014); SE = 0.004 | p(calc) = 0.375 |
|            | Steps (#/day) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 11.42 | — |
|            | Accelerations (g) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 1.32 (2.22, 7.82) | p = 0.76; — |
|            | EE (MJ/day) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 0.69 (0.12, 4.11) | p = 0.68; — |
|            | TPA (% time) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 18.53 | — |
| Cerff 2017 | MVPA (% time) (MPA) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 0.68 (0.15, 3.16) | p = 0.31; — |
|            | LPA (% time) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 1.38 (0.23, 8.19) | p(calc) = 0.48; — |
|            | PA bouts (sec) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 0.94 (0.20, 4.33) | — |
|            | # PA bouts PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 0.53 (0.09, 3.16) | — |
|            | SB (% time) PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | 1.32 (0.22, 8.19) | — |

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Table 2 (continued)

| Author year | PA/SB measure(s) | Cognition | Adjustment | Effect size (95% confidence interval) | p-value used for data syntheses |
|-------------|-----------------|-----------|------------|--------------------------------------|---------------------------------|
|            | Parameter       | Tool      |            |                                      |                                 |
|            | SB bouts (sec)  | PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | Non-cognitively impaired vs dementia: OR = 0.10 (0.02, 0.65) p = 0.02; — |
|            | # SB bouts      | PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Depression and motor impairment | Mild cognitive impairment vs dementia: OR = 0.14 (0.03, 0.69) Non-cognitively impaired vs dementia: OR = 10.30 (1.58, 67.3) |
| Chen 2020  | Steps (#/day)   | Cognitive function | AD8 (0 to 8) | Age, sex, education level, marital status, body mass index, number of chronic diseases, activities of daily living, cognitive ability at baseline, and wear time | RR = 0.89 (0.83, 0.97) p(calc) = 0.003 |
| Eggermont  | Activity counts (#/day) | Cognitive function | MMSE (0 to 30) | Unadjusted | Pearson’s R = 0.07; p = 0.28 p = 0.28 |
| Falck 2017 | # PA bouts      | Cognitive function | ADAS-Cog (0 to 70) | Age, sex, and education | β = −0.17; R^2 = 0.321 p = 0.024 |
| Falck 2017 | SB (%) time     | Cognitive function | ADAS-Cog (0 to 70) | Age, sex, and education | β = −0.203; R^2 = 0.312 p = 0.070 |
|             | # SB bouts      | Cognitive function | ADAS-Cog (0 to 70) | Age, sex, and education | β = 0.007; R^2 = 0.311 p = 0.089 |
| Fulcher 2014 | Steps (#/day)   | Cognitive function | 3MS (0 to 100) | Sex, high blood pressure, diabetes, depression, and heart failure severity | β = 0.28; B = 0.001 (SE = 0.000); p < 0.01 0.001 ≤ p < 0.01 |
|             | MVPA (min/day)  | Cognitive function | 3MS (0 to 100) | Sex, high blood pressure, diabetes, depression, and heart failure severity | β = 0.24; B = 0.03 (SE = 0.01) p(calc) = 0.003 |

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## Table 2 (continued)

| Author year | PA/SB measure(s) | Cognition | Adjustment | Effect size (95% confidence interval) | p-value used for data syntheses |
|-------------|-----------------|-----------|------------|--------------------------------------|--------------------------------|
| Koohsari 2013 | SB bouts (min) | PA across cognitive function groups | MMSE score below or equal to 24 out of 30 indicates dementia | Unadjusted | Dementia vs control subjects: Mann-Whitney test = N/R; \( p = 0.008 \) |
| | # SB bouts | PA across cognitive function groups | MMSE score below or equal to 24 out of 30 indicates dementia | Unadjusted | Dementia vs control subjects: Mann-Whitney test = N/R; \( p = 0.227 \) |
| Hausdorff 2018 | Steps (#/day) (walking) | PA across cognitive function groups | Clinical Dementia Rating Scale score of 0.5 indicates mild cognitive impairment | Education years | Mild cognitive impairment vs control subjects: Cohen’s \( d = 0.537; p = 0.016 \) |
| | Steps (#/day) | Cognitive function | TICS/TELE (N/R) | Age and sex | \( \beta = 0.04 (-0.07, 0.15) \) | \( p(\text{calc}) = 0.971 \) |
| Iso-Markku 2018 | MVPA (min/day) | Cognitive function | TICS/TELE (N/R) | Age and sex | \( \beta = 0.94 (-1.35, 3.24) \) | \( p(\text{calc}) = 0.653 \) |
| | LPA (min/day) | Cognitive function | TICS/TELE (N/R) | Age and sex | \( \beta = 0.18 (-0.51, 0.88) \) | \( p(\text{calc}) = 0.935 \) |
| | SB (min/day) | Cognitive function | TICS/TELE (N/R) | Age and sex | \( \beta = 0.22 (-0.07, 0.52) \) | \( p(\text{calc}) = 0.945 \) |
| Iwata 2013 | TPA (ex/day) | Cognitive function | Diagnostic and Statistical Manual of Mental Disorders IV | Unadjusted | Dementia yes vs no: T-test = N/R; \( p = 0.0006 \) |
| Kimura 2013 | MVPA (min/day) (MIPA brisk walking long vs short) | Cognitive function | MMSE (0 to 30) | Unadjusted | T-test = N/R; \( p = 0.176 \) |
| Koohsari 2019 | MVPA (min/day) | Impaired cognition | MMSE score below or equal to 25 out of 30 | OR = 0.99 (0.98, 1.01) | \( p = 0.41 \) |
| | LPA (min/day) | Impaired cognition | MMSE score below or equal to 25 out of 30 | OR = 0.99 (0.98, 1.01) | \( p = 0.46 \) |
| Ku 2017 | SB (hrs/day) | Cognitive function | AD8 (0 to 8) | Age, sex, and time | OR = 1.13 (1.04, 1.22) | \( p = 0.002 \) |
| Kuhlmei 2013 | Activity counts (#/10 sec epochs) | Cognitive function | DemTect (0 to 18) | Unadjusted | ANOVA = N/R; \( p < 0.001 \) | \( p(\text{calc}) < 0.001 \) |
| Kurse 2019 | Steps (#/day) | Cognitive function | MMSE (0 to 30) | Age, sex, cardiac function, and hypnotics | \( \beta = 0.047 (N/R); p = 0.708 \) | \( p = 0.708 \) |
| Liguori 2020 | Activity counts (#/day) (M10 AVG) | Cognitive function | MMSE (0 to 30) | Unadjusted | Spearman’s Rho = 0.2 | \( p(\text{calc}) = 0.426 \) |
| Loprinzi 2018 | MVPA (min/day) | Cognitive function | MoCA (0 to 30) | Age, sex, and motor function | \( \beta = 0.09 (0.003, 0.19) \) | \( p = 0.05 \) |
| | Activity counts (#/min) | PA across cognitive function groups | MoCA score of median (range) 16 (11 to 21) indicates Alzheimer’s disease | Age, sex, and time | Normal functioning, mild cognitive impairment, and low MoCA only vs Alzheimer’s disease: ES = N/R; \( p < 0.05 \) | \( 0.01 \leq p < 0.05 \) |
| | BST (times/day) | PA across cognitive function groups | MoCA score of median (range) 16 (11 to 21) indicates Alzheimer’s disease | Age, sex, education years, body mass index, usual gait speed, living status, disease burden, and worse time | Normal functioning, mild cognitive impairment, and low MoCA only vs Alzheimer’s disease: ES = N/R; \( p < 0.05 \) | \( 0.01 \leq p < 0.05 \) |
| Lu 2018 | SB bouts (min) | PA across cognitive function groups | MoCA score of median (range) 16 (11 to 21) indicates Alzheimer’s disease | Age, sex, education years, body mass index, usual gait speed, living status, disease burden, and worse time | Normal functioning, mild cognitive impairment, and low MoCA only vs Alzheimer’s disease: ES = N/R; \( p < 0.05 \) | \( 0.01 \leq p < 0.05 \) |
| | # SB bouts | PA across cognitive function groups | MoCA score of median (range) 16 (11 to 21) indicates Alzheimer’s disease | Age, sex, education years, body mass index, usual gait speed, living status, disease burden, and worse time | Normal functioning, mild cognitive impairment, and low MoCA only vs Alzheimer’s disease: ES = N/R; \( p < 0.05 \) | \( 0.01 \leq p < 0.05 \) |
| | # Long SB bouts | PA across cognitive function groups | MoCA score of median (range) 16 (11 to 21) indicates Alzheimer’s disease | Age, sex, education years, body mass index, usual gait speed, living status, disease burden, and worse time | Normal functioning, mild cognitive impairment, and low MoCA only vs Alzheimer’s disease: ES = N/R; \( p < 0.05 \) | \( 0.01 \leq p < 0.05 \) |
| Author year | PA/SB measure(s) | Cognition | Adjustment | Effect size (95% confidence interval) | p-value used for data syntheses |
|-------------|-----------------|-----------|------------|--------------------------------------|---------------------------------|
| Mancia 2020 | MVPA (min/week) | Cognitive function across PA groups | MMSE (0 to 30) | T-test = N/R; p < 0.05 for those physically inactive | p(calc) = 0.06 |
| ----------- | -----------------|-----------|------------|--------------------------------------|---------------------------------|
| Mantri 2019 | Steps (#/day)    | Cognitive function | MoCA (0 to 30) | Age and disease severity Partial Spearman’s Rho = 0.31 p = 0.14 |
| ----------- | -----------------|-----------|------------|--------------------------------------|---------------------------------|
| Marmeleira 2017 | MVPA (min/day) | Cognitive function across PA groups | MMSE score below or equal to 15, 22, or 27 out of 30 indicates mild cognitive impairment | Cognitive impairment yes vs no: T-test = N/R; p < 0.01 p(calc) = 0.029 |
| ----------- | -----------------|-----------|------------|--------------------------------------|---------------------------------|
| Moore 2017 | EE (kJ) | Cognitive function | MoCA score below or equal to 15, 22, or 27 out of 30 indicates mild cognitive impairment | Cognitive impairment yes vs no: T-test = N/R; p < 0.05 p(calc) = 0.137 |
| ----------- | -----------------|-----------|------------|--------------------------------------|---------------------------------|
| Rantalainen 2020 | MVPA (min/day) | Cognitive function across PA groups | MoCA score below or equal to 15, 22, or 27 out of 30 indicates mild cognitive impairment | Cognitive impairment yes vs no: T-test = N/R; p < 0.01 p(calc) = 0.001 |
| ----------- | -----------------|-----------|------------|--------------------------------------|---------------------------------|
| Razjouyan 2020 | Steps (1000/day) | Cognitive function | MoCA score below or equal to 15, 22, or 27 out of 30 indicates mild cognitive impairment | Cognitive impairment yes vs no: T-test = N/R; p < 0.05 p(calc) = 0.926 |
| ----------- | -----------------|-----------|------------|--------------------------------------|---------------------------------|

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Table 2

| Author year | PA/SB measure(s) | Cognition | Adjustment | Effect size (95% confidence interval) | p-value used for data syntheses |
|-------------|------------------|-----------|------------|---------------------------------------|----------------------------------|
| Siddarth 2018 | SB (hrs/day) | Cognitive function | MMSE (0 to 30) | Unadjusted | Spearman’s Rho—0.29 |
| Smagula 2020 | Steps (#/day) high vs low | Cognitive function | MMSE (0 to 30) | Unadjusted | Mann-Whitney test — 134.5; p = 0.07 |
| | Activity counts (#/day) (relative amplitude) | Cognitive function | 3MS (0 to 100) | Age, sex, race, and education | β = 0.00 (-0.30, 0.30) |
| | EE (kcal/week) | Cognitive function | AD8 (0 to 8) | Wear time | Partial Pearson’s R—0.35 |
| Stubbs 2017 | MVPA (hrs/day) | Cognitive function | AD8 (0 to 8) | Age, sex, attainment to education, marital status, income source, smoking, number of ability chronic diseases, depressive symptoms, activities of daily living, and wear time | RR — 0.85 (0.75, 0.95) |
| | LPA (hrs/day) | Cognitive function | AD8 (0 to 8) | Age, sex, attainment to education, marital status, income source, smoking, number of ability chronic diseases, depressive symptoms, activities of daily living, and wear time | RR — 0.75 (0.60, 0.92) |
| Suzuki 2020 | MVPA (min/day) | PA across cognitive function groups | ACE-III score below or equal to 88 (decline) or greater than or equal to 89 (maintain) out of 100 | Unadjusted | Across cognitive decline and maintain, M: Mann-Whitney test — N/R; p = 0.184; F: Mann-Whitney test — N/R; p = 0.370 |
| | LPA (min/day) | PA across cognitive function groups | ACE-III score below or equal to 88 (decline) or greater than or equal to 89 (maintain) out of 100 | Unadjusted | Across cognitive decline and maintain, M: Mann-Whitney test — N/R; p = 0.020; F: Mann-Whitney test — N/R; p = 0.111 |
| Taylor 2019 | SB (min/day) | PA across cognitive function groups | ACE-III score below or equal to 88 (decline) or greater than or equal to 89 (maintain) out of 100 | Unadjusted | Across cognitive decline and maintain, M: Mann-Whitney test — N/R; p = 0.363; F: Mann-Whitney test — N/R; p = 0.357 |
| | Steps (#/day) # PA bouts (walking) | Cognitive function | MoCA and modified ACE-III (0 to 30) | Unadjusted | Pearson’s R = 0.097 (BCa 95% CI: 0.242, 0.391) |
| | Accelerations (m/s²) | Cognitive function | MMSE (0-30) | Age, sex, and education | β — 0.165 (0.479, 0.149) |
| Thapa 2020 | MVPA (min/week) inactive vs active | Cognitive function (dementia) | MMSE (0-30); predict estimated dementia risk | Unadjusted | Age, sex, and body mass index |
| | VPA (min/day) | Cognitive function | MMSE (0-30) | Unadjusted | Partial Pearson’s R—0.054 |
| Umegaki 2018 | MVPA (min/day) (MFA) | Cognitive function | MMSE (0-30) | Unadjusted | Partial Pearson’s R—0.023 |
| | LPA (min/day) | Cognitive function | MMSE (0-30) | Unadjusted | Partial Pearson’s R — 0.070 |
| | Activity counts (#/day) | Cognitive function groups | MMSE score below or equal to 23 out of 30 indicates dementia | Unadjusted | Dementia vs control subjects: ANOVA (1, 116) = 2.955 |
| Van Alphen 2016 | SB (hrs/day) | PA across cognitive function groups | MMSE score below or equal to 23 out of 30 indicates dementia | Unadjusted | Dementia vs control subjects: ANOVA (1, 116) = 4.013 |
| | Steps (#/day) | PA across cognitive function groups | MDS task force level 2 recommendation to (to diagnose dementia) | Unadjusted | Dementia vs no: T-test — N/R; p = 0.43 |
| Van Uem 2018 | EE (kJ/min) | PA across cognitive function groups | MDS task force level 2 recommendation to (to diagnose dementia) | Unadjusted | Dementia vs no: T-test — N/R; p = 0.56 |
| | TPA (% time) | PA across cognitive function groups | MDS task force level 2 recommendation to (to diagnose dementia) | Unadjusted | Dementia vs no: T-test — N/R; p = 0.05 |
| | PA bouts (min) | PA across cognitive function groups | Unadjusted | Dementia vs no: T-test — N/R; p = 0.83 |

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Table 2 (continued)

| Author year | PA/SB measure(s) | Cognition | Adjustment | Effect size (95% confidence interval) | p-value used for data syntheses |
|-------------|------------------|-----------|------------|--------------------------------------|-------------------------------|
|             |                  |           |            | Dementia yes vs no: T-test = N/R; p = 0.08 | p = 0.08 |
| # PA bouts  | PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Unadjusted |                                    |  |
| SB (% time) | PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Unadjusted | Dementia yes vs no: T-test = N/R; p = 0.02 | p = 0.02 |
| SB bouts (min) | PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Unadjusted | Dementia yes vs no: T-test = N/R; p = 0.01 | p = 0.01 |
| # SB bouts  | PA across cognitive function groups | MDS task force level 2 recommendation (to diagnose dementia) | Unadjusted | Dementia yes vs no: T-test = N/R; p = 0.09 | p = 0.09 |
| MVPA (log VM) (MPA) | PA across cognitive function groups | Clinical Dementia Rating Scale (N/R) | Age, sex, body mass index, race, VO2max, and mobility impairment | Alzheimer’s disease vs control subjects: \( \beta = -0.679; \text{SE} = 0.299 \) | p = 0.026 |
| Varma 2017  | LPA (VM)          | Clinical Dementia Rating Scale (N/R) | Age, sex, body mass index, race, VO2max, and mobility impairment | Alzheimer’s disease vs control subjects: \( \beta = -39.538; \text{SE} = 28.931.13 \) | p = 0.176 |
| SB (min/day) | PA across cognitive function groups | Clinical Dementia Rating Scale (N/R) | Age, sex, body mass index, race, VO2max, and mobility impairment | Alzheimer’s disease vs control subjects: \( \beta = -5.738; \text{SE} = 26.691 \) | p = 0.830 |
| Wondergem 2019 | SB (hrs/day) sedentary exercisers, movers, and prolongers | MoCA score below 26 out of 30 | Unadjusted | *T-test = N/R; p = 0.52 | p = 0.52 |
| Wondergem 2020 | MVPA (hrs/day) | MoCA score below or equal to 25 out of 30 | Unadjusted | OR = 0.97 (0.49, 1.89) | p(calc) = 0.936 |
|              | PA bouts (hrs) | MoCA score below or equal to 25 out of 30 | Unadjusted | OR = 1.38 (0.69, 2.77) | p(calc) = 0.370 |
|              | LPA (hrs/day) | MoCA score below or equal to 25 out of 30 | Unadjusted | OR = 2.09 (1.01, 4.33) | p(calc) = 0.047 |
|              | SB (hrs/day) | MoCA score below or equal to 25 out of 30 | Unadjusted | OR = 0.83 (0.41, 1.67) | p(calc) = 0.615 |
|              | SB bouts, median (min) | MoCA score below or equal to 25 out of 30 | Unadjusted | OR = 4.68 (1.23, 17.84) | p(calc) = 0.024 |
| Wu 2020     | TPA (min/day) | Cognitive function | MoCA (0 to 30) | Age, body mass index, highest education, and average monthly income | B = 0.006 (SE = 0.002) | p = 0.002 |
|             | MVPA (min/day) | Cognitive function | MoCA (0 to 30) | Age, body mass index, highest education, and average monthly income | B = 0.065 (SE = 0.004) | p = 0.000 |
|             | LPA (min/day) | Cognitive function | MoCA (0 to 30) | Age, body mass index, highest education, and average monthly income | B = 0.006 (SE = 0.002) | p = 0.003 |
|             | SB (min/day) | Cognitive function | MoCA (0 to 30) | Age, body mass index, highest education, and average monthly income | B = 0.005 (SE = 0.002) | p = 0.005 |
|             | MVPA (min/day) quartiles; Q1–least active | Cognitive function | SIS (0 to 6) | Age, sex, race, region of residence, and education | Q4 vs Q1, OR = 0.57 (0.40, 0.81) | p(calc) = 0.002 |
| Zhu 2017    | LPA (min/day) quartiles; Q1–least active | Cognitive function | SIS (0 to 6) | Age, sex, race, region of residence, and education | Q4 vs Q1, HR = 0.75 (0.52, 1.08) | p(calc) = 0.123 |
|             | SB (min/day) quartiles; Q1–least sedentary | Cognitive function | SIS (0 to 6) | Age, sex, race, region of residence, and education | Q4 vs Q1, HR = 1.28 (0.88, 1.87) | p(calc) = 0.201 |

PA: physical activity, SB: sedentary behavior, MVPA: moderate to vigorous physical activity, LPA: light physical activity, TPA: total physical activity, EE: energy expenditure, VPA: vigorous physical activity, MPA: moderate physical activity, BST: breaks in sedentary time, MET: metabolic equivalent of task, min: minute, g: gravitational acceleration, MJ: megajoule, % time: percent of time, sec: seconds, hrs: hours, kJ: kilojoule, kcal: kilocalories, m/s²: meter per second squared, VM: vector magnitude, Q: quartile, #: number. MMSE: mini-mental state examination, MDS: motor disorder society, AD8: ascertain dementia 8-item questionnaire, ACE-III: Addenbrooke’s cognitive examination, ADAS-Cog: Alzheimer’s Disease assessment scale — cognition sub-scale, 3MS: modified mini-mental state examination, TICS: telephone interview for cognitive status, TELE: telephonic assessment for dementia, RUDAS: Rowland universal dementia
interquartile range of $\beta$s. In longitudinal studies, effect directions indicated higher PA and lower SB to be associated with better global cognitive function. These associations were statistically significant for MVPA in two (Stubbs et al., 2017; Zhu et al., 2017) out of four articles (Manas et al., 2020; Wondergem et al., 2020), for LPA in two (Stubbs et al., 2017; Wondergem et al., 2020) out of three articles, Zhu et al., 2017) and for SB in one (Ku et al., 2017) out of three articles (Wondergem et al., 2020; Zhu et al., 2017). In one article each, higher steps, (Chen et al., 2020) higher EE (Stubbs et al., 2017) and shorter SB bouts (Wondergem et al., 2020) were associated with better global cognitive function. In cross-sectional studies, higher steps, higher activity counts, higher TPA, higher MVPA, higher LPA and lower SB were associated with better global cognitive function. Intensity-based accelerometer measures, reported as MET or EE, were associated with better global cognitive function. Measures of PA/SB accumulation and frequency (bouts) indicated that number and duration of PA bouts were not associated with cognitive function nor were number SB bouts, but shorter duration of SB bouts were associated with better global cognitive function (Fig. 2). From smallest to greatest effect size, median [interquartile range] of standardized $\beta$s indicated that lower SB ($\beta = 0.078 [0.004-0.184]$) and higher LPA ($\beta = 0.096 [0.046-0.188]$), activity counts ($\beta = 0.131 [0.049-0.224]$), number of steps ($\beta = 0.155 [0.096-0.246]$), MVPA ($\beta = 0.163 [0.069-0.285]$) and TPA ($\beta = 0.174 [0.147-0.255]$) were associated with better global cognitive function. (Figs. 3 and 4).

### 4.3. Sub-group analyses

In Appendix Figure D1, sub-group analysis by stratification for population selection (general vs. disease) showed a larger median effect size for general populations in comparison to disease-populations with median $\beta$ [IQR] of $0.140 [0.034-0.225]$ and $0.120 [0.052-0.196]$, respectively. Larger effect sizes were observed for unadjusted associations compared to adjusted associations with $\beta = 0.175 [0.090-0.248]$.
for adjusted and $\beta = 0.078$ [0.026-0.174] for unadjusted associations.

4.4. Article quality

According to the NOS, 36 out of 45 articles were classified as high quality (low risk of bias), including all studies with a longitudinal design (Appendix Table C3).

4.5. Discussion

In this systematic review, longitudinal associations studies a positive association between higher physical activity (PA) and lower sedentary behavior (SB) and better global cognitive function. Cross-sectional studies showed higher PA and lower SB to be associated with better global cognitive function. The strongest cross-sectional associations were found for moderate-to-vigorous PA (MVPA) and total PA (TPA).
Effect sizes of associations were larger for the general population when compared to disease populations, and larger for unadjusted analyses.

Higher PA was associated with better global cognitive function, which is in line with previous systematic reviews investigating similar topics. Previous systematic reviews describing the association between PA and cognitive function, which included self-reported PA found similar results (Carvalho et al., 2014; Falck et al., 2019). Notably, a recent scoping review investigated the association between self-reported and objectively assessed LPA and cognitive function in older adults and suggested LPA to be beneficial (Erlenbach et al., 2021). This is in line with our results, which is an important finding, as functional and physical limitations increase with age, preventing older adults from participating in higher intensity levels of physical activity (Schutzer and Graves, 2004). Systematic reviews investigating the impact/effectiveness of PA interventions (specifically exercise interventions) and cognitive function in older adults, (Falck et al., 2019; Klimova and Dostalova, 2020; Sanders et al., 2019) found that PA has the potential to improve and maintain cognitive function.

Our findings reported the greatest effect sizes for MVPA and TPA, indicating that not only PA at a higher intensity but in fact a greater duration of PA at any intensity might be beneficial for the preservation of global cognitive function in older adults. This is in line with both recommendations that encourage increasing MVPA as well as encouraging the principle that any PA is better than none (World Health Organization, 2019). Not only were associations identified for measures of PA but additionally associations between SB and global cognitive functions were found, indicating that SB could affect global cognitive function. However, it is important to note the possibility of reverse causation, in which disentangling cause and effect is difficult. Possible mechanisms by which SB could affect global cognitive function are suggested to be both cellular and systemic and include hippocampal neurogenesis, modulation of endogenous growth factors as brain-derived neurotrophic factor (BDNF) and inflammation and oxidative stress (Engeroff et al., 2018; Olanrewaju et al., 2020; Voss et al., 2014). Cerebral perfusion is one of the mechanisms suggested to be essential for preserving cognitive function (Leeuwis et al., 2017; Wolters et al., 2016). Higher PA is known to increase cardiac output and positively affecting cerebral perfusion (Jefferson, 2010). On the other hand, a recent study in older adults did not find an association between SB and decreased short-term cerebral perfusion after three hours of sitting (Maasakkers et al., 2020). However, increased blood pressure and cerebrovascular resistance were present, which are two other factors that are known to negatively impact brain health in the long term (Maasakkers et al., 2020). Furthermore, these effects were not mitigated with regular breaks in SB (Maasakkers et al., 2020), suggesting a specific detrimental effect of SB. Other mechanisms explaining the potential benefits and deleterious effects of PA and SB, respectively, on global cognitive function could be found in increases in exercise-induced metabolic factors and muscle-derived myokines, which can stimulate the production of neurotrophins and thereby the promotion of neurogenesis. In addition, anti-inflammatory effects of PA can ameliorate the pathophysiological hallmarks of Alzheimer’s Disease, although these mechanistic pathways need further confirmation in human studies (Valenzuela et al., 2020). However, studies combining objective assessments of PA/SB, cognitive function and mechanistic pathways to monitor the specific effect of PA/SB on the human brain are still lacking and need to be encouraged.

Relatively more included articles described non-significant associations between PA/SB and global cognitive function, although consistent effect directions were found. These findings could be explained by the fact that risk factors for cognitive decline are multifactorial, (World Health Organization, 2019) and PA/SB behaviors only represent two of these factors while other influential factors such as management of cardiovascular risk factors may confound associations (Baumgart et al., 2015). Estimated standardized regression coefficients for the association between SB and global cognitive function were found to be relatively small, according to cut-offs of Cohen’s guidelines of Pearson’s R designated as R = 0.10; 0.30, and 0.50 for small, medium, and large effects, respectively (Cohen, 1992). However, Cohen’s guidelines have been found to overestimate effect sizes in the field of gerontology, and rather cut-offs of R = 0.10; 0.20, and 0.30 have been suggested to estimate small, medium, and large effects more accurately (Brydges, 2019). In case these proposed cut-offs are used, negligible (<small) to approximately medium effects were identified in this review.

4.6. Clinical implications

With an aging population, there is concern over the number of older adults with cognitive impairments as incidence increases with age (World Health Organization, 2012). The lack of an effective treatment for dementia underpins the urgency to understand the modifiable lifestyle factors influencing cognitive function. Subsequently, identifying PA and SB as associated with cognitive impairment using objective measures is not only clinically relevant but also provides a foundation for developing actionable targets. Evidence-based guidelines from the World Health Organization recommend physical activity interventions to people with normal cognition to reduce their risk of cognitive decline (World Health Organization, 2019). However, clear recommendations with regard to dose and duration of PA are missing, as evidence is based upon self-reported measures of PA or specific exercise interventions, whereas favorable specific daily PA patterns could be targeted through lifestyle interventions. Future research should also focus on specific exercise training and its effect on global cognitive function, rather than solely the total duration of PA/SB behaviors.

A crucial issue that needs to be resolved to inform PA/SB guidelines is the standardization of assessment methods of PA/SB. Most commonly used devices are considered valid to assess PA/SB in older adults (Cavanaugh et al., 2007; Clarke et al., 2017; Dijkstra et al., 2010; Heesch et al., 2018; Murphy, 2009; Taraldsen et al., 2011; Valkenet and Veenhof, 2019). However, other factors are known to affect PA/SB...
4.7. Strengths and limitations

A strength of this study is the use of objective measurement methods to assess PA and SB, as subjective measures tend to overlook unstructured PA and LPA (Amagasa et al., 2017; Manns et al., 2012). In addition, older adults are more likely to overestimate PA and underestimate SB if self-reported (Dyrstad et al., 2014; Van Cauwenberg et al., 2014). The inclusion of populations of individuals with specific disease characteristics is also a strength, as comorbidity is highly prevalent in older adults (Barnett et al., 2012), thereby increasing our study’s generalizability. It is important to note that although standardized effect estimates in albatross plots were presented, we were unable to perform a meta-analysis due to heterogeneity in assessment methods at the article level, which would have provided a more precise pooled estimate of associations. Another limitation is the inclusion of relatively few longitudinal studies. With the inclusion of cross-sectional studies, the probability of reversed causality is high and future studies should focus on longitudinal study designs to further unravel the causal direction between PA/SB and global cognitive function. In addition, the specific detrimental effects of SB behavior alone, even in individuals who are physically active, need to be studied. Another essential factor that could not be taken into account was the level of PA during the night, which can often be present in cognitively impaired older adults and does not represent favorable PA behavior. In addition, information on sleep duration and quality were not available in the studies included.

5. Conclusions

Objectively assessed higher PA and lower SB are associated with better global cognitive function, with MVPA and TPA providing the strongest evidence for beneficial effects. Future research, specifically larger longitudinal studies taking standardization of PA/SB measures into account, must be conducted to unravel dose-response relationships and the direction of causality to inform PA/SB related guidelines and establish evidence-based targets for older adults.

Financial disclosure

No financial disclosures were reported by the authors of this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mad.2021.111524.

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