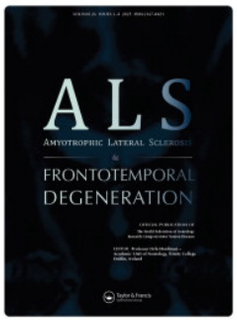

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REVIEW ARTICLE

# Physical activity in amyotrophic lateral sclerosis: a systematic review of the methodologies used to assess a possible association

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**Abstract**

Growing evidence suggests that strenuous physical activity (PA) may be associated with an increased risk of developing Amyotrophic Lateral Sclerosis (ALS), a fatal neurodegenerative disease. However, there are inconsistent findings across studies that may reduce our understanding of any potential associations. We propose that these differences may reflect the tools used to record historical PA. We conducted a systematic review evaluating the risk of developing ALS due to PA. The inclusion criteria were met by 22/113 studies, and an association between increasing PA and ALS was found in 15 studies. Studies that found a positive association were more likely to have longer recall periods and convert data into Metabolic Equivalent of Task values. Studies that did not find an association with increasing PA were more likely to use questionnaires with no validity or reliability data. Questionnaires with validity data all showed at least a moderate correlation of PA compared to objective measures, with reliability ranging from poor to good. Study designs included prospective cohort and case-control, which may also contribute to heterogeneity in findings. This work highlights the need for consensus on the type of questionnaire to use to assess potential associations between PA and ALS.

**Keywords:** *Amyotrophic lateral sclerosis, exercise, physical activity, motor neurone disease*

## 1. Introduction

Motor Neurone Disease (MND) is a neurodegenerative disorder with increasing prevalence (1), of which amyotrophic lateral sclerosis (ALS) is the most common form. Several studies have reported a possible association between strenuous exercise and ALS, but this has not been a consistent finding across all studies (2–6).

Differences in study design, recall bias, and variations in recall periods may contribute to some of these inconsistencies. In this report, we will evaluate the questionnaires used to measure a participant's prior physical activity (PA) before developing ALS and the extent to which variations in these methods may impact the results obtained.

## 2. Methods

### *2.1. Search strategy*

Using OVID, the databases searched were EBM Reviews (Cochrane DSR, ACP Journal Club, DARE, CCA, CCTR, CMR, HTA, and NHSEED), Embase 1980–2024 Week 48, and Ovid Medline® 1946—6 December 2024. The search was restricted to human studies, with no year limit. PRISMA guidelines were followed.

Key terms: "MND" or "Motor neurone disease" or "Amyotrophic Lateral Sclerosis" or "ALS," "Exercise" or "Physical Activity" in MeSH terms, and "Questionnaire" or "Questionnaires" or "Survey" or "Surveys" in the main text. The

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Table 1. Inclusion and exclusion criteria used to select appropriate studies.

| | Inclusion | Exclusion |
|---|---|---|
| Population | Adults (cases and non-cases) | Patients with other neurodegenerative disorders |
| Exposure | Physical activity exposure measured by questionnaires | Exercise measured using other tools<br>Exercise/physical therapy |
| Endpoint | MND/ALS development or mortality | Any other endpoint |
| Study design | Any | Animal studies |
| Language | English papers | Papers written languages, other than English |
| Accessibility | Accessible with institutional access | Not accessible with institutional access |
| Type of article | Full papers | Conference abstracts |

MND: motor neurone disease; ALS: amyotrophic lateral sclerosis.

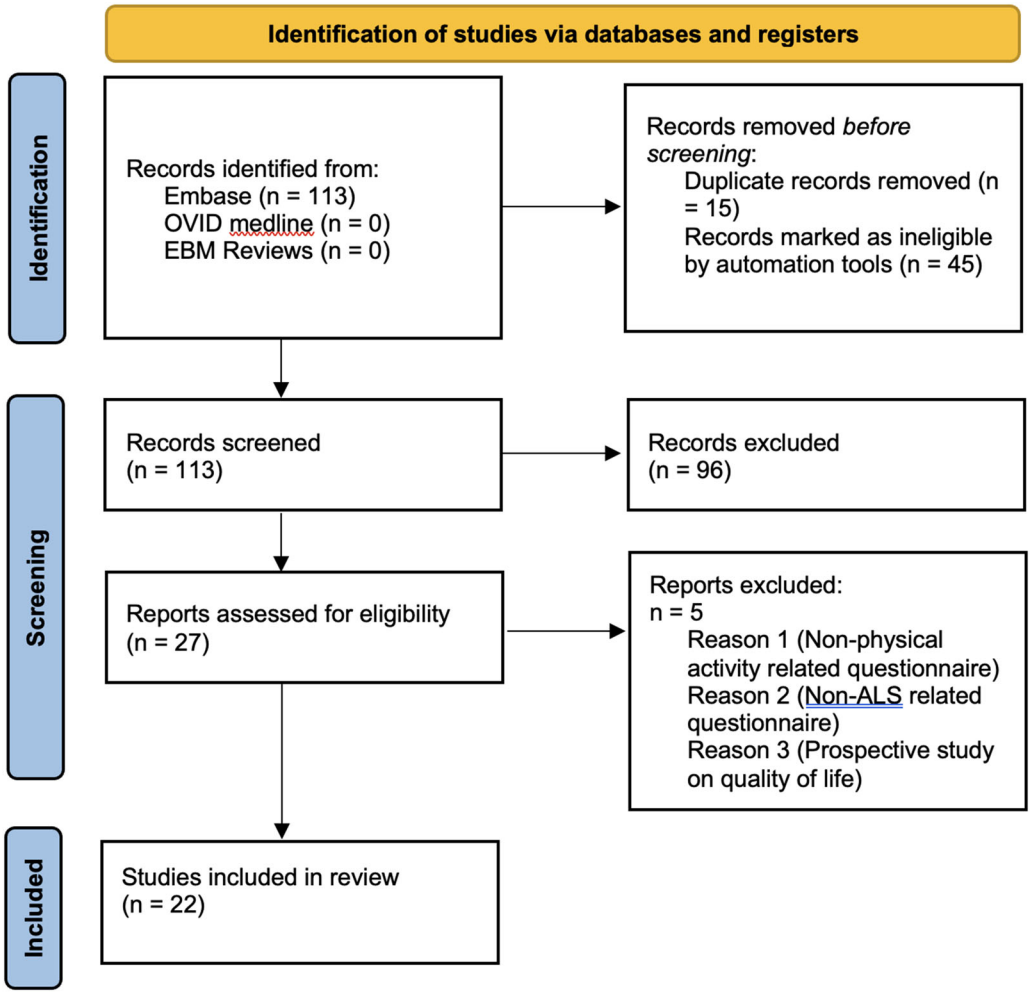


Figure 1. PRISMA diagram providing a summary overview of the search process.
*Source:* Page et al. (57).

inclusion and exclusion criteria applied during this process are summarized in Table 1.

### 2.2. Eligibility and study selection

Twenty-two studies were eligible (Figure 1). References of included studies were manually reviewed to identify additional relevant studies. Article selection was carried out by two reviewers (AC and MM) to reduce the risk of bias.

## 3. Results

### 3.1. Study characteristics

Of the 22 included studies, 15 studied European populations, six studied North American populations, and one studied a Turkish population (Table 2). A range of methods were used to collect information on an individual's PA and its subsequent quantification (Table 3). Studies used either previously established questionnaires or

Table 2. Characteristics of included studies.

| Study | Country | Database | Study design | Sample size | MET used | Questionnaire | PA baseline | Domains collected | Recall period | Follow-up | Positive association |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Scarmeas et al., 2002 | USA | N | Case-control study | Total: 431; ALS: 172; Controls: 152 with other neurologic diseases | N | Study-specific | Retrospective questionnaire assessing lifetime varsity athletic participation | Rec., Occ. | Lifetime | n/a (retrospective) | Yes – Patients with ALS more likely to have been varsity athletes |
| Qureshi et al., 2006 | USA | N | Case-control and prospective longitudinal cohort | Total: 201; ALS: 95; Controls: 106 healthy participants | N | Study-specific | Retrospective recall at enrollment for historical PA | n/a | Unknown | 12 months | No |
| Chio et al., 2009 | Italy | Y | Cohort study | Total: 10,999; Soccer: 7,325; Basketball: 1,973; Cyclists: 1,701 | N | Study-specific | Retrospective assessment of professional careers | Occ. | Lifetime | Soccer cohort: 170,702 person-years; Basketball cohort: 35,273 person-years; Cyclists: 63,346 person-years | Yes – higher risk for careers longer than 5y for footballers. None for basketball players or road cyclists |
| Huisman et al., 2013 | Netherlands | Y | Population-based case-control study | Total: 2,802; ALS: 636; Controls: 2,166 | Y | Study-specific | Retrospective recall of lifetime PA (pre-disease onset for cases) | Rec., Occ. | Whole life | n/a (case-control) | Yes – increased risk with increased leisure PA unrelated to PA intensity, and no effect of VPA or occupational PA. No effect on age of onset or survival |
| Yu et al., 2014 | USA | N | Case-control study | Total: 132; ALS: 66 Controls: 66 | N | NHANES Adaptation | Retrospective recall for PA (past 5 years) | Rec., Hh, Tr. | 5 year | n/a (case-control) | No – No differences between cases and controls regarding involvement in individual sports except recreational dancing, and no difference in number of activities |
| Gallo et al., 2016 | Norway, Sweden, Denmark, UK, Netherland, Germany, France, Spain, Italy, Greece | Y | Prospective cohort | Total: 472,100; ALS deaths: 219 | Y | CPAI | Baseline PA assessment at recruitment (pre-ALS onset) | Rec., Hh, Tr., Occ. | 12 months | 13 years | Yes -Total PA was inversely associated with ALS mortality. However, ALS risk was increased with increased VPA before age 50 |
| Harwood et al., 2016 | UK | N | Case-control study with population-based recruitment | Total: 492; ALS: 175 Controls: 317 | Y | HAPAQ | Retrospective recall of lifetime PA | Rec. Tr, H., Occ. | Age 20 – current age, excluding most recent 5 years | n/a (case-control) | Yes – increased risk observed for casual exercise and total PA but not work or |

(*Continued*)

**Table 2.** (*Continued*).

| Study | Country | Database | Study design | Sample size | MET used | Questionnaire | PA baseline | Domains collected | Recall period | Follow-up | Positive association |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | exertional/ sport-related PA within the most recent 15 years. Extra 10 min/day of vigorous PA was associated with ALS. No effect of PA on age of onset. |
| Albani et al., 2016 | France, Ireland, Italy, UK, Serbia | Y | Case-control study | Total: 202; ALS: 101<br>Controls: 101 | N | Study-specific | Retrospective recall (lifetime PA assessed up to five years before ALS onset for cases) | Rec., Occ. | Whole life | n/a (case-control) | No – Insignificant ALS and sport-related PA association. However, APOE-E2 and SIRT3 variant expression are related to PA |
| Feddermann-Demont et al., 2017 | Switzerland | Y | Retrospective cohort study | 92 ALS patients; No control group | Y | Study-specific | Presymptomatic PA | Rec., Occ., Hh. | Lifetime | n/a (retrospective design) | No – between vigorous PA and age of onset. Higher total MET values were correlated with symptom-onset later in life |
| Eaglehouse et al., 2018 | USA | Y | Prospective cohort study | Total: 161,809; ALS deaths: 165 | Y | WHI-PAQ | Baseline PA assessment at enrollment (pre-ALS onset) | Rec., Hh., Tr., Occ. | 4 weeks, one additional question assessed strenuous/ very hard exercise at ages 18, 35, and 50 | 9.6 years | Yes – Frequency of strenuous PA per week related to increased ALS mortality. No association between duration of strenuous PA episode. Increased ALS mortality with increased strenuous PA for 3 or more days per week at age 50, but not at ages 18 or 35. |
| Visser et al., 2018 | Ireland, Netherlands Italy | Y | Case-control study | ALS: 1,557<br>Controls: 2,922 | Y | Study-specific | Lifetime occupational exposure assessment; all jobs considered | Rec., Occ. | Whole life – up to 3 years prior to survey | n/a (case-control) | Yes – Increased lifetime PA was associated with increased risk of developing ALS for total, leisure- and occupation-related PA. Dose-dependant |

(*Continued*)

**Table 2.** (*Continued*).

| Study | Country | Database | Study design | Sample size | MET used | Questionnaire | PA baseline | Domains collected | Recall period | Follow-up | Positive association |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | response observed. No effect on age-of onset or site-of-onset |
| Pereira et al., 2021 | Portugal – Lisbon | N | Case-control study | ALS: 500 (136 bulbar-onset, 364 spinal-onset); Controls: 327 | N | Study-specific | Presymptomatic lifetime sports practice evaluated | Rec. | Whole life | n/a (data collected cross-sectionally at diagnosis) | Yes – Increased risk of spinal-onset ALS in men |
| Westeneng et al., 2021 | Netherlands | Y | Case-control study | Total: 2,787 (C9orf72+ ALS: 143; C9orf72– ALS: 1,322; Controls: 1,322) | Y | Study-specific | Longitudinal assessment of PA during presymptomatic phase (up to 50 years before symptoms). | Rec., Occ. | Age 20 onwards | Longitudinal data up to 50 years before symptom onset. | Yes – Compared to controls, C9ORF72- cases had higher PA, but C9ORF72+ cases had normal PA |
| Julian et al., 2021 | UK | Y for GWAS, N for Case Control | Mixed-method: Mendelian randomization, transcriptomics, and questionnaire-based | Mendelian randomization: 12,577 ALS cases, 23,475 controls Case-control: 17 C9ORF72-ALS cases, 34 non-C9ORF72-ALS cases, 34 controls | GWAS: N Case Control: Y | Study Specific for GWAS, HAPAQ for Case Control | Retrospective assessment using HAPAQ | Rec., Tr., H., Occ. | GWAS: Last 4 weeks Case Control: 20 years – current age | Historical assessment with no explicit follow-up period. | Yes – GWAS Leisure PA only and genetic liability to strenuous sport and other exercise is associated with ALS, Case control showed C9orf72 ALS cases had earlier age of onset with increased average daily PA but not in C9orf72 negative cases |
| Rosenbohm et al., 2021 | Germany – Swabia | Y | Case-control study | Controls: 791 ALS: 393 | Y | IPAQ Adaptation | Assessed retrospectively at specific life stages (e.g., ages 20, 30, 40, 50, 60) | Rec., Occ. | 20–60 years | Median follow-up of 55.4 months for ALS cases | Yes – Only occupation-related PA, not for total PA |
| Raymond et al., 2021 | USA | Y | Cross-sectional study | Total: 6,419 (5,463 engaged in vigorous PA, 956 did not) | N | GPAQ | Retrospective self-reports on vigorous PA before ALS diagnosis | Rec. | Age 15 – symptom onset | n/a (cross-sectional). | Yes – Earlier age of onset of ALS associated with increased vigorous PA. Diagnosis before 60 associated with increased vigorous PA in early life |
| Wismayer et al., 2021 | Malta | N | Population-based case-control study | Total: 83; ALS: 38; Controls: 45 | Y | Study-specific | Occupational PA assessed retrospectively | Occ. | Longest occupation held | n/a (case-control) | Yes – blue collar workers twice as likely to develop. Mean |

(*Continued*)

**Table 2.** (*Continued*).

| Study | Country | Database | Study design | Sample size | MET used | Questionnaire | PA baseline | Domains collected | Recall period | Follow-up | Positive association |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | occupational-MET scores higher for ALS cases than controls |
| Gulay et al., 2021 | Turkey | N | Case-control study | ALS: 235; Controls: 117 | N | Study-specific | Exercise and activity status were part of the demographic questionnaire | Unknown | Unknown | n/a (cross-sectional data mining study) | No – no association between ALS and daily activity/ regular exercise |
| Li et al., 2023 | UK | Y | Mendelian randomization study | Total: 80,610; ALS: 20,806; Controls: 59,804 | N | Study-specific | Work-related factors assessed at a single point in time via questionnaire | Occ. | Length of current job | n/a (MR study using cross-sectional GWAS data) | Yes – Heavy manual or physical work increased the risk of ALS. No causal relationship of ALS risk with job involving standing/walking |
| Zheng et al., 2024 | UK | Y | Prospective cohort study | Total: 368,934; ALS: 403 | Y | IPAQ Adaptation | Total PA assessed at baseline | Rec., Occ., Hh | Unknown | 13.86 years | No – in relation to total physical activity |
| Vaage et al., 2024 | Norway | Y | Prospective cohort study | 373,696 participants (504 ALS cases) | N | SGPALS | PA assessed at baseline | Rec., Tr. | Last 12 months | 27.2 years | No – in men (increased PA associated with reduced ALS risk) but not in women |
| Goutman et al., 2024 | USA | N | Case-control study | ALS: 400; Controls: 287 | N | Study-specific | Self-reported exposures to hobbies, exercise, and avocational activities five years prior to ALS onset (cases) or survey consent (controls) | Rec., Hh. | 5 years prior to symptom onset | n/a (cross-sectional design) | Yes – ALS risk significant for golfing, recreational dancing, gardening, yard work. None for onset segment and survival. Swimming and weightlifting associated with younger onset |

This table describes the characteristics of the individual studies and the questionnaire/methodology used within each study to quantify physical activity of participants. CPAI = Cambridge Physical Activity Index; NHANES = National Health and Nutritional Examination Survey; HAPAQ = Historical Adulthood Physical Activity Questionnaire; WHI-PAQ = Women's Health Initiative Physical Activity Questionnaire; IPAQ = International Physical Activity Questionnaire; GWAS = Genome Wide Association Study; Rec. = recreational physical activity; Occ. = occupational physical activity; Tr. = travel physical activity; Hh. = household physical activity.

Table 3. Previously-established questionnaires validation and reliability data.

| Tool | Validation method | Recall period | Validation | Reliability |
|---|---|---|---|---|
| IPAQ | Accelerometer | 7 days prior to survey or Average week | Long form pooled $p = 0.33$; Short form pooled $p = 0.30$ (Craig) MVPA $r = 0.43$–$0.56$ (Cleland) Total PA $r = 0.39$; VPA $r = -0.03$ (Mader) | Spearman's coefficient; Long forms $p = 0.81$; Short forms $p = 0.76$ (Craig) |
| HAPAQ | Heart rate, oxygen consumption rates | Lifetime from age 20 | $r = 0.48$ (Besson) | ICC = 0.39 (Besson) |
| WHI-PAQ | Accelerometer, PAR | Prior 4 weeks | Accelerometer $r = 0.73$; PAR $r = 0.88$ (Johnson-Kozlow) | Spearman's coefficient $p = 0.67$–$0.71$ (Manson) ICC = 0.64, 0.77 (Johnson-Kozlow, Manson) |
| CPAI | Heart rate, oxygen consumption rates, accelerometer | Prior 12 months | $r = 0.04$, 0.32 (Wareham, Cust) | Kappa coefficient = 0.6, 0.66 (Wareham, Cust) |
| NHANES | Accelerometer | Average week/day | $r = 0.17$ (Beyler) | N/a |
| GPAQ | Accelerometer Pedometer | Average week | MVPA: $r = -0.01$ to $-0.69$ (Keating) | $r = 0.58$–$0.89$ (Keating) |
| SGPALS | Accelerometer V02 Max | Lifetime from age 20 | $VO_2$ Max $r = 0.40$–$0.44$ (Wilhelmsen) Accelerometer $r = 0.25$–$0.28$ (Emausen) | Test-retest reliability: Kappa = 0.64, Batty) 86% agreement between 2 assessments (Sjol) |

CPAI: Cambridge Physical Activity Index; NHANES: National Health and Nutritional Examination Survey; HAPAQ: Historical Adulthood Physical Activity Questionnaire; WHI-PAQ: Women's Health Initiative Physical Activity Questionnaire; IPAQ: International Physical Activity Questionnaire; SGPALS: Saltin-Grimby Physical Activity Level Scale; PA: physical activity; MVPA: moderate-vigorous physical activity; VPA: vigorous physical activity; n/a: not applicable; PAR: Physical Activity Recall questionnaire; ICC: intraclass correlation coefficient; $VO_2$ max: maximal oxygen consumption.

This table describes the characteristics, validity, and reliability of the 6 previously existing tools used to quantify physical activity within the studies included in this paper.

purpose-specific surveys developed by the authors referred to as "study-specific" questionnaires (Table 2). There were no data available for the validity or reliability of the study-specific questionnaires. Of the seven pre-established questionnaires, seven had data available on validity, and six on reliability.

### *3.2. Validated questionnaires used in selected studies*

**3.2.1. Historical Adulthood Physical Activity Questionnaire (HAPAQ).** The HAPAQ measures PA from age 20 (7). It covers multiple PA domains in two sections: the first 15 years split into 5-year intervals, and the remaining years in 10-year intervals. Validated against heart rate and oxygen consumption-derived PA values (Flex HR), it showed moderate correlation but was prone to overestimations in sedentary individuals and underestimations in active individuals (7). Regarding reliability, HAPAQ and objective measures found a significant Intraclass Correlation Coefficient (ICC) of 0.39 only when unaccounted time was corrected. Two studies used HAPAQ. Julian et al. utilized both a study-specific questionnaire and HAPAQ, conducting a genome-wide association study (GWAS) and a case-control study (8). The resulting analysis reported that increased strenuous leisure PA was associated with increased ALS risk. Case control analysis found that increasing PA correlated with ALS risk in C9orf72+ cases, but not in C9orf72− cases. Similarly, Harwood et al. linked sporadic ALS cases to casual exercise and total PA (9).

**3.2.2. International Physical Activity Questionnaire (IPAQ).** The IPAQ collects PA data over seven days (10,11) and was intended for use within the 15–69-year-old population (12). Validated in multiple countries, it showed moderate correlation with accelerometer data (13–17), with overreporting for vigorous PA (VPA) in some studies (13,14) and underreporting in others (15). The test–retest reliability for the long forms was found to have a pooled Spearman's coefficient of 0.81 and 0.76 for the short form (10). Rosenbohm et al. used an adaptation of IPAQ, finding no significant difference in PA levels between ALS cases and controls when PA was assessed for 5–10 years before diagnosis. A reduction in PA during this period was noted, possibly linked to pre-symptomatic neurodegenerative changes rather than lifetime

PA levels (Table 2) (18). Zheng et al. also found no association between ALS and total PA (19).

**3.2.3. Women's Health Initiative Physical Activity Questionnaire (WHI-PAQ).** The WHI-PAQ assesses typical weekly PA in postmenopausal women for the four weeks immediately before questionnaire administration (20,21). PA reflected baseline activity at a median age of 66 years, and so does not capture earlier-life PA levels (Table 3). Validated in women with breast cancer against accelerometer data and the 7-Day Physical Activity Recall, it showed high correlation but overestimated VPA (22). The test-retest reliability ranged between 0.67 and 0.71, and had an ICC of 0.77 in total Metabolic Equivalent of Task (MET) energy expenditure in all recreational PA (23).

Eaglehouse et al. used WHI-PAQ and found an association between strenuous PA and ALS mortality, with a dose-dependent response unrelated to factors like BMI and age (24). This study assessed four weeks of PA retrospectively, comparing participants by categories, such as above and below specific MET thresholds. An additional question was asked on engagement in strenuous exercise at ages 18, 35, and 50. An association was found only at age 50 between strenuous PA and ALS mortality. This may suggest that the timing of PA may influence observed associations with ALS (Table 2).

**3.2.4. Cambridge Physical Activity Index (CPAI).** The CPAI assesses PA over the prior year and categorizes participants from inactive to active (25,26). Validated with $VO_2$max and heart rate data, it showed moderate correlation with PA energy expenditure and VPA (26). Other validation methods include heart rate data (27), accelerometer data (28), and comparison to the Friedenreich Lifetime Total Activity Questionnaire (LTPAQ) (28). Regarding the reliability of the CPAI, Wareham et al. calculated a weighted kappa statistic of 0.6 with repeats at 18–21 months (26). Cust et al. found reliability at 0.66 weighted kappa coefficient at 10-month repeats (28). A prospective cohort study found an inverse relationship between total PA and ALS mortality. However, they found an increased ALS risk with VPA before age 50 or in high-BMI individuals engaging in sports (29). In this study, PA was assessed at baseline using CPAI, which grouped participants by activity level (Table 2). This comparison was based on categories, such as total PA and VPA above or below specific thresholds (Table 4).

**3.2.5. US ALS Registry and GPAQ.** The US ALS Registry collects data *via* physician records and self-reporting (30). VPA is measured from age 15 in intervals of 9 years. The number of times that the participant is in VPA is then recorded rather than the total elapsed time, contrasting with questionnaires, such as the IPAQ and HAPAQ.

This questionnaire was adapted from GPAQ (31) which utilizes the same definition for VPA as the registry and quantifies the exact time spent in VPA and also moderate PA. PA is reported as values "in a typical week."

GPAQ also covers occupational PA. While collecting occupational data, the US ALS registry does not enquire about occupational PA. This limitation in occupational PA data may restrict the ability to fully explore PA domains beyond leisure activity (Table 4).

A systematic review on the reliability and validity of GPAQ showed a poor-to-moderate correlation for sedentary behavior and work, transport, and leisure-related PA ($r = -0.03$–$0.5$). Moderate-Vigorous Physical Activity (MVPA) validity using accelerometers and pedometers was found to be $-0.01$ to $-0.69$. Overestimation of MVPA and underestimation of sedentary behavior was observed (32). Reliability for overall PA was found to be good at $r = 0.58$–$0.89$ and was similar for MVPA and across work, transport, and recreation-related domains (32).

Raymond et al. utilized the US ALS registry to assess risk with exposure to vigorous leisure activity. They found that over 56% of those diagnosed with ALS before age 60 were more likely to engage with moderate-heavy VPA in adolescence and early adulthood (31). This assessment relied on retrospective reporting of PA before ALS onset, focusing on early-life activity (Table 2). Similarly, they show that VPA engagement correlates with an earlier ALS onset, but this trend does not continue beyond age 34.

**3.2.6. National Health and Nutritional Examination Survey (NHANES).** The NHANES is based on the GPAQ and covers various PA domains over an average week/day. Validated directly against accelerometer data, it showed significant overreporting of PA (33). One study validated NHANES indirectly (34) and found that both objective (accelerometer-based) and self-reported PA correlated with markers, such as skinfold indices and High-Density Lipoprotein. However, only objective PA correlated with markers, such as BMI, waist circumference, and insulin. A modified NHANES questionnaire in one study found no association between ALS and PA, where PA was assessed over the previous 5 years (Table 2) (35).

**3.2.7. Saltin-Grimby Physical Activity Level Scale (SGPALS).** The SGPALS categorizes participants into four levels of PA from sedentary to very active. The original questionnaire asks the participant to categorize themselves from age 20 onwards in periods of 10 years (36). The final

Table 4. Data processing methods between studies.

| Study | PA cat. or cont. | PA metrics reported | Confounders adjusted | Reproducibility | MET values used | Measures of association | Statistical analysis |
|---|---|---|---|---|---|---|---|
| Scarmeas et al. | Cat. (Yes/no if they had been varsity athletes) | Yes/no if they had been varsity athletes | Age, sex, premorbid BMI, and slim body habitus | Self-reported weight and height validated in previous studies (correlation coefficient = 0.82) | N | OR | Logistic regression |
| Qureshi et al. | n/a | Number of activities<br>Mean hours of activities | Age, gender, smoking, toxin exposure, and military service | Not reported for PA measures | N | OR | Univariate logistic regression used to assess risk factors; PA was not statistically associated |
| Chio et al. | Cont. (years engaged as professional athlete, year when professional activity commenced)<br>Cat. (by position played in football) | Football: Categorized years played into <5 or >5 years, categorized starting year into 3 time periods, Categorized into 4 positions in football<br>No ALS cases found for basketball or road cycling | Not explicitly adjusted; comparisons made to national ALS incidence rates | Based on mortality and clinical data from official registries; no reliability metrics for exposure | N | Standardized morbidity ratio | Standardized Morbidity Ratios calculated with Poisson distribution for confidence intervals |
| Huisman et al. | Cont.<br>4 cat. (based on data of controls)<br>2 cat. (yes/no for VPA) | Leisure, occupational, and total activity | Age, gender, BMI, current smoking, current alcohol consumption, and education level | Not reported | Y | OR | Logistic regression |
| Yu et al. | Cat. (3 based on total number of activities, duration, frequency, and intensity) | Low, medium, and high intensity PA | Education, smoking, occupational exposures | Not reported | N | OR | Conditional logistic regression |

(*Continued*)

**Table 4.** (*Continued*).

| Study | PA cat. or cont. | PA metrics reported | Confounders adjusted | Reproducibility | MET values used | Measures of association | Statistical analysis |
|---|---|---|---|---|---|---|---|
| Gallo et al. | 4 cat. | CPAI (moderately active, moderately inactive, active) Occupation activity (sedentary, standing, manual/ heavy manual) Household activity (in quartiles) Recreational activity (in quartiles) Practicing sport (no, above median, below median) Potentially traumatic PA (never, ever) Vigorous PA (above and below 2 h per week) | Age, gender, BMI, smoking, education, and waist-to-hip ratio | CPAI validated against objective measures of cardio-respiratory fitness and energy expenditure | Y | HR | Cox proportional hazard models |
| Harwood et al. | Cont. | Average daily PA in last 5–15 year and Average daily adulthood PA. Both stratified into: Total PA, Time spent in PA >6 METs (min/ day), Work PA, Total leisure PA, Exertional sport PA, Casual exercise PA | Age, smoking, and educational attainment | HAPAQ validated with historical objective activity measures | Y | OR | Conditional logistic regression |
| Albani et al. | Cat. (5 for type of PA, 4 for duration, 4 for type of sport) | PA yes/no Types of PA(leisure, work, sport) Sport yes/no Sport category (amateur, | Smoking, alcohol, coffee use, and traumatic injuries | Not reported | N | OR | Conditional logistic regression |

(*Continued*)

**Table 4.** (*Continued*).

| Study | PA cat. or cont. | PA metrics reported | Confounders adjusted | Reproducibility | MET values used | Measures of association | Statistical analysis |
|---|---|---|---|---|---|---|---|
| | | organized, professional)<br>Duration of PA (years, split into 4 quartiles)<br>Duration of sport (years, split into 4 quartiles)<br>Age at starting sport | | | | | |
| Feddermann-Demont et al. | Cat. (By yes/no participation in 20 activities, and into low/ moderate/ vigorous MET) | Categorized into low/ moderate/vigorous MET. Categorized into non-vigorous or vigorous for football and ice hockey subgroups | Gender differences noted but not specifically adjusted for in multivariate analyses | Not reported | Y | Pearson correlation | ANOVA for total MET values; Odds ratios for associations; Chi-square for categorical variables |
| Eaglehouse et al. | Cont.<br>Cat. (yes/no for strenuous/ very hard exercise for 3 or more days/ week at ages 18, 35, and 50) | Physical activity, total MET-h/week<br>Strenuous PA [episodes per week, duration per episode, energy expenditure (MET hours per week)] strenuous or very hard exercise 3 or more days per week at ages 18, 35, and 50 years | Age, BMI, education, smoking, diabetes, marital status, and region | Self-reported PA validated against accelerometer data; test-retest reliability: $\kappa = 0.67$–$0.71$ | Y | HR<br>OR for strenuous physical activity on 3 or more days per week | Cox proportional hazards models |
| Visser et al. | Cont. | Lifetime MET scores (leisure, occupational, and all activities) | Age, gender, education level, smoking, alcohol use, region | Based on a standardized and validated questionnaire for occupational exposure; no test-retest reliability mentioned | Y | OR | Multivariate logistic regression |
| Pereira et al. | Cat. (2 categories—intense or mild) | Positive or negative history of routine exercise practice | Age, gender, hypertension, smoking, and cardiac events | Based on structured questionnaires, no specific validation or test-retest reliability provided | N | Chi square | Multinomial logistic regression |

(*Continued*)

**Table 4.** (*Continued*).

| Study | PA cat. or cont. | PA metrics reported | Confounders adjusted | Reproducibility | MET values used | Measures of association | Statistical analysis |
|---|---|---|---|---|---|---|---|
| Westeneng et al. | Cont. | Cumulative MET scores (leisure, occupations, total) | Sex, reference age, education, BMI, cigarette pack-years, lifetime alcohol consumption, and daily energy intake | Data collected with a validated structured questionnaire. No test-retest reliability specifically reported | Y | Mean difference | Multivariable models |
| Julian et al. | Cat. for GWAS (dichotomised - two-three days per week or more performing SSOE for a duration of 15–30 min or greater) Cont. for Case Control | Strenuous sport in last 4 weeks, Heavy DIY, Sedentary behavior, Heritability of Strenuous Sport & Other Exercise (SSOE) | Adjusted for genetic predisposition (C9orf72 expansion), age, and physical activity levels | Questionnaire validated for historical PA, moderate reliability | GWAS: N Case Control: Y | F statistic | Cox proportional hazards, Wald test, Mendelian randomization |
| Rosenbohm et al. | Cat. (4 for time, 3 for intensity of occupation, 2 for leisure and work PA intensity) | Total PA, mean (SD), MET-h/ week (7 categories of time before interview) Occupational work intensity (Light, moderate, heavy) | Age, sex, smoking status, and school education | Not explicitly reported; PA converted to MET values | Y | OR | Conditional logistic regression |
| Raymond et al | Cont. (number of times engaged in vigorous PA, measured at different ages) | 4 categories based on less or more than 3 sessions of VPA per week at different age groups | Sex, race, BMI, family history of ALS, physically active job, and military service | Based on the GPAQ, validated in prior studies | N | *t*-Test | Generalised linear models |
| Wismayer et al | Cat. (2 based on above or below 4 Met values) | Moderate or Strenuous work-related PA in occupation | Age, sex, geographical region, smoking, and alcohol history | Occupational data based on structured interviews and ISCO-08 classification; MET scores from Compendium of Physical Activities | Y | OR, *t*-test | Logistic regression |

(*Continued*)

**Table 4.** (*Continued*).

| Study | PA cat. or cont. | PA metrics reported | Confounders adjusted | Reproducibility | MET values used | Measures of association | Statistical analysis |
|---|---|---|---|---|---|---|---|
| Gulay et al | Cat. (Yes/no) | Categorized (Yes/no) | No specific adjustments; categorical variables analyzed independently | Not reported | N | Chi squared/ Fisher's exact *t*-test | Clustering and decision tree algorithms |
| Li et al | Cat. (4 based on frequency for heavy manual/ physical work, shift work, and walking/ standing) | Not specified | Smoking intensity, systolic blood pressure | GWAS summary data from UK Biobank; no direct validation for work-related factor data collection | N | OR | Univariable and multivariable mendelian randomization analyses |
| Zheng et al. | Cat. (4 quartiles by MET value) | MET min/wk | Age, sex, race, education, BMI, socioeconomic status, smoking status, drinking status, APOE genotype | Not explicitly reported; data derived using a modified version of the IPAQ | Y | HR | Cox proportional hazards models |
| Vaage et al. | Cat. (3 by intensity) | Light, intermediate, and high intensity PA | Age, sex, BMI, and smoking | None reported | N | HR | Cox proportional hazards models |
| Goutman et al | Cat. (Yes/no participation in 9 exercises) | Yes/no participation in 9 exercises | Age, sex, education, military service, family history of ALS | None reported | N | OR | Logistic regression for ALS risk; Cox proportional hazards models for survival; linear regression for age of onset |

ALS: amyotrophic lateral sclerosis; PA: physical activity; Cat.: categorical; Cont.: continuous; OR: odds ratio; HR: hazard ratio; Y: yes; N: no; GWAS: Genome Wide Association Study; BMI: Body Mass Index; IPAQ: International Physical Activity Questionnaire; HAPAQ: Historical Adulthood Physical Activity Questionnaire; CPAI: Cambridge Physical Activity Index; MET: Metabolic Equivalent of Task.

This table shows the physical activity endpoints reported by each individual study and the statistical analyses used to assess the significance of results.

time-period counted is "Over 60." Validation against $VO_2$max showed a moderate correlation of 0.40–0.44 (37) and against accelerometer data $r = 0.25$–$0.28$ (38). Batty et al., reported a test-retest reliability of 0.64 at 4–6-week repeats (39), and similarly, Sjol et al., reported 86% agreement at 1-month repeats (40). Vaage et al., utilized SGPALS, asking participants to categorize themselves for the last 12 months (41), and showed higher PA levels were associated with lower ALS prevalence in men (41).

### *3.3. Study-specific questionnaires used in ALS studies (Table 2)*

Fourteen studies used study-specific questionnaires.

**3.3.1. Studies with positive association observed.** Two reports from the Prospective ALS study in the Netherlands (PAN) used study-specific questionnaires, and both found a link that suggested a genetic component to ALS (6,42). Both study questionnaires asked participants to list the number of years and hours per week that they engaged in leisure PA, and list their current and previous occupations. Specific questions were asked about activities constituting VPA.

Two studies (Li et al., and Wismayer et al.,) found an association between ALS risk and occupational PA while utilizing different study-specific questionnaires (43,44). The questionnaire utilized by Li et al. involved three questions revolving around the physicality and shift pattern of their occupation. Frequency was obtained by allowing participants to choose from four options (i.e., never/rarely, sometimes, usually, always). In contrast, Wismayer et al. focused on type of job longest held by the participant. Visser et al. utilized the EuroMOTOR questionnaire which has a similar structure to those of the PAN studies. A positive association with leisure PA alongside occupational PA was observed (45).

Pereira et al. used a questionnaire asking if the participant engaged in PA, defined as "sports practice for more than 1 year." They assessed cardiovascular comorbidities in ALS by categorizing participants' aerobic activity as "intense" or "mild," and observed an "intense" exercise history was associated with spinal-onset ALS, particularly in males (46).

Goutman et al. used a questionnaire formed from the Agency for Toxic Substances and Disease Registry. The questionnaire requested a binary indicator of participation in specific activities 5 years before symptom onset for ALS cases, and before questionnaire administration for controls. They found significant association in 4/9 activities for ALS risk. On stratification, this association did not remain for females (47).

Three studies focused on professional sport. Feddermann-Demont et al. reviewed 20 activities and performed a subgroup analysis on football and ice-hockey players. The questionnaire asked about the total duration and hours per week engaged in PA, and specific questions for football and ice-hockey participation in similar detail. They found that higher total MET was associated with later symptom onset and no association between lifetime VPA and age of ALS onset (48). Chio et al. reviewed the risk of ALS in three athlete populations: football, basketball, and road cycling. Details regarding the questionnaire are not available in the report. They found an increased risk only for footballers with careers longer than 5 years (4). The questionnaire from Scarmeas et al. included a question with a binary answer on whether the participant had engaged in varsity athletics. They found that participants with ALS were more likely to report a positive history of varsity athletics (49).

**3.3.2. Studies with no association observed.** Two case control (5,50), and another utilizing data mining (51), found no association between PA and ALS. There are no details available regarding the PA assessment by two of the studies (5,51). One study assessed occupational and sport PA by collecting information regarding dates of participation, level of PA, and hours engaged per month (50).

## 4. Discussion

Several types of questionnaires have been used to assess associations between ALS and PA. Some studies have not described their exact methodology including recall periods, questions asked, or details on statistical analysis.

### *4.1. Study characteristics*

The most common outcome of the studies was a positive association between PA and ALS, reported in 15 studies, evidenced by higher prevalence of ALS or increased mortality. The median total sample size in studies that did find an association was larger than studies that did not (2795 and 202 participants, respectively), a feature that has been identified in previous reviews (52). Fourteen of 22 studies relied on established patient cohort databases and tended to cover large geographical areas up to multiple countries. 4/7 studies that did not find a positive association used a previously established database, compared to the 10/16 studies that found a positive association.

Studies, such as Gallo et al., and Eaglehouse et al., utilized large established cohorts and included longer follow-up periods (13 and 9.6 years, respectively) compared to smaller case-

control studies like Qureshi et al. This difference in follow-up duration likely contributes to variability in detecting associations. The domains of PA also varied between studies. The most common domain assessed was recreational PA, followed by occupational PA.

### *4.2. Recall periods*

The total time involved in an activity was not consistently asked, as many questionnaires are concerned with only an "average" time period (e.g., week/month). To overcome this, some studies repeated the questions with the participant recalling previous periods of their life, i.e., recall an average week/month when you were in your 20s. While this may allow for the collection of lifetime PA data, this method would need revalidation as the previously established questionnaires were designed to assess short-term PA. This can be seen in the studies by Rosenbohm et al. (18), Yu et al. (35), and Raymond et al. (31).

We noted variable recall periods between studies, ranging from 4 weeks prior (8,24) to the participant's entire lifetime (6,42,45,46,50). This raises issues in assessing risk linked to long-term PA. 10/12 studies with recall periods of beyond 5 years found an association. Six studies found no association. Of these, only two had recall periods beyond 5 years. For example, HAPAQ captures lifetime PA starting at age 20 in 5- and 10-year intervals, whereas WHI-PAQ focuses on PA during the previous 4 weeks, limiting its ability to assess long-term patterns. One way to better approximate lifetime PA may be to emulate HAPAQ where lifetime is divided into distinct periods based on age (8,9).

### *4.3. The use of MET values*

MET values allow for standardization of energy expenditure and are based on a collation of multiple sources. One MET represents the energy expended for quiet sitting, which is ~3.5 ml $O_2$ per kg body weight per minute (53). This reflects a 70 kg young person's rest metabolism.

11/22 studies used MET values to estimate energy expenditure. Of the seven studies that did not find a positive association between PA and ALS, only two converted PA data into MET values for analysis. In contrast, nine of the 16 studies that found an association used MET values. This could suggest that MET values offer a more accurate estimation of the PA data. For example, studies like Gallo et al. and Julian et al. converted PA data into MET values to allow for comparison across activity intensities (Table 4). However, MET values have limitations as they do not consider components, such as body mass, body fat percentage, age, cardiorespiratory fitness, and activity environment (54).

### *4.4. Validation and reliability of pre-established questionnaires*

Nine studies used pre-established questionnaires, whereas 14 studies utilized study-specific questionnaires (Julian et al., utilized both). Six/nine validated studies found a positive association, compared to 10/14 of study-specific questionnaires, making the difference insignificant. The questionnaires were validated on different populations, and varying information on validity and reliability were available. There was also no head-to-head comparison between questionnaires.

Accelerometery was the most common way to validate questionnaires. Some studies used heart rate, oxygen consumption, and the flex HR method. Some studies also opted to compare their questionnaire against another preexisting questionnaire secondary to objective measures (22,26,28).

Validation found moderate-to-good correlations for most questionnaires (Table 3). WHI-PAQ observed the best validity coefficients out of the validated questionnaires, but the validation was conducted only on women with breast cancer. This population specificity may limit generalizability to ALS studies, which involve older, mixed-gender cohorts. Despite these limitations, WHI-PAQ was consistent in ranking high *versus* low activity groups, suggesting it may still be useful in categorical comparisons.

IPAQ, WHI-PAQ, CPAI, GPAQ, and NHANES all overestimated moderate or vigorous PA, with better correlation or underestimation seen for light-to-sedentary activity. In comparison, HAPAQ underestimated VPA in active individuals and overestimated sedentary behavior. Besson et al. noted that this may be due to inaccurate objective measurements which were recorded over two sets of four days, which may not accurately reflect the long-term self-reported data obtained by HAPAQ (7). IPAQ, WHI-PAQ, GPAQ, CPAI, and NHANES all have significantly shorter recall periods. Longer objective measurements at different points in life may be required to assess the validity of questionnaires with longer recall periods. It seems that regardless of recall period, there is usually some degree of over or underestimation with different activity intensities.

In addition, questionnaire reliability assessments were not homogeneous, particularly regarding the time between repeat administration to the participants, ranging from months to years between studies. Despite this, all the validation studies showed at least a moderate correlation of estimated PA and the objective measure in at least one measure of PA. The reliability of the questionnaires ranged from poor to good for the five questionnaires for which this data was available. By purely looking at the extent of lifetime assessment in each questionnaire, the most thorough tool is

likely to be HAPAQ due to its collection of PA data in both 5- and 10-year intervals from age 20 and the use of a life calendar to help improve recall. HAPAQ also demonstrated reliable ranking for lifetime PA categories, which may enhance its utility in dose-response analyses. Childhood PA is not included in HAPAQ and was not included in most of the other questionnaires, except for the Euro-MOTOR questionnaire.

### *4.5. Non-questionnaire related factors*

The type of questionnaire used does not seem to be the only factor influencing the outcome of a study. For example, Julian et al., and Harwood et al., both used HAPAQ but reported opposing results on the association between PA and the development of sporadic ALS (8,9). This may be due to different study designs. For example, Harwood et al. did not employ a GWAS or accelerometery for a control but had a sample size three times that of Julian et al. Furthermore, the lack of standardized confounder adjustments across studies complicates comparisons and underscores the need for tools that account for critical variables like age, BMI, smoking, and occupational exposures.

Another factor which may affect outcome in these studies relates to the post-questionnaire data processing. This ranged from keeping PA as a continuous variable to categorizing by intensity and/or frequency. The extent of grouping also varied, ranging from simple yes/no categories to multiple groups, allowing the assessment of a dose-dependent response.

Some studies, such as Gallo et al., and Eaglehouse et al., utilized quintile-based grouping or comparisons between high and low PA categories (e.g., quintile 5 *vs.* quintile 1) to assess PA, even if exact PA levels were not captured. While ranking participants in terms of activity levels can help provide consistent results, the presence of differential or non-differential measurement error may influence the strength and direction of observed associations. The consistent ranking ability of tools like HAPAQ and IPAQ highlights their utility in such categorical comparisons, despite differences in their recall periods or validation metrics. Additionally, the final reported endpoints and statistical analyses differed between studies which may further hinder direct comparison.

### *4.6. Future research and conclusion*

Well-validated questionnaires have been used to assess PA in other patient populations. For example, in cardiovascular research where studies were more likely (20/22 studies) to use pre-established and validated questionnaires (55).

Furthermore, it has been reported that electronic measures of PA correlated better with health indices as compared to self-reporting in recall periods as short as 30 days (56). Whilst usage may decrease recall bias and any subjectivity, accelerometers would require decades of follow-up, the appropriate technology and data governance to facilitate analysis, and ethical use of data. As such methods are a long way from being established, it is important that the tools currently used to estimate PA are as accurate as possible.

Overall, there have been multiple efforts to assess the possibility of an association between PA and ALS and the nature of such association. However, no consensus has yet been reached to select or further develop robustly validated questionnaires to assess lifetime PA. This exploration further emphasizes the need for collaborations to focus on developing guidance and consensus for ALS research methodology.

## Ethical approval

Not applicable.

## Consent for publication

Not applicable.

## Author contributions

AC and MM contributed to the conception of the study and to the development of the search strategy. MM conducted the systematic search. MM and TB completed the acquisition of data. MM, TB, EHT, and AC performed the data analysis. MM took the lead in writing the manuscript. All the authors discussed the results and contributed to the final manuscript.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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## Data availability statement

All data supporting the findings of this study are available in this published article.

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