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VAN GEEL, Fanny; MOUMDJIAN, Lousin; LAMERS, Ilse; Bielen, Hanne & FEYS, Peter (2020) Measuring walking-related performance fatigability in clinical practice: a systematic review. In: European Journal of Physical and Rehabilitation Medicine, 56 (1), p. 88-103..

DOI: 10.23736/S1973-9087.19.05878-7
Handle: http://hdl.handle.net/1942/30387

European Journal of Physical and Rehabilitation Medicine
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European Journal of Physical and Rehabilitation Medicine 2019 Nov 18
DOI: 10.23736/S1973-9087.19.05878-7

Article type: Systematic reviews and meta-analyses

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Article first published online: November 18, 2019
Manuscript accepted: October 31, 2019
Manuscript revised: October 15, 2019
Manuscript received: June 3, 2019

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Measuring walking-related performance fatigability in clinical practice: a systematic review

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ABSTRACT

BACKGROUND: Fatigability, a change in performance according to tasks and circumstances, can contribute to walking limitations in daily life. Walking-related fatigability (WF) has been assessed subjectively, but current knowledge on best objective measurement methods is limited.

OBJECTIVE: To provide an overview of objective clinical measurement methods assessing WF in different populations.

DATA SOURCES: Articles were searched in Pubmed and Web Of Science by two independent raters.

STUDY ELIGIBILITY CRITERIA AND SYNTHESIS METHODS: Studies were included when meeting inclusion criteria of measuring WF objectively in a clinical setting, with no exclusion towards any population. Case studies and reviews were not included in the review (systematic review registration number: PROSPERO - CRD42017074121).

PARTICIPANTS: In total, 28 articles were included. The study populations were older adults (n=7), multiple sclerosis (n=14), spinal muscle atrophy (n=3), osteoarthritis (n=3), interstitial lung diseases (n=1), and myasthenia gravis (n=1).

STUDY APPRAISAL: Data about patient characteristics, walking task, WF formula and interpretation (cut-off values and/or psychometric properties) got extracted from included literature. Every included article got checked for quality and risk of bias.

RESULTS: WF was mostly measured during longer walking test such as six minute walking test (6MWT) and 500 or 400-m walking test, by comparing the first and last minute or lap for spatiotemporal or kinematic changes in well-defined formulas.

LIMITATIONS: No gold standard is however available yet given different tasks or outcome measures across study populations.

CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: Longer walking test were most often used, with a preference towards the 6MWT, thereby comparing the changes over the last and first part of the test. Psychometric properties need more documentation before inclusion as experimental outcome.

Keywords: Fatigue; Motor fatigability; Walking; Assessment; Clinical Practice

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TEXT

1. Introduction

Difficulties during walking is often perceived as one of the most challenging aspect of living in any (diseased) population, such as persons with musculoskeletal, respiratory, ageing, and neurological conditions; where for example almost 80% of all the people with Multiple Sclerosis (PwMS) experience walking difficulties. Walking distance and walking impairments may be connected to fatigue[1-9], which is highly prevalent in neurological populations, such as stroke patient (20-40%), Parkinson's disease, traumatic brain injuries and is one of the most common and first symptoms of PwMS (40-80%)[3, 10-12]. Fatigue is also reported in non-neurological conditions, amongst others, lung diseases, musculoskeletal disorders and ageing[7, 8, 13-16].

Throughout literature, many different terms and definitions have been used to describe fatigue, which makes this research field quite confusing. Based on different recent taxonomies[11, 16, 17], and literature[10, 18-22] [18], we have divided it into two main domains: trait fatigue and state fatigue. Trait fatigue is a general feeling of fatigue that is always present in an individual. It is therefore more a characteristic and does not importantly fluctuate over time, and is examined by fatigue questionnaires reflecting over a longer period in time (for example Fatigue Severity Scale[20]). State fatigue is a form of fatigue that changes according to tasks and circumstances, also described as an activity based fatigue or fatigability. Fatigability therefore has a performance (objective) and perceived (subjective) component that is essentially measured during or after a certain performance at a certain moment. One can distinguish motor and cognitive fatigability. For this review, we focus on motor fatigability. The performance component can be objectively measured through a fatigability task (e.g. 6MWT). The perceived component can be measured during or after a fatigability task, as perceived exertion through for example a subjective VAS or BORG

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score[20], or self-reported by for example the Pittsburgh Fatigability Scale[21-23]. Loy et al. (2017)[18] hypotheses the reciprocal influence of trait fatigue on state fatigue or vice versa. A schematic figure based on Kluger et al. (2010)[11] updated by the most recent literature about taxonomies and definitions of fatigue in various populations is shown in figure 1. This scheme also describes possible underlying and related factors.

Insert Figure 1. New taxonomy of fatigue adapted from Kluger, Rudroff, Enoka, and Kim et al.

Motor fatigability can be measured at different levels of the international classification of functioning (ICF). A recent review about assessment in PwMS documented that motor performance fatigability on a body function level has been widely investigated with a plenitude of measurement methods. Strength decline was the most common indicator, and is mostly calculated by the static or dynamic fatigue index[20]. The majority of studies investigated the upper limb, mostly assessing hand grip strength and index finger abduction[20]. Methods of measuring walking-related motor performance fatigability on activity level, were rarely applied[3, 4, 20]. This is surprising given the hypothesized clinical relevance of fatigability in daily-life mobility within the home and especially the community environment.

This systematic literature review focused on motor performance fatigability, presented by a walking task, to provide an overview of all the methods that objectively assess walking-related performance fatigability in any healthy or a diseased population, by focussing on three aspects: (1) spatiotemporal outcomes (2) kinetic and kinematic outcomes (3) psychometric properties. The aim was to provide an overview of methods currently used in clinical settings across different populations, to find measurement methods that are transferable to different diseases.

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2. Methods

2.1 Data Sources and Study Selection

This literature search was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered at PROSPERO (CRD42017074121). PubMed and Web Of Science databases were searched up to the 15th of June 2018. The research strategy applied in PubMed was: (((((Muscle fatigue[Title/Abstract]) OR Motor fatigue[Title/Abstract]) OR Motor fatigability[Title/Abstract]) OR Fatigability[Title/Abstract])) AND ((walking[Title/Abstract]) OR gait[Title/Abstract]). Through Web Of Science the following search strategy was used: ((motor fatigue OR motor muscle fatigue OR motor fatigability OR fatigability) AND (Walking OR Gait)).

According to the components of PICO, the articles had no exclusion based on population, intervention or comparator group (PICO), which made the outcome the main reason for inclusion of exclusion (PICO). Articles were included if clinically quantifying the motor performance fatigability during walking, thereby excluding for example instrumented peripheral nerve or brain stimulation tests, EMG or exoskeletons. Other exclusion criteria were particular study designs (reviews, case reports (n=1)), animal studies, conference abstracts) and articles discussing non-walking-related performance fatigability (such as in the upper extremity or during cycling, stair walking, running etc) or other topics not related to the research question. Articles were also excluded if only perceived fatigability or fatigue assessments were reported. Primary authors or co-authors were contacted through mail or research gate, in case a full text was not found. For hand searching, the reference lists of included articles were further checked for any other relevant articles.

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The study search, selection process and data extraction was performed by the lead author FVG and a master student LD. Discussion took place in case of discrepancies. Co-authors were consulted in case of doubt.

2.2 Quality assessment

The quality assessment was conducted by means of the Downs and Black checklist[24], identically as in Severijns et al. (2017)[20], who performed a similar review methodology and protocol to identify all measures of fatigability, at both body function and activity level of the ICF, in persons with MS. Questions 6, 8, 14, 15, 19, 23 and 24 were removed from this scale, as they were not applicable for assessing observational studies, in line with a previous review about fatigability. These scores were consequently converted to a percentage score, where >65% shows sufficient methodological quality[20].

2.3 Data Extraction

The following data were extracted from the included studies: (1) the walking task that participants had to perform, (2) the sample characteristics of the investigated population such as walking impairment, pathology, sample size, age,... (3) parameter or formula that determined motor performance fatigability and, if reported; (4) the interpretation of the test score and (5) cut-off scores for determining normal versus abnormal walking-related performance fatigability and psychometric properties.

3. Results

Twenty-eight articles were retained from the 785 articles. Figure 2 displays the flow chart of the study selection.

Insert Figure 2. Literature search strategy and results

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3.1 Quality assessment

Supplementary table 1 contains the result of the quality assessment of the included studies. Overall scores ranged from 47 -100 % for the observational studies, where the main problems of the studies were found in questions 12 (subpopulation representative for the entire population) and 22 (recruitment of controls during the same period of time). However only one observational study was scored with a low quality (<65%). Within the intervention studies, with scores ranging from 63 - 70%, also only one study showed low quality. Question 8 (adverse events of the intervention), 14 (blinding subjects), 15 (blinding testers), 23 (randomized groups) and 24 (concealing) indicated mostly blinding bias of the study. In general, as the review aims to include multiple disease populations, a lot of information is needed to determine if the study populations would be representative for the respective full populations, and therefore were scored with an 'unable to determine'. No bias of drop out, incomplete data or internal validity bias was prominent. Selection bias was only interfering with the quality in one of the intervention studies. These elements are crucial for rating the quality of the intervention study but do not affect the data extraction purpose of the current study. None of the articles were excluded due to low quality, as the review only aimed to provide an overview of the methods currently used in literature. In fact, only two articles scored below the limit of 65%, proposed by the Down and Black checklist[24]. One most however take into account the differences in sample size, ranging from 7 to 605 (twelve articles recruited more than 50 subjects and only four articles recruited less than 15 subjects), participants characteristics (because of different populations) and selection bias due to non-blinding interventions in the interventional articles.

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3.2 Study characteristics

From the 28 articles included in this study, a substantial number of studies (n = 7) investigated fatigability in older adults (age range: 60-97 years, 1387 participants)[8, 13, 14, 23, 25-27]. There were 14 studies with pwMS (822 participants, EDSS range 0-7,5)[3-5, 28-38]. The other studies (n = 10) had participants with different pathologies e.g. Spinal Muscle Atrophy (SMA) (n=3, 34 participants) [6, 39, 40], osteoarthritis (n=3, 242 participants)[2, 26, 41], stroke (n=1, 10 participants)[37], Interstitial lung disease (ILD) (n=1, 13 participants)[7], and myasthenia gravis (MG) (n=1, 32 participants)[15]. Nine articles also included a control group with healthy volunteers, age- and gender matched to the disease population[4, 15, 28, 31-33, 35-37]. One article in older adults used a non-fatigued group as a control group to the fatigued group[14].

3.3 Walking-related performance fatigability assessment

A schematic overview of the different clinical test methods used to assess walking-related performance fatigability is shown in Figure 3. Six clinical overground walking tests were applied and one treadmill walking test. The results are divided in two main categories (1) fatigability based on spatiotemporal outcomes (distances, velocities and accelerations) during clinical walking tests as the100-m walk, 400m-walk, 500-m walk, Timed 25 Foot Walk test (T25FW), 6 minute walk test (6MWT), 10 minute walk test (10MWT), and 12 minute walk test (12MWT), and (2) fatigability based on kinetic or kinematic changes, during a 100-m walk, 6MWT and treadmill walking. Within these categories, studies applied self-selected usual (n = 8) [2, 5, 8, 26, 35-37, 41] and fastest speed (n = 20) [3, 4, 6, 7, 13-15, 23, 25, 27-34, 38-40]. Thirdly (3), we will discuss reported psychometric properties of the used tests.

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Insert Figure 3. A schematic overview of the protocols assessing walking-related performance fatigability in different populations

3.3.1 Fatigability based on spatiotemporal outcomes in clinical walking tests (n=21)

A detailed overview of the diagnostic test for walking-related performance fatigability based on spatiotemporal outcomes is provided in table 1a.

- 400-m long-distance corridor walk (n=4)

Most studies used a marked 20 meter hallway[14, 25, 27]. Some describe the use of laps (=40m), so subjects had to complete 10 laps to complete the 400-m walk test [14, 23, 27].

In older adults, comparison of walking speed in the first meters of the test compared to the last meters was used to indicate fatigability[23, 25, 27]. Valiani et al. (2016) used a similar method by assessing walking-related performance fatigability based on walking speed measured per lap time.

- Timed 500-m walking test (n=3)

Participants were asked to walk 500-m in a 50-m[35, 38], or a 100-m straight course[4]. During a 500-meter walking test, an ambulatory fatigability index was calculated dividing the velocity during the final 50-m lap by the velocity during the initial 50-m lap[35, 38]. A deceleration index to determine locomotor fatigability in PwMS was defined by Phan-Ba et al. (2012). To calculate this index they used a combination of walking tests: the Timed 500-meter walk test (T500) and the Timed 25-foot walk test with a dynamic start (T25-FW corrected version), both at fastest speed. The ratio between the lowest (last 100 meter of T500 (T400-T500)) and highest (T25-FW corrected version) measurable walking speed was set as the deceleration index to objectively assess motor fatigability[4].

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- 6MWT (n=13)

In total, 13 articles compared walking speed or distance during the 6MWT[3, 6, 7, 13, 15, 26, 28-31, 33, 39, 40]. In general, most studies applied a protocol for the 6MWT, that was similar to Goldman et al. (2008)[42]. This includes a marked 20-30 meter hallway where patients have to walk as fast as possible for 6 minutes back and forth[3, 6, 13, 26, 29, 31, 39, 40]. Some studies used circular hallways of 80-m[7], while two studies used a straight walkway of 10-m[28, 33] or 53-m[30]. Other differences between tests were speed instructions (fastest vs usual speed) and level of encouragement. See table 1a. for a more detailed overview.

To measure walking-related performance fatigability, mostly the percentage in changes of distance or velocity between the first and 6th minute of the 6MWT was used in pwMS[3, 28-30], older adults[13] and SMA[6, 40]. Another method was to compare other or all minutes to measure performance fatigability in pwMS[31, 33], MG[15], and SMA[39]. The percentage of change of the average velocity of the full 6MWT with the first lap (expressed in meters) of the 6MWT is applied in ILD[7] and older adults[26].

- 10MWT (n=1)

Participants had to walk in a 51m circular course at usual speed. They calculate the performance fatigability severity by taking the average velocity of the time walked (10 min or less, if the patients had to stop the test earlier), divided by the average velocity of first 2,5 min. To place the change of performance in the context of performed physical activity, they also divide the previous outcome by the total distance walked[8].

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- 12MWT (n=1)

This article used the same protocol for the 6MWT, similar to Goldman et al. (2008)[42], which includes a marked 20m hallway where patients have to walk as fast as possible for 12 minutes back and forth. They indicate a linear trend for calculating fatigability[31].

Insert Table 1a. (see appendix B)

3.3.2 Fatigability based on kinetic and kinematic changes in gait parameters over time (n = 7)

Changes in kinetic and kinematic parameters were measured during different walking tests in the populations of PwMS[5, 32, 34, 36, 37] and arthritis[2, 41]. A detailed summary is given in the following table 1b.

- 100-m Walk (n=2)

Participants with arthritis walked on a 100-m course outdoor with the Intelligent Device for Energy Expenditure and Activity (IDEEA device), consisting of 5 sensors (chest, thighs and feet) and one recorder (waist), for measuring kinematic changes during the 100-m walk. Lester et al. (2010) indicates a fatigability percentage as the difference between the mean value of the gait variables for the 20 last steps, and the mean values of the full 100 meter walking test, which is similar to the procedure of Zhang et al. (2006) in arthritis[2, 41]. They investigated many gait parameters, such as, cadence, mean walking speed, as well as pulling power (maximum forward acceleration of the foot during initial swing phase) for fatigability, and comparisons between the healthy and affected leg[2].

- 6MWT (n=2)

PwMS had to walk in a 20-30 m hallway at fastest speed. Engelhard et al.(2016) and Qureshi et al. (2016) compare the differences in gait cycles at baseline and in later minutes

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of the 6MWT, with the use of the actigraphs activity trackers and a wearable body sensor network (BSN) platform, respectively[32, 34].

- Treadmill walking till maximal exhaustion (n=3)

PwMS had to walk on a treadmill until they indicated a maximal score of 17 on the BORG scale, indicating maximal exhaustion, with a maximum of 60min. Sehle et al. (2011) measured fatigability by extracting three dimensional marker data and video images at the beginning of the test (t_1) and one minute at the end of the test (after stating complete exhaustion, and right before the end of the test) (t_2). Changes in variability of kinematic gait parameters impacted on the fatigue index[5]. Later (2014), Sehle et al. developed the Fatigue Index Kliniken Schmieder (FKS) which was applied on PwMS and later also on stroke patients[36, 37]. The FKS (δF) is the product of δM and δD, where δM is a measure of the difference between two attractors quantifying the differences between two movement patterns. The difference between the two associated deviations of the state vector away from the attractor representing the change in movement variation describes δD.

Insert Table 1b. (see appendix B)

3.3.3 Psychometric properties

Table 2 shows the results regarding psychometric properties: (1) Cut-off values for determining walking-related performance fatigability, (2) test-retest reliability and (3) validity.

- Cut-off values for determining abnormal walking-related performance fatigability (n=8)

Eight studies proposed a diagnostic cut-off criterion for indicating walking-related performance fatigability[3, 5, 15, 23, 25, 27, 36, 37]. Some articles state percentages[3, 23,

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27], while other use specific indexes for their measurement methods[5, 36, 37]. Sometimes, the criterion was put forward without comparison with healthy controls[3, 5, 23, 27], as only three studies included a control group[15, 36, 37].

- Test-retest reliability

Only Schwid et al. (1999) documented test-retest reliability for the ambulatory fatigue index (AFI) but Intra Class Correlations Coefficient (ICC) values were low, being 0.36 in MS, and 0.21 in healthy controls[35].

- Validity

In older adults, Schnelle et al. (2012) documented a correlation between performance and perceived fatigability of 0.94, indicating high concurrent validity. Besides, they reported a correlation of performance fatigability with FSS of 0.53[8]. Murphy et al. (2016) showed a moderate correlation between perceived fatigability and performance fatigability (r= 0.62) in older adults with osteoarthritis, and a high correlation of perceived and performance fatigability with perceived exertion fatigability (r= 0.80 and 0.74, respectively). Barbosa et al. also found a moderate correlation between the severity of perceived and performance fatigability (r=0.69), suggesting clinical validity of measuring perceived walking fatigability[26]. They showed that usual level of physical activity and performance fatigability together represented 84% of the variation in perceived fatigability severity. In PwMS, Qureshi et al.(2016) found that a subgroup of patients with abnormal trait fatigue (MFIS > 42) slowed down and took unequal length gait cycles during 6MWT, which might be a suggestion for good face validity[34]. Sehle et al. (2011) reported a significant correlation of -0.59 with the FSMC motor domain[5].

Simonsick et al. (2014) demonstrated good concurrent validity by strong associations with fatigue related symptoms (including tiredness, weakness and low energy in the past

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month). Performance deterioration (or fatigability) also showed a robust relationship with reported walking ability[27]. In MG, Jordan et al. (2017) reported there is no correlation between the MG fatigue scale and the performance fatigability during walking[15].

Other studies investigated discriminant validity. Glynn et al. (2015) found good discrimination for correctly classifying of performance fatigability with the Pittsburgh Fatigability Scale (PFS) questionnaire for older adults[23]. In PwMS, Sehle et al (2014) reported 97% correctly diagnosed for fatigued patients and 91% correctly diagnosed for non-fatigued patients, determined by the neurologist by judgment of the following symptoms: 'abnormal rapid physical exhaustion in daily living and a severe reduction in gait distance that could not be explained by the degree of paresis, spasticity or ataxia'. For the video analysis, during treadmill walking by the physiotherapist, a random classification was found, as only 50% was correctly diagnosed[36].

Insert Table 2. (see appendix B)

4. Discussion

The aim of this systematic review was to provide an overview of methods used to investigate walking-related performance fatigability in clinical settings, while considering three outcome aspects: (1) spatiotemporal outcomes (2) kinetic and kinematic outcomes (3) psychometric properties. The main findings of this review were that (1) walking-related performance fatigability is investigated in a wide range of pathologies and older adults suggesting its clinical importance; (2) in different populations, similar tests and formulas to calculate an outcome measure were common with mostly longer walking tests (i.e. 6MWT) being used with comparison of the first and last minute or distance of the test; (3) walking fatigability seems to be correlated with perceived fatigability and fatigue and (4)

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discriminative cut-off data and test-retest reliability and variability values are insufficiently documented.

Walking-related performance fatigability was investigated in older adults and different pathologies, such as myasthenia gravis, interstitial lung diseases, arthritis, MS, and stroke, showing its clinical relevance. Studies were most frequently performed in the MS population, followed by older adults. Within these different populations, many similarities where found regarding applied walking tests and formulas to determine walking fatigability. However, even within the same tests, some differences in test protocol occurred. For example, the majority of the included studies conducted the 6WMT according the protocol described by Goldman et al. (2008)[42] and American Thoracic Society (ATS)[43], where differences between these two protocols are present regarding encouragement and length of the course. A study in older adults with COPD compared to healthy control concluded that the use of verbal encouragement does not substantially promote an improvement in the performance of the 6MWT[44]. For reasons of standardized assessment, especially in subjects at risk for motor fatigability, our personal viewpoint is to omit random verbal encouragement and only provide temporal information on the elapse of minutes. The length of the course of the 6MWT varied between a straight course of 10-100m and 50-80m in a circular course setting. It has been documented, in respiratory diseases and MS, that the length or layout of the course has some impact on the total distance walked. Subjects walk lower distances if more 180° turns need to be made[45-48]. It is not thought that these track differences across studies substantially matter for this review, as methods aim to detect changes over time within a particular track.

Although the 6MWT was most commonly used in our systematic review, one could question the optimal length of a walking test to identify motor-related fatigability. The 2MWT has been proposed as an alternative for the 6MWT to measure walking capacity[49].

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However, for detecting performance fatigability during walking, 2 minutes are too short and, shown by Barbosa et al. (2016), accompanied with most O_2 uptake variance reflecting energy expenditure that not reached a steady state yet[13]. Longer tests than 6MWT, or fixed long distance tests, seem not always appropriate neither, as Schwid et al. (1999) observed that 60% of the older adults could not walk 500m. Simonsick et al. (2014) compared the 400-m walk test with the 10 minute test of Schnelle et al. (2012), and stated that 10 minutes would be too long for more disabled patients or older adults and could give bias towards drop out[8, 27].

The included studies had different speed instructions or conditions. Schnelle et al. (2012) prefers a self-selected pace of walking for measuring fatigability above fixed speed conditions on treadmills given an assumed better relationship with daily living health outcomes in older adults[8]. The instruction of self-selected usual speed was mostly applied in older adults and arthritis, while in neurological populations, self-paced fastest speed was more frequent. In MS, Schwid et al. (1999) used usual speed in their test protocol, but found a low test-retest reliability[35]. Given the above, and the standardized protocols of Goldman et al (2008) and the ATS[42, 43], it is recommended to apply fastest speed instructions.

Motor fatigability while walking at fixed speed on a treadmill was applied in the studies of Sehle et al. (2011,2014). Their camera-based gait analysis techniques were included as authors compared kinematic defined walking-related performance fatigability with clinical observation of overground walking by the neurologist and physiotherapists. The clinical observation appeared accurate for diagnosing motor performance fatigability [5, 36, 37].

Psychometric properties of walking fatigability were insufficiently documented. Only three articles included a healthy control group, but did not necessarily base their cut-off values on the results of this control group. Discriminative values are still lacking and need further investigation. Test-retest reliability was only investigated by Schwid et al., who

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reported a low ICC value. The presented formulas and measurement methods need further investigation towards test-retest reliability before applying them as an experimental outcome measure in trials. Additionally, despite face validity, the relation of motor fatigability parameters with real-life walking behavior needs better understanding. Advances in sensor-based recording of walking in daily life can enable this research on ecological validity.

This systematic review documented various test methods in a range of pathological conditions, older adults, different tests and parameters which unfortunately did not allow for a meta-analysis approach. Besides these differences, heterogeneity of terminology in fatigability in older literature (where the term fatigability was not used yet for example) might have caused that this review missed some studies with other measurement methods for measuring the concept of walking fatigability. As well, the causality of slowing down during walking, and related factors as illustrated in figure 1, may however be very different between the study populations such as predominantly respiratory compared to neurological conditions. Recommendations for future research can include peripheral and central factors in the investigation of walking-related performance fatigability. For example, one may focus on the cognitive control during walking in neurological conditions, as Neumann et al. (2014) and Claros-Salinas et al. (2014) already stated in MS the influence of walking on cognitive performance fatigability in terms of reaction time[50, 51] while other documented the presence of cognitive fatigability in MS[52]. Barbosa et al. (2016) also applied energy expenditure measures in older women, which might be related to fatigability[13]. Other factors can related to other peripheral factors, such as muscle force, abnormal joint functioning or aerobic fitness parameters, as probably mostly seen in arthritis and respiratory patients. In MS, the central voluntary drive might have a causal influence on walking fatigability[19, 20, 53]. Slowing down may be caused by a reduced neural drive or alternatively be a compensatory strategy for reduced endurance capacity. In persons with

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stroke, slowing down was associated with reduced lateral sway during walking, which is known to relate to falls risk[54]. In-depth gait analyses studies are recommended to also understand biomechanical mechanisms, which were not included in this review. Investigating all the factors contributing to walking-related performance fatigability will provide more insights, which consequently can enhance rehabilitation approaches.

5. Conclusions

The included articles applied different methods to objectively measure the walking-related performance fatigability in a wide range of pathologies and older adults. In these different populations, similar formulas were applied, mostly during the 6MWT. Psychometric properties were scarcely investigated, with a need of documenting the test-retest reliability of the proposed outcome measures, cut-off values based on discriminative and normative data, and ecological validity.

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NOTES

Conflicts of Interest: The authors declare no conflict of interest.

Author Contributions: conceptualization, F.V.G., L.M., I.L. and P.F.; methodology, F.V.G., I.L., H.B. and P.F.; formal analysis, F.V.G. and P.F..; X.X.; writing—original draft preparation, F.V.G., ; writing—review and editing, F.V.G., L.M., H.B., I.L. and P.F.; visualization, F.V.G., and H.B.; supervision, F.V.G., and P.F.

*Acknowledgments***:** We would like to acknowledge master thesis student Lien Dejaegere from the University of Hasselt for her assistance in screening the articles. Every co-author that made a substantial contribution to the concept and design, interpretation of data and revised the manuscript critically for important intellectual content and afterwards approved the version to be published.

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TABLES

Table Ia: Walking fatigability assessment based on spatiotemporal changes only. [3,4,6-8, 13-15, 23, 25-31, 33, 35, 38-40]

Population					Walking-related performance Fatigability	
Pathology	Article	Sample size (S) and age (years)	Walking descriptives	Instructions and measurement	Formula and interpretation	Results
400m walk						
400m walk – end vs begin – FASTEST SPEED						
Older adults	Glynn et al. 2015[23]	S = 467 Mean age range: 74.30±8.20	Gait speed < 1m/s (n=101)	1 lap = 40m Based on Schnelle et al. 2012 (8) and Simonsick et al. 2014 (25)	*Performance deterioration (PD)* Difference in MWS between lap 9 and lap 2 *Interpretation* High PD when lap 9 time was at least 6.5% slower than lap 2 time	18,1% showed a decline of 17.3±1.8
Older adults	Simonsick et al. 2014[27]	S = 605 Age range: 65-97	MWS range: 1.05-1.10 m/s	20m course 1 lap = 40m	*Performance deterioration (PD)* Difference in MWS between lap 9 and lap 2 *Interpretation* High PD when lap 9 time was at least 6.5% slower than lap 2 time	22,8% showed a decline of ≥ 6,5%
Older adults	Gonzales et al. 2014[25]	S = 45 Age: 67.40±5.20	Time for 400m walk: 277.8±32.3 s	65.5ft/20m course	Decline in MWS between first 100m and last 100m *Interpretation:* Decline ≥ 0.02 m/s	26% showed a decline of ≥ 0.02m/s
400m walk – lap vs lap – FASTEST SPEED						
Fatigued older adults (≤35 on FACIT-F) and a non fatigued control group (≥42 on FACIT-F)	Valiani et al. 2016[14]	*Patient* S = 20 Age: 73.16±5.06 *Control* S = 25 Age: 70.80±4.87	*Patient* MWS: 1.09±0.14m/s *Control* MWS: 1.11±0.12m/s	20m course 1 lap = 40m	*Performance-related fatigue*: Decrease in MWS each lap *Interpretation* Decrease in MWS	Starting from lap 7 there was a decrease in walking speed

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500m walk						
500m walk – end vs begin – USUAL SPEED						
MS and Healthy Control group	Schwid et al. 1999[35]	*Patient* S = 20 Age: 47.90±7.40 *Control* S = 20 Age: 46.80±6.90	*Patient* MWS: 0.6 m/s *Control* MWS: 1.6 m/s	50m course	*Ambulatory Fatigue Index (AFI)* $100\% \, x \left[1 - \left(\frac{MWS \text{ during final } 50m \text{ lap}}{MWS \text{ during initial } 50m \text{ lap}}\right)\right]$ *Interpretation* Non given	*Patient*: -16.80% *Control*: 2.00%
500m walk – end vs begin – FASTEST SPEED						
MS	Surakka et al. 2004[38]	S = 99 Age range: 30-54	/	50m course	*Ambulatory Fatigue Index (AFI)* $100\% \, x \left[1 - \left(\frac{MWS \text{ during final } 50m \text{ lap}}{MWS \text{ during initial } 50m \text{ lap}}\right)\right]$ *Interpretation* Non given	AFI range: -16.7 – 43.5
500m walk – end vs T25FW – FASTEST SPEED						
MS and Healthy Control group	Phan-Ba et al. 2012[4]	*Patient* S = 81 Age: 40.16±11.35 *Control* S = 30 Age: 30.30±10.40	*Patient* 500m in 338.32±134.23s *Control* 500m in 235.28±27.80s	100m course	*Deceleration Index (DI)* $\frac{MWS \text{ of the last 100 m of the } T500 \text{ meter walk test}}{\text{MWS of the T25FW +}}$ *Interpretation* The lower the DI, the higher performance related fatigability	Significant difference between Patient and Control group
6min walk						
6MWT – end vs begin – FASTEST SPEED						
Female older adults	Barbosa et al. 2016[13]	S = 44 Age: 75.00±7.20	6MWD: 355.7±79.9 m	30m course Standard set of encouragement each minute (ATS)	*Performance fatigability severity* $\left[\frac{MWS \text{ min. } 6 / MWS \text{ min. } 1}{6MWD}\right] x1000$ *Interpretation* Percentages change in walking speed indicated fatigability (Based on Schelle et al. (8))	Performance fatigability severity: 2.8±0.8

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MS	Aldughmi et al. 2016[30]	S = 51 Age: 47.00±10.10	Non given	175 ft/53m No encouragement (Goldman et al.)	*Performance/physical fatigability* % change in distance walked between 1st and 6th minute *Interpretation* Decrease in percentage	Significant 12.7% decrease in meters
MS	Leone et al. 2015[3]	S = 208 Age: 47.90±10.70	6MWD: 361.2±169.8m	30m course No encouragement (Goldman et al.)	*Distance Walked Index (DWI)* $\left[\frac{(Distance\ walked\ in\ min.6 - Distance\ walked\ in\ min.1)}{Distance\ walked\ in\ min.1}\right]x100$ *Interpretation* -15% was chosen to categorize walking-related performance fatigability	64 patients showed a decline of 15% or more
MS	Proessl et al. (2018)[29]	S = 19 Age: 53.74±9.68	MWS: 1.19±0.36m/s	30m course Based on Leone et al. 2015 (3)	*Distance Walked Index (DWI)* $\left[\frac{(Distance\ walked\ in\ min.6 - Distance\ walked\ in\ min.1)}{Distance\ walked\ in\ min.1}\right]x100$ *Interpretation* -15% was chosen to categorize walking-related performance fatigability (based on Leone et al. 2015) (3)	Mean DWI: -7.57±13.30%
MS and Healthy Control group	Ramari et al. (2018)[28]	*Patient* S = 28 Age: 33.90±9.20 *Control* S = 21 Age: 32.10±7.70	*Patient* 6MWD: 506.20±61.10 *Control* 6MWD: 588.00±46.60	10m course No encouragement (Goldman et al.) Based on Leone et al. 2015 (3)	*Distance Walked Index (DWI)* $\left[\frac{(Distance\ walked\ in\ min.n - Distance\ walked\ in\ min.1)}{Distance\ walked\ in\ min.1}\right]x100$ *Interpretation* -15% was chosen to categorize walking-related performance fatigability (based on Leone et al. 2015) (3)	Significant slowing down over course of 6MWT by MS patients (not in controls) Significant lower DWI_{6-1} in MS compared to controls
SMA	Montes et al. 2012[40]	S = 7 Age range : 10 – 48	6MWD range: 117 – 513 m	25m course Encouragement at neutral tones (ATS)	% difference in the MWS during the first and last passes over the gaitRITE *Interpretation* Non given	Non given
SMA	Montes et al. 2016[6]	S = 9 Age: 27.90±17.10	6MWD: 303.60±75.20m	25m course Encouragement at neutral tones (ATS)	Percentages changes in MWS, stride length, and cadence between first and last minute of 6MWT *Interpretation* Decline in percentages	Decline of: Walking speed with 11,6±9,1% Stride length with 6,7±5,6% Cadence with 5,5±4,0%

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6MWT – average vs first lap – USUAL SPEED						
Fatigued older adults with Arthritis (mean of 4.6/10 on Brief Fatigue Inventory)	Murphy et al. 2016[26]	S = 163 Age: 71.90±5.90	MWS 6MWT: 1.06±0.22 m/s	30m course Encouragement (Butland et al.)	*Performance fatigability severity* $\left[\frac{MWS\ over\ 6\ min. / MWS\ over\ 2\ min.}{6MWD}\right] x1000$ *Interpretation* Higher scores indicated greater fatigability	Performance fatigability severity: 3.10 ± 1.1
6MWT – average vs first lap – FASTEST SPEED						
ILD	Keyser et al. 2015[7]	S = 13 Age: 57.10±9.10	6MWD: 433±92.6m	80m circular course Encouragement at neutral tone (ATS)	*Performance fatigability index (PFI)* $\frac{\left[\left(\frac{MWS\ of\ the\ 6MWT}{MWS\ of\ the\ first\ lap}\right)\right]}{6MWD}$ *Interpretation* The higher (the % of) the PFI, the more physical performance fatigability during walking	PFI: 0.225 ± 0.064 (22.5% ± 6.4%)
6MWT – min vs min – FASTEST SPEED						
MS and Healthy Control group	Mcloughlin et al. 2016[33]	*Patient* S = 34 Age: 49.10±10.40 *Control* S = 10 Age matched	*Patient* More affected leg MWS: 6MWT: 1.14±0.29 m/s *Control* MWS 6MWT: 1.50±0.19 m/s	10m course Encouragement at neutral tone (ATS) VICON MX3 camera	*Performance Fatigability/Walking–induced fatigue* Decline in total distance walked and distance walked in each minute *Interpretation* Decline in distance	Significant trend in lower distance walked and distance decline between final 3 min. and the 1st min. compared to HC
MS and Healthy Control group	Burschka et al. 2012[31]	*Patient* S = 37 Age: 39.70±12.80 *Control* S = 25 Age: 38.40±11.90	*Patient* 6MWD: Severe MS (n=18):422±69m Mild MS (n=19): 586±73m *Control* 6MWD: 681±88m	20m course No encouragements (Goldman et al.) Visually, stopwatch	*Linear trend 6MWT (LT6MWT):* $\frac{[(-5xD1)+(-3xD2)+(-1xD3)+(1xD4)+(3xD5)+(5xD6)]}{70}$ *Interpretation* Non given	*Patient:* Severe MS group: -1.00±0.78 Mild MS group: -0.37±0.35 *Control*: -0.42±0.55

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MG and Healthy Control group	Jordan et al. 2017[15]	*Patient* S = 32 Age: 55.70±17.30 *Control* S = 17 Age: 46.50±17.90	*Patient* MWS: 61.60±21.80 m/min *Control* 90.10±17.30 m/min	Encouragement at neutral tones (ATS)	*Linear trend 6MWT (LT6MWT)* $\frac{[(-5xD1)+(-3xD2)+(-1xD3)+(5xD4)+(3xD5)+(1xD6)]}{70}$ *Interpretation* LT < 0 (LT = 0 means stable performance)	*Patient:* -0.62±1.43 *Control*: 0.24±0.73
SMA	Montes et al. 2010[39]	S = 18 Age: 15.30±13.30	6MWD: 288.9±161.9m	25m course Encouragement at neutral tones (ATS)	Decrease in MWS and distance for the first minute compared to each minute *Interpretation* Decrease MWS and distance	Significant decline of 9.5m between 1st and 6th min.
10min walk						
10min walk – average vs begin – USUAL SPEED						
Older adults	Schnelle et al. 2012[8]	S = 43 Age: 85.33±5.90	MWS: 0.65±0.20m/s	170 ft/51m circular course	*Performance fatigability severity* $\left(\frac{\text{(MWS over the full time walked/MWS in the firts 2,5 minutes)}}{\text{Total distance walked}}\right)\text{x}1000$ *Interpretation* Percentages change in walking speed indicated fatigability	3.50±2.60 (range 1.19-13.34)
12min walk						
12MWT – min vs min - FASTEST SPEED						
MS and Healthy Control Group	Burschka et al. 2012[31]	*Patient* S = 37 Age: 39.70±12.80 *Control* S = 25 Age: 38.40±11.90	*Patient* 6MWD: Severe MS (n=18): 422±69m Mild MS (n=19): 586±73m *Control* 6MWD: 681±88m	20m course Visually, stopwatch No encouragements (Goldman et al.)	*Linear trend 12MWT (LT12MWT)* See 6MWT; adapted for distance until the 12th minute *Interpretation* Non given	*Patient:* Severe MS group: -0.73±0.51 Mild MS group: -0.22±0.33 *Control:* -0.00±0.25

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Table Ib : Walking fatigability assessment based on kinetic and kinematic changes.[2,5,32,34,36-37,41]

Population					Walking-related performance Fatigability	
Pathology	Article	Sample size (S) and age (years)	Walking descriptives	Instructions and measurement	Formula and interpretation	Results
100m walk						
100m walk – last vs average – USUAL SPEED						
Arthritis	Lester et al. 2010[2]	S = 53 Age: 61.8±8.98	MWS: 64.48±11.79m/s	100m course outdoor IDEEA-device	$\left[\frac{\text{mean value gait variables for the last 20 steps}}{\text{mean value of overall gait variables}}\right] x\ 100\%$ *Interpretation* Non given	Percentages ranged from 0.62 – 1.32 for all the different gait parameters.
Arthritis	Zhang et al. 2006[41]	S = 26 Age: 63.80±10.80	MWS: 65.60±14.39 m/min	100m course outdoor Stopwatch metered tap device IDEEA-device	$\left[\frac{\text{mean value gait variables for the last 20 steps}}{\text{mean value of overall gait variables}}\right] x\ 100\%$ *Interpretation* Non given	MWS: -2.7% Cadence: -3.3% Pulling power of foot at initial swing: -6.3%
6min walk						
6MWT – end vs begin - FASTEST SPEED						
MS and Healthy Control Group	Engelhard et al. 2016[32]	*Patient* S = 86 Age range: 19 – 61 *Control* S = 29 Age range: 19 – 54	*Patient* 6MWD: 1574 ft (range 129-2281) *Control* 6MWD: 2009 ft (range 1529-2587)	75ft/23m course Actigraphs GTBX	Dynamic Time Warping (DTW) = a measure of similarity between gait cycles where cycles from later minutes of the 6MWT are compared to baseline cycles of the 6MWT. *Interpretation* A higher Warp score shows more variability (due to fatigability)	Warp score is higher between 3th and 6th min.
MS	Qureshi et al. 2016[34]	S = 28 Age range: 18 – 65	/	30m course No encouragement (Goldman et al.) Wearable BSN platform	Changes in gait cycle length and speed for each minute of the 6MWT though gait time series. *Interpretation* Changes in gait parameters	Non given

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Treadmill walking						
Treadmill walking – end vs begin – FIXED SPEED BASED ON INDIVIDUAL USUAL SPEED						
MS	Sehle et al. 2011[5]	S = 14 Age: 42.00±7.60	Walking distance until exhaustion: 362±439m	Until exhaustion (Borg score of 17) AS200 system	*Performance fatigability: Fatigue Index* $\frac{1}{2} x \left(\frac{Nsignificant\ mean\ changes}{Ngait\ parameters} + \frac{Nsignificant\ SD\ changes}{Ngait\ parameters}\right)$ *Interpretation* In between 0 and 1	range 0.33 – 0.92
MS and Healthy Control Group	Sehle et al. 2014[36]	*Patient* S = 40 Age range: 45.90±7.00 *Control* S = 20 Age range: 43.10±8.60	*Patient* MWS MS fatigue: 0.81±0.36km/h MWS MS non fatigue : 4.7±0.5km/h *Control* MWS: 5.00±0.00km/h	Until exhaustion (Borg score of 17) AS200 system	*Fatigue index Kliniken Schmieder (FKS)* δF = δM x δD *Interpretation* >4 = cut-off for determining fatigue	*Patient* Range fatigue group: 4.2 – 125 Range non-fatigue group: 0.5 – 3.4 Range HC: 0.3 – 3.9
MS, stroke and Healthy Control group	Sehle et al. 2014[37]	*Patient* Stroke: S = 10 Age: 51.60±8.30 MS: S = 40 Age: 45.90±7.00 *Control* S=20 Age: 43.10±8.60	*Patient* MWS Stroke: 2.20±0.80km/h MWS MS: 3.40±1.40km/h *Control* MWS: 5.00±0.00km/h	Until exhaustion (Borg score of 17) AS200 system	*Fatigue index Kliniken Schmieder (FKS)* δF = δM x δD *Interpretation* >4 = cut-off for determining fatigue	*Patient* Range stroke fatigue group: 5.3 – 15.3 Range stroke non-fatigue group: 2.20 –3.20 Range MS fatigue group: 4.2 – 125 Range MS non-fatigue group: 0.5 – 3.4 *Control* Range: 0.30 - 3.90

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MWS: Mean Walking Speed, PFS: Pittsburgh Fatigability scale, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, MS: Multiple Sclerosis, FSS: Fatigue Severity Scale, HC: healthy controls, T25WF: Timed 25 foot walk, 6MWT: Six minute walking test, ATS: American Thoracic Society, 6MWD: Six minute walking distance, MFIS: Modified Fatigue Impact Scale, SMA: Spinal Muscular Atrophy, ILD: interstitial lung disease, VAS-F: Visual Analogue Score-Fatigue, MG: Myasthenia Gravis, $N_{significant\ mean\ changes}$: number of parameters with a significant mean change from t_1 to t_2, $N_{significant\ SD\ changes}$: number of parameter with a significant SD change from t_1 to t_2, $N_{gait\ parameters}$: number of gait parameters, FSMC: Fatigue Scale for Motor and Cognitive functions,

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Table II: Psychometric properties of the walking-related performance fatigability assessment [3,5,8,13,15,23,25-27,33,36-37]

Pathology	Article	Fatigability Formula	Diagnostic criteria	Psychometric properties
400m walk				
Older adults	Glynn et al., 2015[23]	Performance deterioration (PD) $1-(\frac{\text{walking speed lap 9}}{\text{walking speed lap 2}})$	≤ -6.5%	Discriminative validity AUC indicated good discrimination for classifying of performance fatigability with the PFS questionnaire (AUC: 0.68 – 0.73, p<0.001)
Older adults	Simonsick et al., 2014[27]	Performance deterioration (PD) $1-(\frac{\text{walking speed lap 9}}{\text{walking speed lap 2}})$	≤ -6.5%	Concurrent validity *Performance fatigability vs trait fatigue* Strong association with every fatigue symptom Predictive validity Robust relationship with reported walking ability
Older adults	Gonzales et al., 2014[25]	Decline in MWS between first 100m and last 100m	≤ -0.02 m/s	/
500m walk				
MS	Schwid et al., 1999[35]	Ambulatory Fatigue Index (AFI) $100\%\ x\ \left[1-\left(\frac{Velocity\ during\ final\ 50m\ lap}{Velocity\ during\ initial\ 50m\ lap}\right)\right]$	/	Test-retest reliability MS: ICC=0.36 HC: ICC=0.21
6MWT				
MS	Leone et al., 2015[3]	Distance Walked Index (DWI) $\left[\frac{(\text{Distance walked in min 6} - \text{Distance walked in min 1})}{\text{Distance walked in min 1}}\right]\text{x}100$	≤ -15%	Concurrent validity *2 type of measurements for performance fatigability* DWI vs DI (Phan-Ba et al., 2012) Total group: r=0.84, p<0.001 Walking fatigability group: r=0.92, p<0.001
MG	Jordan et al., 2017[15]	Linear trend (LT) $\frac{[(-5xD1)+(-3xD2)+(-1xD3)+(5xD4)+(3xD5)+(1xD6)]}{70}$	< 0	/
Fatigued older adults with arthritis	Murphy et al., 2016[26]	*Performance fatigability severity* $\left[\frac{MWS\ over\ 6\ min./MWS\ over\ 2\ min.}{6MWD}\right]x1000$	/	Concurrent validity *Perceived vs performance fatigability* r=0.62, p-value not given

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Older adults (women)	Barbosa et al., 2016[13]	*Performance fatigability severity* $\left[\frac{MWS\ min.\ 6 / MWS\ min.\ 1}{6MWD}\right] x1000$	/	Concurrent validity *Perceived vs performance fatigability* r=0.69, p < 0.01 physical activity and performance fatigability together represented 84% of the variation in perceived fatigability severity
10min walk				
Older adults	Schnelle et al., 2012[8]	Performance fatigability severity $\left(\frac{\text{(MWS over the full time walked/MWS in the firts 2,5 minutes)}}{\text{Total distance walked}}\right)$ x1000	/	Concurrent validity *Perceived vs performance fatigability* r=0.93 and 0.94, p < 0.01 *Performance fatigability vs trait fatigue* FSS: r=0.53, p < 0.01
Treadmill				
MS	Sehle et al., 2011[5]	Fatigue index $\frac{1}{2} x \left(\frac{\text{Nsignificant mean changes}}{\text{Ngait parameters}} + \frac{\text{Nsignificant SD changes}}{\text{Ngait parameters}}\right)$	[0 - 1]	Concurrent validity *Performance fatigability vs trait fatigue* FSMC motoric domain: r=-0.592, p=0.023
MS, stroke	Sehle et al., 2014[36, 37]	Fatigue index Kliniken Schmieder (FKS) $\delta F = \delta M \times \delta D$	> 4	Discriminative validity 97% correctly diagnosed (3% false positive) for fatigued patients and 91% (9 false negative) correctly diagnosed for non-fatigued by the neurologist compared to the FKS: cohens kappa K=0.88 Video analysis (during treadmill walking) by the physiotherapist, only 50% was correctly diagnosed: cohens kappa K=0.32-0.49.

6MWT: six-minute walking test, MG: myasthenia gravis, MS: multiple sclerosis, MWS: mean walking speed, AUC: Area Under The Curve, PFS: Pittsburgh Fatigability Scale, ICC: intra-class correlation coefficient, HC: Healthy Control, DI: Deceleration Index, FSMC= Fatigue Scale for Motor and Cognitive Functions, FSS: Fatigue Severity Scale. $N_{significant\ mean\ changes}$: number of parameters with a significant mean change from t_1 to t_2, $N_{significant\ SD\ changes}$: number of parameter with a significant SD change from t_1 to t_2, $N_{gait\ parameters}$: number of gait parameters, δM: measure of the difference between two attractors quantifying the differences between two movement patterns, δD: difference between the two associated deviations of the state vector away from the attractor representing the change in movement variation, δF: product of δM and δD that represents an index of the change.

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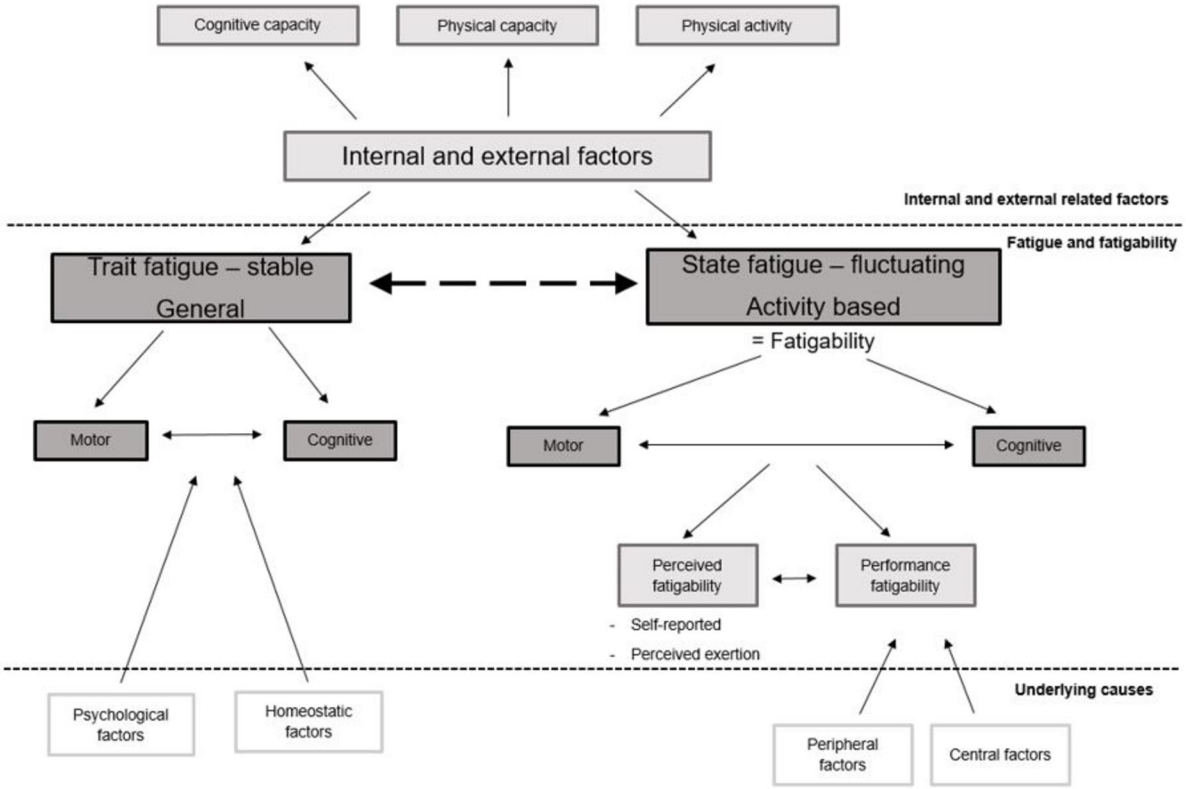

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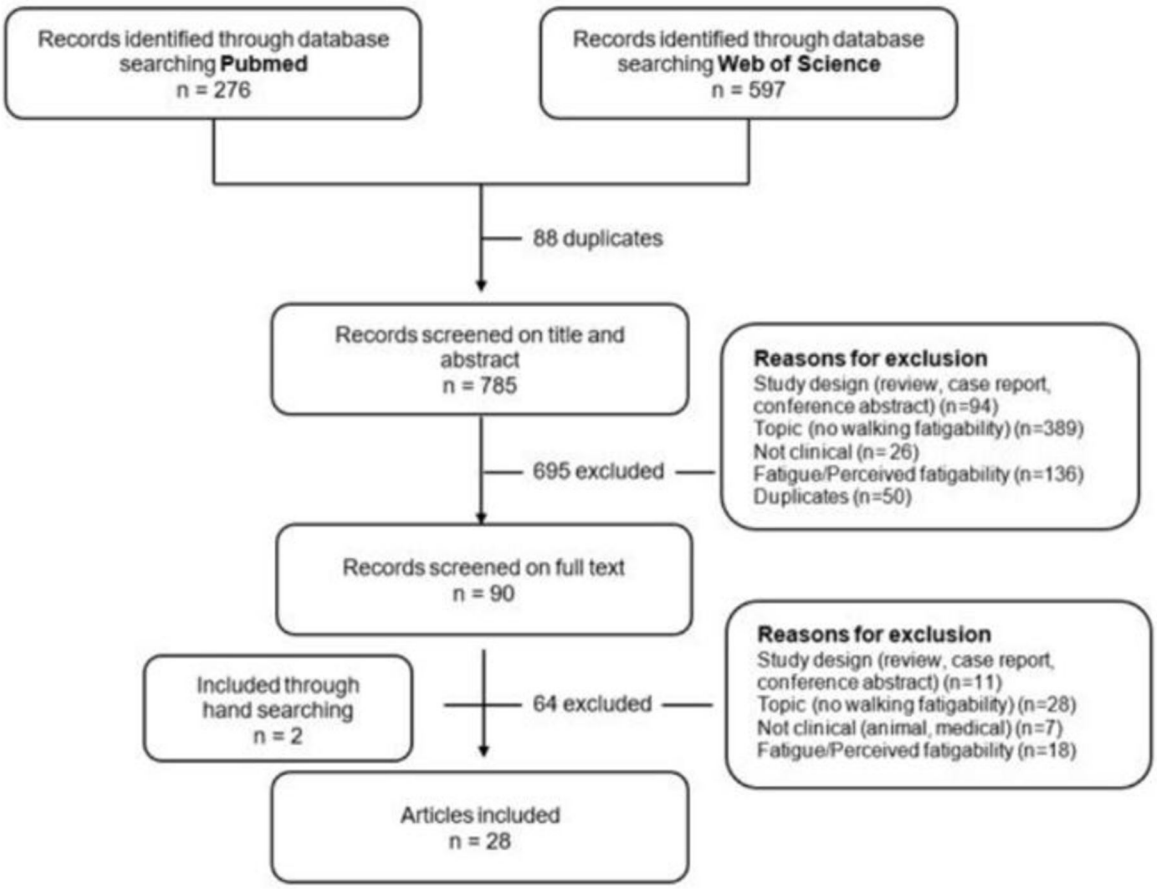

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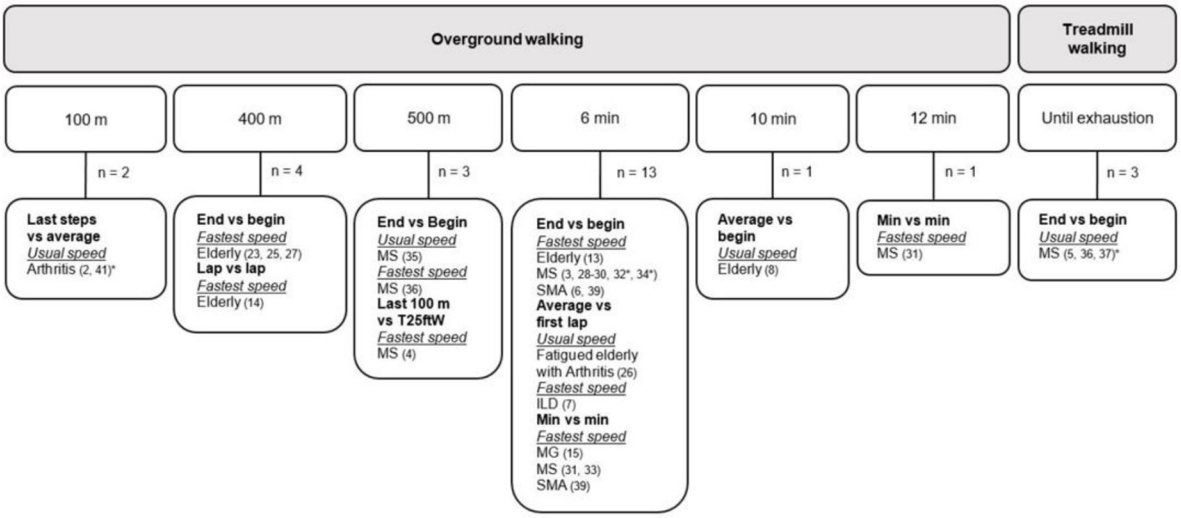
Figure 3. A schematic overview of the protocols assessing walking-related performance fatigability in different populations



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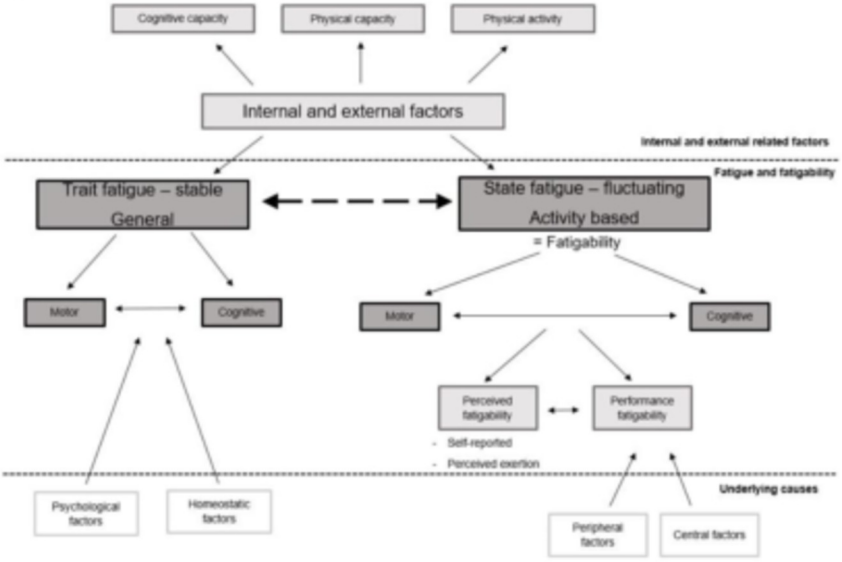

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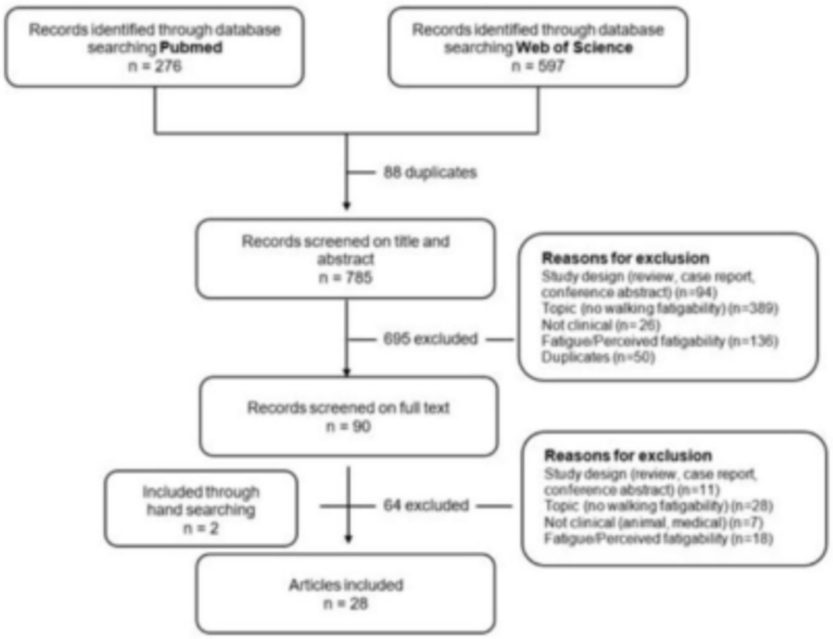

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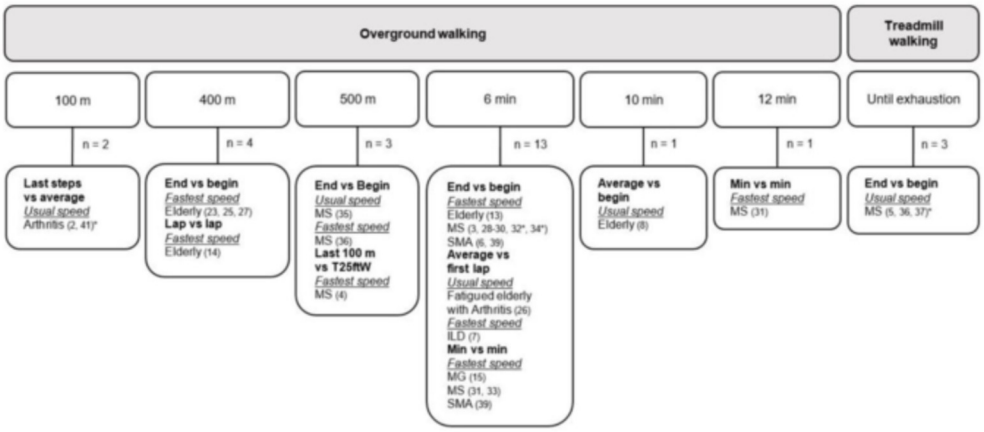

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