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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de revalidatiewetenschappen en de kinesitherapie

Masterproef deel 1

Assesement of walking-related performance fatigability

Promotor :
Prof. dr. Peter FEYS

Copromotor :
Mevrouw Fanny VAN GEEL

Lien Dejaegere

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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ASSESSMENT OF WALKING-RELATED PERFORMANCE FATIGABILITY

Outline

Fatigue and walking are major symptoms in many neurological and other disorders, such as Multiple Sclerosis (MS), Spinal Muscular Atrophy (SMA), stroke and Fibromyalgia. Not only chronically ill patients, but also older adults, especially those who are frail, suffer from those disease characteristics. However, fatigue is mostly assessed through self-reported questionnaires based on the subjective feelings of the patient.

Therefore, the focus in this paper is finding objective methods which are currently used to assess walking-related performance fatigability. To find sufficient literature in this regard, the research question stated was: 'How is motor fatigability objectively measured in walking?'.

The most important information extracted from the literature study to answer this research question, is provided in the highlights below:

- Methods to assess walking-related performance fatigability can be based on walking speed, distance walked or both of these or other parameters e.g. heart rate and characteristics of gait analysis.
- There was a wide variability in the walking tasks participants had to perform. These variance can be explained in time, distance and sort of walking: treadmill or overground gait.
- Walking-related performance fatigability has been investigated in different study populations: young and older community-dwelling adults, patients with Multiple Sclerosis, Spinal Muscle Atrophy subjects, stroke patients and men with stable Intermittent Claudication.
- Only a few studies stated a clear criterion to distinguish fatigued and non-fatigued individuals based on objective assessment.
- The most important conclusion of this literature review, is that there is no golden standard measure for motor fatigability during walking. Normative data based on performance of healthy individuals and psychometric properties are lacking.

Lien Dejaegere

Promotor: Prof. Dr. P. Feys

Co-promotor: Dra. F. Van Geel

Context of the master thesis

This paper can be situated in the wider research context of neurological rehabilitation. As already introduced in the outline, both walking and fatigability are major symptoms which are often impaired severely in neurological and other chronic conditions.

Fatigability during the performance of a physical activity, can be investigated through several questionnaires such as the Fatigue Severity Scale, the Fatigue Descriptive Scale, a Visual Analogue Scale and the Fatigue Impact Scale. However, this way of assessing fatigability, is based on the patient’s perception that more effort is required to perform a task such as walking.

Since a qualitative good clinical examination is mostly based on objective outcome measures to increase the reliability and comparison of results, there is a need for objective ways to assess walking-related performance fatigability. Therefore, the literature study of this paper focused on the following research question: ‘How is motor fatigability objectively measured in walking?’.

The goal of the literature study provided in part one is to investigate the currently used methods in the objective assessment of walking-related performance fatigability. The different parameters which are used to measure walking-related motor fatigability, the pathology, the technique and the criterion that distinguished fatigued from non-fatigued individuals were extracted.

During part two of the paper which will take place next year, the aim is to apply one of these common methods on patients with Multiple Sclerosis performing the 6MWT and to compare these outcomes with the performance of the 6MWT in healthy controls. A few possible influencing variables will also be investigated. This part of the study will be done in Diepenbeek at the research centre REVAL of UHasselt. A detailed description of the research protocol is provided in part two of this master thesis.

A central format was applied for this master thesis.

In co-operation with Prof. Dr. P. Feys and Dra. F. Van Geel, the final research question and literature search strategy were developed in January 2017. The detailed analysis of the articles selected through the search strategy was especially supervised by Dra. F. Van Geel, although Prof. Dr. P. Feys also provided feedback on consecutive moments.

This was a single master thesis.

The task of the master student was to extract all the different ongoing objective measures for walking-related motor fatigability and to determine which one of these would be interesting to use in the research protocol. Furthermore, it was the task of the master student to write a totally new detailed research design and to determine which parameters could influence walking-related motor fatigability.

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Part one: overview of the literature

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Part one: overview of the literature

1 Abstract

Background: Fatigue and walking are complaints which are often reported in patients with neurological conditions. Fatigue during the performance of physical activities, can be defined as ‘fatigability’ introduced by Barbosa et al. 2016. Several questionnaires based on self-report of the subjective feeling that more effort is required to perform a task are currently used to assess fatigability.

Methods: The main research question this literature review focused on is ‘How is motor fatigability objectively measured in walking?’. The research strategy applied in PubMed and Web Of Science was: Assessment AND (Muscle Fatigue OR Motor Fatigue OR Motor Fatigability OR Fatigability) AND (Walking OR Gait).

Results: In total, 388 articles were found from which 297 articles were excluded. After screening full texts, 22 articles remained. Through hand-searching, 3 new articles were included. Data extracted from the remaining 25 articles, handled about the walking task, motor disability at baseline, pathology, sample size, criterion, technique and parameters used to define fatigability.

Discussion: Overall, all the included articles had a moderate to good quality. A consistent method for assessing walking-related performance fatigability is lacking, due to differences in study population, terminology and definition of fatigability or variance in the walking task (e.g. speed, distance, protocol).

Conclusion: Motor fatigability is currently measured using different methods. There is no golden standard in the measurement of walking-related motor fatigability. Normative data based on performance of healthy individuals and psychometric properties are scarce.

Most important key words: Walking-related fatigability, Motor fatigability, Performance, Walking Assessment and Objectivity

2 Introduction

Multiple Sclerosis (MS) is an autoimmune disorder characterized by inflammation and destruction of mostly the white matter of the Central Nervous System myelin. Globally, 2.1 million people, mainly younger adults between 20 – 30 years, are affected by this disease (Porth's Pathophysiology, 9th edition). The damage to the central nervous system leads to a wide range of different physical and cognitive (mental processes) symptoms.

Those symptoms include cognitive decline, muscle weakness, spasticity, and excessive fatigue (Heine et al. 2015). For this paper, focus will be made on fatigue, because this is one of the most common symptoms in MS, which nearly half of the patients describe as their most disabling feature (Ben-Zacharia et al. 2011).

This fatigue can be defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (MS Council, 1998).

A distinction is made between performance and perceived fatigability. Perceived fatigability reflects the self-reported change in tiredness, where the performance part refers to the objective change or decline during a performance: physical e.g. decreased walking speed or cognitive (Barbosa et al. 2016, Schnelle et al. 2012).

However, recently new definitions of fatigue arise. Sehle et al. (2011) defined motor fatigue as "a reduction in maximal walking distance that cannot be explained by the degree of paresis, ataxia or spasticity". Fatigue can also be described as "a transient decrease in the ability to perform physical activities (performance component) and an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work (perceived component)" (Morrison et al. 2016).

Several questionnaires have been used to assess perceived fatigue e.g. the Fatigue Severity Scale, the Fatigue Impact Scale, the Fatigue Descriptive Scale and a Visual Analogue Scale. These instruments are based on the self-report of subjective fatigue or the perception of the patient that more effort is required to perform a task (Sehle et al. 2011, 2014).

Aiming to measure fatigability more objectively, a new construct was built. The concept 'fatigability' describes how fatigued an individual gets in relation to defined activities (Barbosa et al. 2016). This approach measures the change in fatigue level as a function of the change in intensity, duration or frequency of activity (Barbosa et al., Glynn et al. 2015).

Not only fatigue, but also difficulty walking is often rated as the most challenging aspect of living with Multiple Sclerosis (McLoughlin et al. 2015). From the beginning of the disease, decreased walking capacity and physical activity levels are present (Motl et al. 2005; Dlugonski et al. 2013 & Gijbels et al. 2010). During their disease, almost 80% of all the PwMS experience walking difficulties (Ben-Zacharia et al. 2011). Consequently, patients have a reduced quality of life (McLoughlin et al. 2015).

Not just in neurological conditions such as MS but also in older adults perceived fatigability is a common complaint. Older adults may reduce their level of being physically active aiming to keep their feelings of fatigability in an acceptable range. Therefore, misleading conclusions could be made if the focus exclusively would be on fatigability, without the understanding of the activity context in which this fatigability occurs (Barbosa et al. 2016).

Recently, a few methods were developed for assessing fatigability in a more objective way. Although, psychometric properties and consensus are lacking. Therefore, this paper focused on all the different ways in which walking-related performance fatigability is objectively assessed and calculated.

3 Methods

3.1 Research question

For this literature review, the main question is: 'How is motor fatigability objectively measured in walking?'. The focus in this paper is motor or performance fatigability, rather than the perceived component of this concept. However, data on perceived fatigue or fatigability will be extracted if documented in the retrieved studies.

The aim was to provide an overview of which methods clinicians and researchers currently use to assess performance fatigability and possibly apply one of these in the research protocol in a specific neurological population as Multiple Sclerosis (see part II – experimental design).

3.2 Literature search

PubMed and Web Of Science were the two databases used for this literature search. As there is currently no Medical Subject Heading (MeSH) term for motor fatigability, the following synonyms were used as key words: 'Motor Fatigue', 'Motor Fatigability', 'Muscle Fatigue' and 'Fatigability'. Given the focus on fatigability during walking, 'Walking' and 'Gait' were added in the combination of the search strategy. Finally 'Assessment' was combined with the previous key words.

In PubMed the following search strategy was applied: Assessment AND (Muscle Fatigue OR Motor Fatigue OR Motor Fatigability OR Fatigability) AND (Walking OR Gait). This combination gave 174 hits. The search strategy applied in Web Of Science was as followed: TS = Assessment AND (TS = Muscle Fatigue OR TS = Motor Fatigue OR TS = Motor Fatigability OR TS = Fatigability) AND (TS = Walking OR TS = Gait). The result of this combination was 214 hits.

A final update of this literature search was performed on April 27, 2017. This last update was used to determine the final set of articles that would be included.

3.3 Selection criteria

At first, articles with the following study designs were excluded: a review, a case report (one individual) or an animal study. Articles discussing the upper extremity, walking and fatigue as descriptive characteristics of frailty or other topics not related to the research question, were also rejected.

The articles which were retained for further screening should at least include both aspects: walking or gait and fatigability. It was important that the article handled about the performance component of fatigability, otherwise the article was excluded. In case that the authors only made use of a questionnaire to assess fatigue or fatigability and so there was no walking performance, this article was not included. Furthermore, the measurement of walking fatigability must be clearly stated.

Therefore a link between walking and fatigability which was only provided through the proof of a statistic correlation was not sufficient.

3.4 Quality assessment

The quality assessment was based on a checklist derived from the website of the National Institutes of Health. In the department of National Heart, Lung and Blood Institute, the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies” was applied on the included articles.

3.5 Data extraction

First of all, the walking task that participants had to perform was extracted from the included studies. Data selected in relation to fatigability were: the parameter or formula that determined motor fatigability, the criterion which stated when a participant was seen as abnormally fatigued and the technique (e.g. stopwatch) used to measure fatigability. If the article reported any psychometric properties, values were extracted. Descriptive characteristics of the investigated population such as motor disability at baseline (m/s), pathology, size and age were extracted.

4 Results

4.1 Study selection

The combination of key terms resulted in 174 articles in PubMed and 214 articles in Web Of Science. Table 1 in appendix presents an overview of the key words and applied search strategy. Consequently the total outcome of the search strategy was 388 articles. Ninety-one duplicates were found so the screening started with 297 articles. During the whole screening procedure, the previously stated selection criteria were applied.

At first, these articles were screened making use of title and abstract, to determine if the content could be interesting in relation to the research question.

Afterwards, the remaining articles (n = 87) were screened on full text. Only three of these articles were excluded based on study design. The remaining 65 articles were excluded for different reasons based on outcome.

Table 2 in appendix represents in more detail the number and reason of the excluded articles such as: no fatigability and/or walking or gait; no link, a secondary or an other link between fatigability and/or walking or gait; other aspects of fatigability and/or walking or gait. For some articles, the full text was not available before the final update on 27 April, 2017.

Finally 18 articles from the PubMed database and 4 articles from the Web Of Science database remained to analyse in full detail. Three extra articles were included through hand-searching. A flowchart of the study selection process is provided in Figure 1 on the next page.

4.2 Quality assessment

The results of the quality assessment, based on the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies” from the National Institutes of Health, are provided in Table 3 in appendix. Table 4 represents an overview of the strengths and weaknesses for each study.

The research question or objective, was clearly stated in all the included articles (n = 25). Furthermore, for each article both the exposure measure, which is seen here as the walking task the participants had to perform, as well as the outcome measures (e.g. walking speed, total distance walked, motor fatigability, …) were clearly defined, valid, reliable and implemented consistently across all study participants.

Fourteen articles clearly specified and defined the study population, however in the remaining 8 articles the answer on this question had to be no. These studies didn’t provide a detailed description of patient recruitment, lacking information about demographics, location and/or time period. There were only 5 articles in which there was ambiguity regarding the selection procedure of the participants. In all the other articles, subjects were recruited from the same population and the same underlying inclusion and exclusion criteria were used for all the subjects involved.

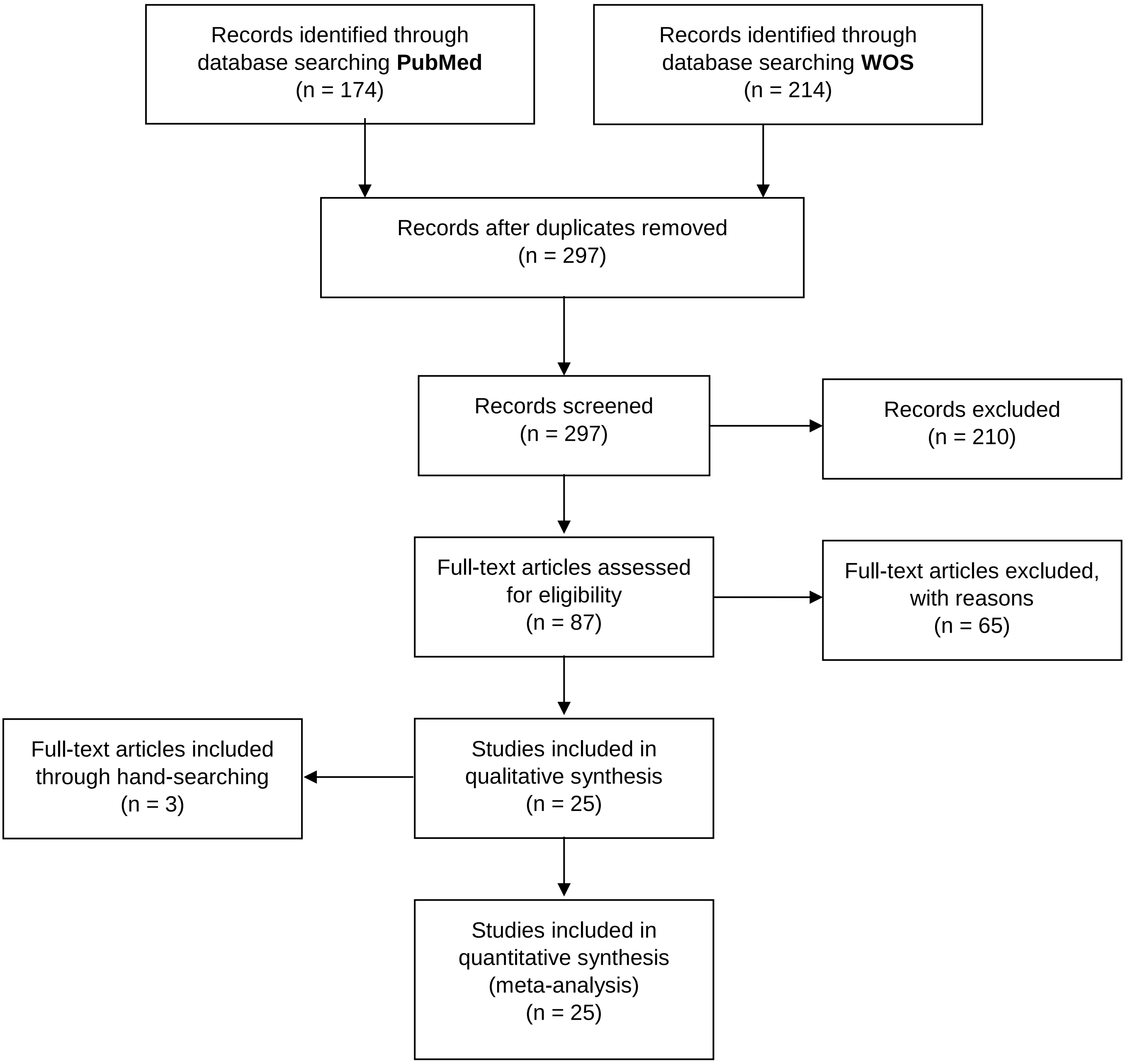

Figure 1 – Flow chart search strategy

Only three articles provided a sample size justification, power description or variance and effect estimates.

The answer on questions 6, 7, 10 and 12, concerning exposure assessment prior to outcome measurement, sufficient timeframe to see an effect, repeated exposure assessment and blinding of outcome assessors, was oftentimes ‘no’ or ‘Not Applicable (NA)’. However, this doesn’t mean the quality of these studies decreases. The included studies are most of the time an observational study instead of a cohort study what explains the negative answer.

As provided in Table 4 in the appendix, each study reported some strengths and limitations. For a lot of the included articles (n = 8), a major weakness was the small sample size, which made it more difficult to generalize the results to the entire population (Barbosa et al. 2016, McLoughlin et al. 2015, Montes et al. 2010, Richardson et al. 2015, Schnelle et al. 2012, Sehle et al. 2011, Tuner et al. 2008 and Valiani et al. 2016).

An other limitation which was often reported, concerns the selection of the walking task. Since different walking tests such as the 6-minute walk test, 10-minute walk test, Timed 25-foot walk, 400-meter long distance walk, … are being used to assess motor fatigability, comparison and consensus are impossible (McLoughlin et al. 2015, Murphy et al. 2017). At least, the influence of age, pathology, severity, drugs used and other parameters, make representativeness of the results difficult (Granacher et al. 2010, Leone et al. 2015, McLoughlin et al. 2015, Phan-Ba et al. 2012 & Surakka et al. 2004).

The most important weakness there is for all the articles, is that there is no golden standard measure which qualifies motor fatigability during walking. Normative data based on performance of healthy individuals and psychometric properties are lacking (Leone et al. 2015).

4.3 Data-extraction

Table 5 in appendix describes the most important information extracted from the included studies. For each article, the walking task, population or pathology, sample size and age are represented, as well as the motor fatigability parameter, technique and criterion for the measurement of fatigability. We extracted as well the baseline walking velocity and the overall fatigue level if provided as descriptive characteristic.

A substantial number of studies (n = 8) investigated fatigability in a population of healthy (older) individuals. There were twelve studies in which patients with Multiple Sclerosis (MS) were included as the study population. The other studies (n = 5) had participants with different pathologies e.g. Spinal Muscle Atrophy (SMA), osteoarthritis, stroke and Intermittent Claudication (IC).

Although all the articles provided a formula or a way to determine fatigability, only a few studies (n = 7) stated a criterion which clearly distinguish fatigued participants from non-fatigued participants based on objective measurement of fatigability.

4.3.1 Fatigability based on walking speed, distance walked or both (n = 15)

Montes et al. (2010, 2013 & 2016) measured fatigability during the 6-minute walk test on patients with Spinal Muscle Atrophy. At first, the assessment of fatigability was based on the distance walked. The mean distance walked in the first minute was then compared to the mean distance walked during the sixth minute to measure the concept of fatigability. Later in 2013, fatigability was defined as the % difference in average velocity during the 1st and the last passes over the gait mat during a 6-minute walk test. A similar way to determine fatigability was applied in 2016, where this was seen as a decrease in walking speed from the 1st to the last minute of the 6MWT.

A deceleration index to determine locomotor fatigability was defined by Phan-Ba et al. (2012). Participants with relapsing-remitting or progressive MS and healthy controls performed a combination of walking tests: namely the Timed 100-meter walk test, the Timed 500-meter walk test, the Timed 25-foot walk test and a corrected version of the Timed 25-foot walk test (dynamic start) .

The ratio between the minimal (T400 500) and maximal (T25-FW corrected version) measurable walking speed was set as the deceleration index to objectively assess motor fatigability. Persons with MS with a low level of disability (EDSS ≤ 2.0, Maximum reported Walking Distance MrWD ≥ 4000 m or all FS scores ≤ 1) significantly decelerated during the 500 m walk task. In more disabled persons with MS with an EDSS-score of 2.5 – 3.5 and 4.0 – 6.0, a highly significant slowing down was consistently observed.

Previously, two older studies already tried to objectively measure this motor fatigability. 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. Tuner et al. (2008) made up a definition for volitional fatigue: “the point at which subjects could no longer maintain the present walking pace”. In this study, patients with IC had to perform a treadmill-walking test on a wide-bodied motorized treadmill. The protocol used was as follows: starting at a speed of 2 km/h at 0% gradient for 2 minutes, and then a speed of 3.2 km/h with an increase in gradient of 0.5% every 30 seconds.

Later, Valiani et al. (2016) also based their method for the assessment of walking-related motor fatigability on walking speed measured per lap time on adults aged between 70 – 90 years. Lap times were measured at the completion of each lap during a 400-m walk test at rapid pace on a 20-m course for 10 laps (40 m per lap).

Two studies used the distance walked by the participant to determine the formula for walking-related performance fatigability. In the study of Leone et al. (2015), PwMS had to perform a 6-minute walk test. The decline in distance walked from the first to all the other minutes of the 6MWT was expressed in a % and defined as the Distance Walked Index (DWI). A threshold of – 15% was chosen to categorize walking-related motor fatigability.

A similar method for assessing motor fatigability was provided in the study of McLoughlin et al. (2015). The authors implemented decline in total distance walked and the distance walked in each minute of the 6-minute walk test as variables to assess walking-induced fatigability in patients with MS and healthy controls.

Glynn et al. (2015), is the only other article that stated a clear criterion for high performance deterioration. If a participant’s Lap 9 time was at least 6,5% slower than Lap 2 time during the 400-meter long-distance corridor walk, the authors stated this participant as being fatigued. Participants in this study were older adults with a mean age range between 72 – 75 years.

In the study of Simonsick et al. (2014), participants performed a 20-m course walking task. Individual lap times were collected for ten 40-m laps during the 400-m walk. To determine performance deterioration, the authors used a few criteria:

2. Inability to complete the 400-m walk without stopping.
3. Marked slowing down (Lap 9 time at least 6,5 % slower than lap 2 time) over the ten laps.

If both walking speed and distance walked are implemented, the parameter for fatigability can be defined in a similar way. The difference is the minutes in which walking speed was measured.

The oldest study (Schwid et al. 1999), compared adult patients with MS to healthy controls during an 8- and 500- m walk. The authors stated walking-related motor fatigability as the ratio between distance walked and the time required by the individual.

A 10-minute walking assessment was applied on older adults. The following formula for performance fatigability was provided: speed over the full time walked divided by the speed in the first 2,5 minutes and this number divided by the total distance walked (Schnelle et al. 2012).

Although the participants (older women) in the study of Barbosa et al. (2016) performed a 6-minute walk test, the authors used the same formula to determine fatigability as Schnelle et al. (2012). The authors make a comparison of the 6th relative to the 1st minute.

In the study of Murphy et al. (2017) community-dwelling older adults with osteoarthritis also performed a 6MWT. Performance fatigability was calculated as the ratio between the mean speed over 6 minutes divided by the mean speed in the first 2 minutes, this divided by the total distance walked and multiplied by 1000.

4.3.2 Fatigability based on patients perspective (n = 3)

An acute level of fatigability was assessed in MS-patients and healthy controls immediately before and after the performance of a 6-minute walk test or a 6-minute rest period through. Participants indicated this feeling on a 100mm Visual Analogue Scale for Fatigue (VAS-F) (McLoughlin et al. 2014).

In the study of Richardson et al. (2015), community-dwelling older adults had to perform a 400-m overground walk. Fatigability was measured making use of different methods: the Situational Fatigue Scale (during an interview) and a Rating of Perceived Exertion at the end of the overground 400-m walk and after a standard (5 minutes, 0.72 m/s) and preferred speed (5 minutes) treadmill walking.

Simonsick et al. (2014) used 3 criteria to determine performance deterioration:

1. Inability to begin the 400-m walk after completing the first stage, which consisted of walking 2,5 minutes at usual pace.
2. Inability to complete the 400-m walk without stopping.
3. Marked slowing down (Lap 9 time at least 6,5% slower than Lap 2 time) over the ten laps.

The walking task here was performed over a 20-m course. Individual lap times were collected for ten 40-m laps during the 400-m walk.

4.3.4 Fatigability based on other methods (n = 8)

Instead of using walking speed and/or walking distance as the parameter to determine fatigue, a few studies (McLoughlin et al. 2012 & Morrison et al. 2016) decided to use the heart rate.

During the study of McLoughlin et al., community-dwelling persons with Multiple Sclerosis had to perform a modified version of the 6-minute walk test. Afterwards a cost index of walking was calculated with a formula as follows: the average heart rate (beats/min) during the 6-MWT – the average resting heart rate divided by the walking speed (m/min).

Morrison et al. also used heart rate as a parameter to define the physiological effort for walking on healthy individuals. Here, fatigue was elicited during three 5-minute trials on a treadmill by increasing the incline in increments of 2° every minute to a maximum of 8°. The maximal heart rate and the overall change in this parameter (maximal HR – baseline HR) determined physiological effort for walking.

In the article of Granacher et al. (2010), young and elderly community-dwelling participants walked for 5 – 8 strides on a pressure sensitive 10-m walkway before and after an isokinetic fatigability protocol. Bilateral fatigue was induced by performing repetitive isokinetic knee extension movements of the quadriceps. Each subject had to perform four maximal contractions. Before, immediately after and after 5 minutes of rest, fatigability was rated with a Borg scale ranging from 6 – 20.

At least, Sehle et al. related changes in gait parameters to fatigability. In their earlier study (2011), Multiple Sclerosis patients performed a physical exertion test on a treadmill. Both at the beginning of the test (t_1) and one minute after complete exhaustion (t_2) was reached, three dimensional marker data and video images were extracted. Changes in variability and mean gait changes formed the fatigue index: $\frac{1}{2}\ x\ \left(\frac{Nsignificant\ mean\ changes}{Ngait\ parameters} + \frac{Nsignificant\ SD\ changes}{Ngait\ parameters}\right)$.

Later (2014), the authors developed the Fatigue Index Kliniken Schmieder (FKS) which was applied on persons with Multiple Sclerosis and stroke patients. The method used to derive parameters for the FKS, is similar to the one described earlier. The Fatigue Index Kliniken Schmieder (δF) is the product of δM and δD. 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.

The Fatigue Index Kliniken Schmieder can clearly distinguish fatigued and non-fatigued persons, as a score > 4 indicated the presence of fatigabilty and a score ≤ 4 indicated no fatigability.

Also Qureshi et al. (2016) used gait parameters to assess walking-related motor fatigability during the 6-minute walk test on patients with Multiple Sclerosis. The authors used the following parameters to decide on fatigability: gait cycle length variance and walking speed for each minute. A clear criterion for high motor-related fatigability was stated, namely a slowing down and high variance in the last minute.

5 Discussion

5.1 Reflection on the quality of the included studies

The quality of the studies in this literature review was rated based on the “Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies” from the National Institutes of Health. Overall, all the included articles had a moderate to good quality, since non of the articles was excluded based on the total score on the questionnaire.

Although the answer on several questions (e.g. question 3, 6, 7, 10 and 12) seems negative on the first sight, this doesn’t mean the quality of this studies diminishes. These questions negotiated some important aspects for a cohort study such as exposure assessment prior to outcome measurement, sufficient timeframe to see an effect, repeated exposure assessment and blinding of outcome assessors. However since a lot of the included articles had a more observational cross-sectional design, these questions were answered negatively.

The most mentioned limitations in the included studies are a small sample size, inability to make a comparison with other articles because a different walking task or protocol for this task was used and the fact that nog enough account was taken into possible influencing factors (e.g. age, severity of disability, drugs used, …).

5.2 Reflection on the findings in relation to the research question

The research question investigated through this literature review was ‘How is motor fatigability objectively measured in walking?’. Although the included articles offered different ways to objectively measure walking-related performance fatigability, a consistent method is still lacking.

The lack for this consistency can be explained in different ways. Firstly, the study population varied among the included articles. Some studies made a comparison between healthy participants and patients with Multiple Sclerosis, others only investigated a method to assess fatigability on a specific population as Spinal Muscle Atrophy (Montes et al. 2010, 2013, 2016) or Intermittent Claudication (Tuner et al. 2008). At least, some articles only included older healthy subjects as study population.

Terminology for describing the phenomena of walking-related performance fatigability varied a lot across the included articles going from performance fatigability, performance deterioration, distance walked index, walking-induced fatigue, locomotor fatigue to ambulatory fatigue, volitional fatigue and muscle fatigue.

The way in which fatigability is defined also explains the many differences between the included articles. Barbosa et al. (2016) described the concept ‘fatigability’ as “how fatigued an individual gets in relation to defined activities”. This approach measures the change in fatigue level as a function of the change in intensity, duration or frequency of activity (Barbosa et al., Glynn et al. 2015).

Sehle et al. (2011) defined motor fatigue as “a reduction in maximal walking distance that cannot be explained by the degree of paresis, ataxia or spasticity”.

Fatigue can also be described as “a transient decrease in the ability to perform physical activities (performance component) and an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work (perceived component)” (Morrison et al. 2016).

Finally, several walking tasks were used to assess the concept of walking-related motor fatigability e.g. the 6-minute walk test, a 10-m walk or run, a 400-m long distance corridor walk, the Timed 25-foot Walk test at fast speed, the Timed 100- or 500-m walk test, a 10-minute walking assessment or walking on a treadmill.

Not only the walking task, but also the protocol that described the performance of the activity differed. Sometimes, the participant had to walk at his general pace, but in other studies a constant walking speed was maintained. All this variations can also explain inconsistencies among the included studies.

5.3 Reflection on the strengths and weaknesses of the literature study

Two persons, Dra. F. Van Geel and I, implemented the study selection process. In this way, the articles found with the search strategy applied in PubMed and Web Of Science were screened by two different persons. This screening was blinded, first each of us screened all the articles and afterwards the results were assembled. In case of disagreement, we discussed together regarding the inclusion or exclusion of an article.

Therefore, one of the strengths of this literature review is a higher interrater reliability, as two independent individuals screened the articles during the study selection process.

Another strength of the literature review conducted in this master thesis, is the broad searching strategy that was applied. In this way, all kind of study populations were included and a good general overview could be provided.

One of the weaknesses already mentioned in the study of Valiani et al. (2016) is that the investigation of the currently used methods to objectively assess performance fatigability, was limited to a walking task. As such, other physical activities such as climbing stairs, balance exercises or bicycling were not included although fatigability can also occur during these activities.

Furthermore, for some articles the full text was not available before the update on 27 April 2017. Since these articles could have provided interesting information, it is a major weakness we couldn’t include them.

5.4 Recommendations for further research

Lots of aspects should still be investigated in this rehabilitation domain, starting with uniformity in the terminology used. Furthermore, some methods provided in healthy individuals should be compared to patients with a neurological condition. Psychometry and a criterion to distinguish participants experiencing fatigability from participants who don’t experience fatigability are lacking.

6 Conclusion

Motor fatigability is currently measured using very different methods based on variable walking tasks, parameters to base fatigability on and various populations wherein this phenomena is investigated.

The methods provided can be a more objective way to assess walking-related motor fatigability instead of questionnaires based on self-report, but still there is no golden standard which quantifies this motor fatigability.

Normative data based on performance of healthy individuals and psychometric properties are lacking.

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8 Appendix

Table 1a - Overview search terms, combinations and number of hits in PubMed

	Key words PubMed	Hits January 2017	Hits April 2017
#1	Assessment	1074961	1086544
#2	Muscle Fatigue	17462	17617
#3	Motor Fatigue	5271	5318
#4	Motor Fatigability	270	279
#5	Fatigability	1865	1884
#6	Walking	75965	76733
#7	Gait	47204	47853
#8	#2 OR #3 OR #4 OR #5	211153	21342
#9	#6 OR #7	95670	96853
#10	#1 AND #8 AND #9	169	174

Table 1b - Overview search terms, combinations and number of hits in Web Of Science

	Key words Web Of Science	Hits January 2017	Hits April 2017
#1	Assessment	1217082	1237917
#2	Muscle Fatigue	19640	19889
#3	Motor Fatigue	5508	5627
#4	Motor Fatigability	284	287
#5	Fatigability	1602	1628
#6	Walking	146735	148994
#7	Gait	53061	54047
#8	#2 OR #3 OR #4 OR #5	22891	23221
#9	#6 OR #7	175996	178707
#10	#1 AND #8 AND #9	203	214

Table 2 – Overview excluded studies and reason for exclusion (n = 274)

Reason for exclusion	Number of studies excluded	Authors, year
Fatigability and/or walking or gait but ▪ *No link* between these	36	Balzini et al. 2003; Boer et al. 2014; De Vries et al. 2013; Dean et al. 1991; D'Hooghe et al. 2014; Dimeo et al. 2008; Elbers et al. 2013; Erdmann et al. 2010; Fontaine et al. 2011; Fried et al. 2001; Friedberg et al. 2009; Gandolfi et al. 2014; Han et al. 2014; Haseen et al. 2010; Iwamura et al. 2017; Izquierdo et al. 2008; Johansen et al. 1999; Kimata et al. 2000; Knols et al. 2011; Miyahara et al. 2000; Monteiro et al. 2013; Morey et al. 2003; Negahban et al. 2013; Nilsagard et al. 2006; Ruck et al. 2014; Strookappe et al. 2015; Tiffreau et al. 2016; Tiffreau et al. 2017; Van der Linden et al. 2007; Van Wely et al. 2014; Van Wilgen et al. 2009; Vantallie et al. 2003; Vanvugt et al. 1997; Vloothuis et al. 2016; Wallis et al. 2013; White et al. 2004
▪ *Secondary link*: no outcome measures[1] or secondary outcome measures[2]	6	Brunton et al. 2013[1]; Coote et al. 2009[2]; Drent et al. 2014[2] Eriksen et al. 2002[1]; Ghika et al. 1999[1]; Zhao et al. 2017[2]
▪ *Other link*: to e.g. spasticity[1], pain[2] balance[3], falling[4], …	8	Bryant et al. 2015[4]; Dashtipour et al. 2016[1]; Fernandez-Pablos et al. 2016[1]; Houdijk et al. 2010[3]; Maddali Bongi et al. 2011[2]; Mailhan et al. 2012; Simmonds et al. 2006[2]; Springer et al. 2009[3]
Frailty assumed as reason for fatigue, but fatigability was not investigated	14	Bollwein et al. 2013; Bollwein et al. 2013; Buchman et al. 2011; Da Camara et al. 2013; De Fanis et al. 2008; Heuberger et al. 2011; Nunes et al. 2015; Reijnierse et al. 2016; Romero-Ortuno et al. 2013; Tan et al. 2012; Theou et al. 2011; Widagdo et al. 2015; Wilson et al. 2006; Yeolekar et al. 2014
Full text not available	6	Elleuch et al. 2007; Jankowski et al. 1990; Kopciuch et al. 2016; Lisboa et al. 2001; Oka et al. 1993; Swedberg et al. 1993

No fatigability and/or walking or gait	109	Abdel-Malek et al. 2007; Abellan van Kan et al. 2010; Agre et al. 1995; Akin et al. 1997; Akyol et al. 2013; Alexanderson et al. 2014; Alguacil et al. 2012; Allanson et al. 2002; Arndt et al. 2003; Balzien et al. 2014; Barbeau et al.2007; Barbieri et al. 2015; Bautmans et al. 2011; Boccia et al. 2015; Bocker et al. 2012; Canning et al. 2012; Castelli et al. 2016; Cattaneo et al. 2014; Cederholm et al. 2015; Chen et al. 2016; Coleman et al. 2012; Colloca et al. 2015; Cortes et al. 2014; Cousin et al. 2011; Cremers et al. 2013; Dailey et al. 2016; Depaul et al. 2013; Draicchio et al. 2010; Dujmovic et al. 2016; Dunaway et al. 2014; Dutta et al. 1997; Dutta et al. 2012; Fairhall et al. 2008; Faught et al. 2013; Ferriolli et al. 2012; Forsberg et al. 2004; Frevel et al. 2015; Garcia-Garcia et al. 2011; Ghroubi et al. 2007; HajGhanbari et al. 2013; Hanuszkiewicz et al. 2014; Hewson et al. 2013; Hojan et al. 2016; Hooke et al. 2013; Horstman et al. 2010; Hur et al. 2013; Hyde et al. 2010; Ielpo et al. 2014; Ingle et al. 2007; Jensen et al. 2016; Jobbagy et al. 2008; Kalron et al. 2012; Kojovic et al. 2011; Laurin et al. 2009; Lee et al. 2015; Lima et al. 2015; Lindholm et al. 2015; Lingner et al. 2015; Marcellis et al. 2013; Mckeon et al. 2015; Mckercher et al. 2013; Miller et al. 2015; Morris et al. 2012; Mount et al. 2006; Murray et al. 2014; Neamtu et al. 2011; Newitt et al. 2016; Nisenzon et al. 2011; Nollet et al. 1999; Norberg et al. 2015; Ozalevli et al. 2011; Papuc et al. 2012; Paul et al. 2001; Paul et al. 2014; Peruzzi et al. 2015; Petry et al. 2016; Pettee Gabriel et al. 2009; Pilutti et al. 2015; Quist et al. 2012; Rajendran et al. 2016; Ries et al. 1995; Rochester et al. 2004; Rombaut et al. 2012; Roseguini et al. 2015; Sancho et al. 2015; Sandroff et al. 2013; Schenck et al. 2013; Schneiders et al. 2008; Schneiders et al. 2012; Schrack et al. 2010; Shahrbanian et al. 2015; Shipp et al. 2000; Simpson et al. 2015; Singh et al. 2011; Singh et al. 2014; Snyder et al. 2016; Stone et al. 2012; Straudi et al. 2013; Temel et al. 2009; Thelen et al. 2013; Thomas et al. 2013; Tomas et al. 2011; Tramonti et al. 2016; Tyson et al. 2008; Valkeinen et al. 2008; Vallance et al. 2008; Wang et al. 2015; Young et al. 2016; Zanini et al. 2015

Other aspects of fatigability and/or walking or gait ▪ Subjective or perceived fatigability	45	Alahmari et al. 2016; Basso et al. 2010; Ben-Zacharia et al. 2011; Bethoux et al. 2016; Carbonell-Baeza et al. 2013; Carter et al. 2003; Coleman et al. 2011; Collet et al. 2011; Costa et al. 2017; Dieruf et al. 2009; Elbers et al. 2009; Furlanetto et al. 2014; Goodman et al. 2007; Gracey et al. 2016; Guerra et al. 2014; Habers et al. 2016; Hubacher et al. 2012; Kammoun et al. 2015; Kelly et al. 2014; Kuehr et al. 2014; Lewko et al. 2014; Magnin et al. 2015; Malaguarnera et al. 2011; Manty et al. 2012; Manty et al. 2012; Marcellis et al. 2011; Marcellis et al. 2013; Marcellis et al. 2015; Meilleur et al. 2015; Miller et al. 2013; Motta et al. 2016; Muller et al. 2013; Murray et al. 2012; Newman et al. 2007; Provinciali et al. 1999; Rogeau et al. 2014; Romenets et al. 2015; Schwid et al. 2003; Simonsick et al. 2016; Stock et al. 1991; Straudi et al. 2014; Strookappe et al. 2016; Van den Berg et al. 2016; Tanaka et al. 2014; Wegrzynowska-Teodorczyk et al. 2016
▪ Other forms of fatigue e.g. sleepiness[1], mental fatigue[2], exhaustion[3], isokinetic fatigue[4], muscle fatigue[5], …	8	Gell et al. 2011[5]; Guler et al. 2016[4]; Hoglund et al. 2015[1]; Leunkeu et al. 2010[4]; Neyroud et al. 2017[4]; Stevenson et al. 2009[2]; Vancampfort et al. 2015[5]; Xue et al. 2008[3]
▪ Stair walking or running	3	Ameli et al. 2015; Brown et al. 2016; Hanon et al. 2005
Study design – Animal study	9	Beastrom et al. 2011; Butcher et al. 2007; Caron et al. 2014; Cockram et al. 2012; Cozzoli et al. 2013; Durmus et al. 2016; Nawrotek et al. 2017; Ramos et al. 2012; Takahashi et al. 2010
Study design – Case report	11	Benedetti et al. 2009; Chan et al. 2002; Del-Ama et al, 2012; Derubin et al. 1997; Eraso et al. 2012; Eyigor et al. 2010; Goulipian et al. 2008; Hanson et al. 2010; Mirlicourtois et al. 2009; Neamtu et al. 2014; Turhan et al. 2013
Study design – Review	13	Bethoux et al. 2011; Braam et al. 2013; Cavalheri et al. 2013; Clapp et al. 2012; Cooper et al. 2013; Del-Ama et al. 2012; Heine et al. 2015; Kieseier et al. 2012; Latimer-Cheung et al. 2013; Papa et al. 2015; Potvin et al. 1981; Quinlivan et al. 2004; Storer et al. 2012
Upper extremity	6	Balzarini et al. 2006; Chen et al. 2017; Murgia et al. 2010; Reuter et al. 2011; Troiano et al. 2008; Wang et al. 2015

Table 3 - Quality assessment included studies (n = 25)

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analysis in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were the key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Abbreviations: CD = Cannot Determine, NA = Not Applicable, NR = Not Reported

	Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies													
Article	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*
Barbosa et al. 2016	Yes	Yes	CD	Yes	NR	No	No	Yes	Yes	No	Yes	NR	Yes	Yes
Engelhard et al. 2016	Yes	Yes	CD	Yes	NR	No	No	Yes	Yes	No	Yes	NR	NR	Yes
Glynn et al. 2015	Yes	No	Yes	CD	NR	No	No	Yes	Yes	Yes	Yes	NR	No	Yes
Granacher et al. 2010	Yes	No	No	Yes	Yes	Yes	CD	NA	Yes	No	Yes	NR	Yes	Yes
Leone et al. 2015	Yes	Yes	Yes	Yes	No	NA	NA	Yes	Yes	No	Yes	NR	NR	Yes
McLoughlin et al. 2012	Yes	Yes	CD	Yes	Yes	NA	NA	CD	Yes	Yes	Yes	NR	NR	Yes
McLoughlin et al. 2014	Yes	No	CD	Yes	No	NA	NA	No	Yes	CD	Yes	NR	Yes	No
McLoughlin et al. 2015	Yes	Yes	CD	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes
Montes et al. 2010	Yes	Yes	CD	Yes	No	NA	NA	NA	Yes	No	Yes	NR	NR	Yes
Montes et al. 2013	Yes	No	CD	NR	NR	No	No	NA	Yes	No	Yes	NR	Yes	Yes
Montes et al. 2016	Yes	Yes	CD	NR	NR	No	No	NA	Yes	CD	Yes	NR	Yes	NR
Morrison et al. 2016	Yes	No	CD	Yes	NR	Yes	No	CD	Yes	No	Yes	NR	NR	Yes

Murphy et al. 2017	Yes	No	CD	Yes	NR	No	No	Yes	Yes	No	Yes	NR	Yes	NR
Phan-Ba et al. 2012	Yes	No	CD	Yes	NR	No	No	NA	Yes	Yes	Yes	NR	NR	NR
Qureshi et al. 2016	Yes	No	CD	No	No	No	NA	Yes	Yes	CD	Yes	NR	NR	CD
Richardson et al. 2015	Yes	Yes	CD	Yes	NR	No	No	Yes	Yes	No	Yes	NR	NR	NR
Schnelle et al. 2012	Yes	Yes	CD	Yes	NR	No	No	CD	Yes	No	Yes	NR	Yes	NR
Schwid et al. 1999	Yes	No	CD	Yes	NR	NA	NA	CD	Yes	Yes	Yes	No	NR	NR
Sehle et al. 2011	Yes	No	CD	No	NR	No	No	Yes	Yes	No	Yes	NR	NR	Yes
Sehle et al. 2014	Yes	Yes	CD	Yes	NR	No	No	Yes	Yes	No	Yes	Yes	CD	NR
Sehle et al. 2014	Yes	Yes	CD	Yes	NR	No	No	Yes	Yes	No	Yes	Yes	CD	NR
Simonsick et al. 2014	Yes	Yes	CD	Yes	NR	No	No	Yes	Yes	No	Yes	NR	CD	Yes
Surakka et al. 2004	Yes	Yes	CD	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes
Tuner et al. 2008	Yes	Yes	CD	Yes	Yes	No	No	NA	Yes	No	Yes	NR	Yes	NR
Valiani et al. 2016	Yes	No	CD	Yes	No	NA	NA	Yes	Yes	Yes	Yes	NR	Yes	Yes

Table 4 – Strengths and weaknesses included studies (n = 21)

Authors, year	Strengths	Weaknesses
Barbosa et al. 2016	▪ First study to investigate the relationship between perceived fatigability and energy requirements in a walking test in older adults. ▪ The findings may provide useful insight about how to manage experiences of fatigue in older adults.	▪ Small number of participants & recruitment by convenience → not possible to consider the representativeness of the results to the general population. ▪ Speed during the 6MWT was auto-selected, so it was not possible to observe the relationship between metabolic measures and perceived fatigability. ▪ Changes in speed over the 6 minutes can have a large effect on the results, mainly with regard to performance fatigability.
Glynn et al. 2015	▪ The PFS is a brief, simple tool designed to measure perceived fatigability in older adults that demonstrates high concurrent and convergent validity against measures of performance fatigability, mobility, physical function and fitness.	▪ The scale development sample came from older adult research registries, which may be prone to selection an response bias and thus may not be representative of the general older adult population. ▪ There was a lack of minority participation in the scale development sample, but the validation sample, which included more than 30% blacks, mitigated this. ▪ Twenty-seven % of returned 26-item scales had missing data, not surprising given the large quantity of items and the unknown cognitive status of those that participated through the mail in the scale development sample.
Granacher et al. 2010		▪ Older adults may have learned how to compensate for age-related and/or fatigue-induced muscle deficits during walking by increasing muscle power of synergistic muscle groups. ▪ A practice and/or learning effect may have occurred from pre to post testing.
Leone et al. 2015	▪ The index (DI) reported in previous work, is easy to calculate based on 2 walking distances. ▪ The DWI correlated highly with a proxy of the DI, supporting concurrent validity. ▪ The 15% threshold can be considered a valid criterion to identify walking-related motor fatigue because the patients	▪ There is no gold standard measure that quantifies motor fatigue during walking. ▪ Normative data based on performance of healthy reference persons and psychometric properties such as test-retest reliability of the DWI are lacking. ▪ Lack of familiarization to the 6MWT might affect pacing patterns.

	in this subgroup showed a continuous slowing down throughout the 6MWT. ▪ The proposed method individually identifies walking-related motor fatigue that shows face and concurrent validity. ▪ The DWI index has high clinical utility because it is easy to calculate by any clinician and can be applied during a single, standard, long walking capacity test.	▪ There is a lack of complete functional system scores of the EDSS, which hampered the evaluation of potential covariates of the DWI and, thereby, prevented the authors from gaining a better understanding of the underlying factors contributing to walking-related motor fatigue. ▪ Lacking of complete records of the type of symptomatic drugs used by the participants. Data were collected in different countries, with differences in pharmacological availability and reimbursement.
McLoughlin et al. 2014		▪ The administration of multiple tests may have allowed some recovery from fatigue.
McLoughlin et al. 2015	▪ The method (180° turns instead of 90° turns) was consistent throughout the study and did not result in a 'fatiguing walk'.	▪ Distances, fatigue and effort can not be compared with other studies, as the authors used a modified version of the 6MWT with a 10-m walkway and frequent 180° turns, instead of a more standardised 6MWT protocol with longer walking paths. ▪ The gait analysis was limited to the sagittal plane → movement compensations in other planes were not characterised in the present study. ▪ The results may only be inferred to people with moderate levels of disability, as the study did not include people with MS with more severe disability. ▪ The sample of healthy normal participants included for comparison purposes was small (n = 10) and therefore not an ideal control group for the larger sample of MS participants (n = 30).
Montes et al.2010	▪ The 6MWT is a validated measure of exercise capacity and motor function. This test has de ability to quantify functional endurance and is sensitive to change. ▪ The 6MWT may serve as a valuable tool to quantify fatigue in this population. ▪ The change in walking speed during the 6MWT should be investigated as a useful measure of fatigue in clinical trials.	▪ The walking speed assessed during the 10-m walk/run test does not capture deficits in endurance, as might be expected because it allows for running and may not be a good predictor of ability to function in the community. ▪ Caution is needed regarding the generalizability of the results. Larger studies are needed to confirm reliability and sensitivity of the 6MWT in this population.

Montes et al.2013	▪ Gait analysis yields useful measures of function not provided by standard clinical assessments.	
Montes et al.2016	▪ Instrumented footwear can be a valid alternative to laboratory equipment for assessing a basic set of spatiotemporal gait parameters in an unconstrained environment. ▪ Gait and fatigue can be well characterized using instrumented footwear. ▪ The validation suggests that linear corrections can effectively reduce systematic errors. ▪ The calibration method can be carried out online and does not depend on precise alignment between sensors and human limbs.	▪ The use of sensory feedback function, besides increasing the overall weight of the device, may not be useful for SMA patients. ▪ Validation of the SoleSound estimation of the ankle angle during gait, is lacking.
Murphy et al. 2017	▪ The study involved a larger sample than most current studies that have examined the validity of lab-based fatigability measures.	▪ The calculated values may not be directly comparable due to differences in the walking test used (6MWT vs. 400-m test) or for performance fatigability, when distance intervals were recorded. ▪ The characteristics (osteoarthritis and clinically relevant fatigue) limit generalizability of findings to other populations.
Phan-Ba et al. 2012	▪ All walking tests were performed in the "as fast as you can" configuration of the task in order to downsize motivational interferences, which are probably more prominent in a "preferred pace" modality. ▪ The results indicate that the DI measures the alteration of a sustained performance throughout a long demanding walking task.	▪ The higher age in the pMS population compared to healthy volunteers may have slightly influenced the observed differences since the mean WS probably decrease with age.
Richardson et al. 2015		▪ Cross-sectional study with a small sample size. ▪ Some nonsignificant trends in baseline characteristics between slow and fast walkers (e.g. BMI, number of medical conditipns) would likely be significant in a larger study. ▪ The standard speed used in this study, 0.72 m/s, was quite slow → a faster standard speed would have elicited

		differences in VO_2, given that the energetic cost of walking at preferred gait speed was elevated among slow walkers. ▪ Preferred overground and preferred treadmill speeds sometimes differ, which some, but not all have attributed to differences in gait kinematics and kinetics.
Schnelle et al. 2012	▪ The two fatigability severity measures were highly correlated and stable over two assessments, which suggest that these measures offer a concurrently valid and reproducible method for assessing the same, or highly related, constructs. ▪ Participants were asked directly about their change in tiredness or energy level because "change" represents the key element that differentiates fatigue and fatigability and, as such, this approach has face or content validity. ▪ The methodology described in this study is easy to implement and generates both a subjective and objective measure of fatigability severity.	▪ The absence of standardization on speed and distance walked created problems in calculating the change in speed variable necessary to estimate performance fatigability. ▪ The study is limited by the small number of participants, a 100% Caucasian sample, and the absence of an intervention to demonstrate the causal link between fatigability severity and PA. ▪ The performance measures described in this paper may not be able to measure aspects of fatigue related to psychological or behavioural issues.
Schwid et al. 1999	▪ Quantitative measures of strength and fatigue were highly reliable in this group of patients with MS. ▪ The reliability of static fatigue measures in MS patients and their ability to distinguish differences between MS patients and healthy control subjects indicates that this is a valid method for assessing pathological fatigue.	▪ The frequency of contractions (one per second) may have been too rapid, because some patients were not able to achieve maximal contractions at this pace. ▪ Variability during the ambulation task may have been caused by allowing patients to choose a "comfortable" pace for walking a prolonged distance. More detailed instructions might have ensured that patients would start at a more reproducible pace, perhaps improving the reproducibility of this test.
Sehle et al. 2011		▪ The FSMC is a self-administered questionnaire, and data obtained with the FSMC may be distorted by overestimation because of a deficient self-awareness or underestimation because of depression. ▪ While the study sample in this study was rather small, it is possible that in the general MS population the extent of gait changes with fatigue is associated with the severity of symptoms.

Sehle et al. 2014	▪ The FKS is a more sensitive and reliable measure for motor fatigue in patients with MS compared to traditional methods. ▪ The novel classification method can attribute changes in gait patterns to the presence or absence of fatigue. ▪ The FKS is an objective method for assessing motor fatigue on an individual basis using kinematic gait analysis. ▪ The classification of patients with MS into fatigue and non-fatigue groups was correctly.	▪ Only one neurologist performed the classical fatigue assessment. ▪ The applicability and validity of this method using the FKS in other groups of MS patients is unknown, particularly for those with a more severely compromised walking distance.
Sehle et al. 2014	▪ The FKS can also be used in stroke patients for objectively measuring motor fatigue. ▪ The FKS is an important tool for detecting motor fatigue objectively and independent of the presence or absence of depression. ▪ Through using the Physical Functioning Scale of the SF-36, rough comparison of motor impairment and disabilities in daily life was possible.	▪ Difficulties in assessing the changes in gait pattern, as all stroke patients had a hemiparesis and hence an abnormal gait pattern at both times. ▪ The analysis is subjective and depends on many factors and particularly on the therapist's experience.
Simonsick et al. 2014	▪ Both performance deterioration and perceived exertion demonstrated good concurrent validity in showing consistently strong associations with each fatigue symptom.	▪ The primarily limitation concerns use a treadmill which may render this specific approach impractical for some research centers and clinics. ▪ The study used a sample of generally motivated compliant individuals with no overt mobility limitations.
Surakka et al. 2004	▪ The reliability of the Fatigue Index used has been shown to be good (ICC 0.68 – 0.86).	▪ It can be speculated that six months was too long for a training period and that the progression of the disease may have hidden some positive training effects, especially in men. ▪ Subjects were chosen from MS patients who had sent their application to participate in an inpatient rehabilitation course. This is a potential source of bias. ▪ The subjects were no more than mildly or moderately disabled. Exercise intervention trials among severely affected patients are needed before generalizations concerning the entire MS population can be made. ▪ The male exercise should have been larger to ensure a better statistical power.

Tuner et al. 2008	▪ This study is the first to show that exercise testing using cycle ergometry incurred a significantly higher cardiovascular and metabolic response than treadmill walking and was better tolerated by subjects. ▪ The alternative objective performance outcome measures reflect whole-body performance rather than peripheral muscle limitation in isolation. ▪ Strict entry criteria were chosen to create a homogenous population in terms of symptoms and cardiopulmonary and metabolic responses without other disease that could confound the results and thus ensure a greater power to detect differences in cardiopulmonary responses.	▪ A select group of patients were studied; therefore, extrapolating these findings to a more generalized population with IC may not be possible. ▪ Patients with ischemic pain in different locations may not necessarily respond in the same manner to the different exercise modalities as those in the present study.
Valiani et al. 2016	▪ Extensive screening criteria were applied to older adults with ICF to rule out contributory disease conditions. ▪ A comprehensive evaluation of metabolic cost of walking and peak exercise performance measures.	▪ As the study has a cross-sectional design, it is impossible to reveal cause and effect. ▪ Because of the numerous tests conducted, the sample was relatively small and would need to be repeated in a larger study, preferably one that is longitudinal in nature. ▪ The results of this study are limited to walking; other activities may demonstrate different results (stair climbing or cycling).

Table 5 – Data extraction included studies (n = 25)

Table 5a – Fatigability based on walking speed, distance walked or both

Article	**Protocol**						**Motor disability (baseline m/s)**
	Walking task	*Fatigability*			*Population and/or pathology*	*Sample size (S) and age*	
		Parameter	Criterion	Technique			
Barbosa et al. 2016	6-minute walk test (6MWT)	Level of tiredness on numeric scale 1 – 7 Perceived fatigability $\frac{\text{Change in self-reported fatigue after 6MWT}}{\text{Distance walked in the 6MWT}}$ Performance fatigability $\frac{\text{Walking speed in the 6th minute}/\text{Walking speed in the 1st minute}}{\text{Total distance walked}}$		Stopwatch	Older women	S = 44 Mean age 75 years (SD 7.2 years)	Able to walk indepen-dently
Glynn et al. 2015	400-m long-distance corridor walk	Performance deterioration PD ▪ Ten 40-m lap segments for which split times were recorded	High PD when lap 9 time was at least 6.5% slower than lap 2 time	Stopwatch	Older adults	S = 1496 Mean age range 71.9 – 74.3 years (SD 6.4 – 8.2)	
Leone et al. 2015	Timed 25-foot Walk at Fast Speed (T25FW) 6-minute walk test (6MWT) MS Walking Scale- 12	Decline in distance walked from the 1st to all the other minutes of the 6MWT → % change in distance walked = Distance Walked Index DWI $\frac{\text{Distance walked in minute n} - \text{Distance walked at minute 1}}{\text{Distance walked at minute 1}}$ x 100 The lower the DWI and the DI values, the greater is the slowing down over a longer walking distance.	Threshold of – 15% was chosen to categorize walking-related motor fatigue	Handheld stopwatch	Multiple Sclerosis	S = 208 Mean age 47.9 years (SD 10.7 years)	Maximal EDSS score of 6.5 Mean walking speed during a 10-m walk > 0.3 m/s

McLoughlin et al. 2015	6-minute walk test (6MWT) OR 6-minute rest test	Fatigue levels before and after each 6-minute trial using the Visual Analogue Scale for Fatigue (VAS-F) Perceived exertion at each minute using the 10-point Modified Borg Rating of Perceived Exertion scale Decline in total distance walked and distance walked in each minute was seen as walking-induced fatigue		Gait analysis with an eight-camera Vicon MX3 system	Multiple Sclerosis (n = 34) and healthy controls (n = 10)	S = 44 No age-related information	Moderate disability = EDSS between 3 and 6
Montes et al. 2010	6-minute walk test (6MWT) 10-m walk or run	Distance walked each minute and time to complete each 25-m segment were recorded Comparison of the mean distance walked in the first and sixth minutes: $\frac{DW\ 1st\ minute}{DW\ 6th\ minute}$			Ambulatory patients with SMA type 3	S = 18 Mean age 15.3 years (SD 13.3 years)	Walk safely without assistance
Montes et al. 2013	6-minute walk test (6MWT)	Fatigue during 6MWT = % difference in the average velocity during the 1st and last passes over the gait mat			Ambulatory patients with Spinal Muscular Atrophy SMA	S = 7 Age range 10 – 48 years	
Montes et al. 2016	6-minute walk test (6MWT)	Fatigue = decrease in walking speed form the 1st to the last minute of the 6MWT			Spinal Muscular Atrophy SMA	S = 9 Age range 11 – 51 years Mean age 27.9 years (SD 17.1 years)	

Murphy et al. 2017	6-minute walk test (6MWT)	Perceived fatigability severity $\frac{\text{Change in fatigue (posttest} - \text{pretest)}}{\text{Distance walked}}$ x 1000 Perceived exertion fatigability $\frac{\text{Change in exertion (posttest} - \text{pretest)}}{\text{Distance walked}}$ x 1000 Performance fatigability $\frac{\text{Mean speed over 6 minutes/Mean speed over 2 minutes}}{\text{Total distance walked}}$ x 1000 Ecological fatigability = weekly sum of 'fatigable bouts' where mean physical activity for an activity 'bout' (between 2 fatigue ratings) ≥ 1 SD above a person's weekly mean activity AND fatigue severity increased from pre- to post-activity bout			Community-dwelling older adults with osteoarthritis	S = 163 Age range 65 – 90 years Mean age 71.9 years (SD 5.9 years)	
Phan-Ba et al. 2012	Timed 25-Foot Walk Test Corrected version T25FW with dynamic start Timed 100-Meter Walk Test Timed 500-Meter Walk Test	Mean walking speed MWS was calculated over the five successive 100 m interval laps in order to capture the motor fatigue related deceleration occurring over time during the T500MW → comparison between the MWS of the 1st 100 m and the MWS of the last 100 m. In order to quantify ambulation fatigability over a demanding distance of effort, we proposed to integrate the fastest and the lowest measurable walking speeds over the different tested walking paradigms. Deceleration Index DI → locomotor fatigue $\frac{\text{MWS of the T400} - \text{500MW}}{\text{MWS of the T25WF+}}$			Relapsing-remitting or progressive Multiple Sclerosis MS (n = 81) Healthy controls (n = 30)	S = 111 Mean age MS 40 years (SD 11.35 years) Mean age healthy controls 30 years (SD 10.4 years)	Maximum reported walking distance ≥ 500 m EDSS 4.5 – 6

Schnelle et al. 2012	10-minute walking assessment	Perceived fatigability severity $\frac{Perceived\ rating\ of\ change\ in\ tiredness}{Number\ of\ metres\ walked}$ Performance fatigability severity $\frac{Speed\ over\ the\ full\ time\ walked/Speed\ in\ the\ firts\ 2{,}5\ minutes}{Total\ distance\ walked}$			Older adults	S = 43 Age range 72 – 96 years Mean age 85.33 years (SD 5.9 years)	Able to walk without human assistance
Schwid et al. 1999	8-m walk 500-m walk	Ambulatory velocities: $\frac{Distance\ walked}{Time\ required}$			Adult patients with Multiple Sclerosis PwMs Healthy controls HC	S = 40 Mean age PwMS 47.9 years (SD 7.4 years) Mean age HC 46.8 years (SD 6.9 years)	EDSS 1.5 – 6.5
Surakka et al. 2004	500-m walking test	Ambulatory Fatigue Index AFI $\frac{Velocity\ during\ the\ final\ 50\!-\!m\ lap}{Velocity\ during\ the\ initial\ 50\!-\!m\ lap}$			Multiple Sclerosis MS	S = 99 Age range 30 – 54 years (SD 6 – 7 years)	EDSS 1 – 5.5
Tuner et al. 2008	Two incremental exercise tests on a treadmill & a cycle ergometer	Volitional fatigue = the point at which subjects could no longer maintain the present walking pace			Men with stable Intermittent Claudication IC	S = 10 Mean age 52 years (SD 6 years)	

Valiani et al. 2016	400-m walk test at rapid pace	Fatigued group: score 35 or less on FACIT-F Non-fatigued group: score of 42 or more on FACIT-F Performance-related fatigue: lap times measured at the completion of each ▪ Walking speed per lap time ▪ Rating of Perceived exertion per lap time			Healthy adults	S = 45 Fatigued group: mean age 73.16 years (SD 5.06 years) Non-fatigued group: mean age 70.8 years (SD 4.87 years)	

Table 5b – Fatigability based on patients perspective

Article	**Protocol**						**Motor disability (baseline m/s)**
	Walking task	*Fatigability*			*Population and/or pathology*	*Sample size (S) and age*	
		Parameter	Criterion	Technique			
McLoughlin et al. 2014	6-minute walk test (6MWT) OR 6-minute rest test	Acute level of fatigue immediately before and after the 6MWT or rest periods through indicating this on a 100mm Visual Analogue Scale for Fatigue (VAS-F)	Significant condition by time interaction (p<0.01)		Moderate Multiple Sclerosis PwMS Age and sex-matched healthy controls HC	S = 34 PwMS + 10 HC Mean age PwMS 49.1 years (SD 10.4 years) Mean age HC 45.1 (SD 14 years)	Median EDSS score of 3.5 Range EDSS 3 – 6 Perceived fatigue with MFIS
Richardson et al. 2015	400-m overground walk	Global perceived fatigue = 4 questions from Physical Energy Scale from the Motivation and Energy Inventory Fatigability ▪ Situational Fatigue Scale SFS ▪ RPE at the end of the 400 m ▪ Standard & preferred speed treadmill		Individual item score of the SFS: 5 = extreme fatigue	Community-dwelling older adults	S = 38 Age range 70 – 89 years Mean age78.4 years (SD 5 years)	Able to walk without assistance of a device or another person
Simonsick et al. 2014	Long Distance Corridor Walk 400-m walk	Performance deterioration ▪ Unable to begin the 400m walk after completing the first stage ▪ Unable to complete 400 without stopping ▪ Marked slowing over the ten laps	Marked slowing = increase in lap time between the 2nd and 9th laps of at least 6,5%		Older adults participating in the Baltimore Longitudinal Study of Aging	S = 1058 Age range 65 – 97 years (SD 7 – 8 years)	

	Slow paced 5-minute walk	Rating of Perceived Exertion immediately after the slow paced 5-minute walk using the Borg RPE scale ranging from 6 – 20	High fatigability = RPE ≥ 10				

Table 5c – Fatigability based on other methods

Article	**Protocol**						**Motor disability (baseline m/s)**
	Walking task	*Fatigability*			*Population and/or pathology*	*Sample size (S) and age*	
		Parameter	Criterion	Technique			
Engelhard et al. 2016	6-minute walk test (6MWT)	Distance Time Warping ▪ Template cycles = gait cycles from the 1st & 2nd minutes of the 6MWT ▪ Test cycles = cycles from subsequent minutes ▪ Warping length = difference in length between input cycles & DTW-aligned counterparts ▪ Distance Score = DTW distances from each minute ▪ Warp Score = warping lengths from each minute Modified Fatigue Impact Scale		ActiGraph GT3X accelerometer on one hip	Multiple Sclerosis MS (n = 86) Healthy controls (n = 29)	S = 115 Age range MS 19 – 61 years Age range healthy controls 19 – 54 years	Ambulatory Median EDSS 2.5 SD 0 – 7
Granacher et al. 2010	Walking for 5 – 8 strides on a pressure sensitive 10-m walkway before & after an isokinetic fatigue protocol	Muscle fatigue with an isokinetic fatigue protocol: bilateral fatigue induced by performing repetitive isokinetic knee extension movements of the quadriceps; each subject performed 4 maximal contractions Rate of perceived exertion on a 6 to 20 Borg Scale Walking before fatigue protocol, immediately after the fatigue protocol and after 5 minutes of rest			Young & elderly community-dwelling participants	S = 32 Mean age young participants 24.3 years (SD 1.4 years) Mean age elderly participants 71.9 years (SD 5.5 years)	

McLoughlin et al. 2012	Modified 6-minute walk test (6MWT) → maximise effort & induce fatigue	10-point Modified Borg Rating of Perceived Exertion (RPE) each minute ▪ Distance walked ▪ Perceived exertion Visual Analogue Scale (VAS) for Fatigue before and after 6MWT as indication of perceived fatigue levels Cost Index of Walking $\frac{Average\ 6MWTHR - Average\ restingHR}{Walk\ speed}$			Community-dwelling persons with Multiple Sclerosis	S = 40	Mild to moderate difficulty in mobility with an EDSS score of 3 – 6 Able to walk for 6 minutes unaided if with the aid of a walking stick
Morrison et al. 2016	Three 5-minute trials on a treadmill Fatigue during walking was elicited by increasing the treadmill incline in increments of 2° every minute to a maximum of 8°	Heart rate → physiological effort for walking = maximal HR and overall change in HR (Maximum HR – baseline HR) Rating of Perceived Exertion (RPE) with a modified Borg 10-point scale at beginning & end of each fatigue walking task			Healthy individuals	S = 75 Age range 30 – 79 years	

Qureshi et al. 2016	6-minute walk test (6MWT)	Gait cycle length variance and speed for each minute	High motor-related fatigue = slowing down and high variance in the last minute	Technology-Enabled Medical Precision Observation TEMPO 3.1 Body Sensor Networks BSNs	Multiple Sclerosis	S = 28 18 – 65 years	FSS 0 – 3 MFIS 0 – 66 MSWS 12 – 60
Sehle et al. 2011	Physical exertion test on a treadmill	Fatigue Index $\frac{1}{2}\ x\left(\frac{Nsignificant\ mean\ changes}{Ngait\ parameters}+\frac{Nsignificant\ SD\ changes}{Ngait\ parameters}\right)$ ▪ $N_{significant\ mean\ changes}$ = number of parameters with a significant mean change from t_1 to t_2 ▪ $N_{significant\ SD\ changes}$ = number of parameters with a significant SD change from t_1 to t_2 ▪ $N_{gait\ parameters}$ = number of gait parameters		Wireless AS200 system	Multiple Sclerosis	S = 14 Mean age 42 years (SD 7.6 years)	EDSS range 1 – 5.5
Sehle et al. 2014	Walking test on a treadmill until complete exhaustion or for a maximum of 60 minutes	Fatigue index Kliniken Schmieder FKS δF = δM x δD ▪ δF = product of δM and δD that represents an index of the change ▪ δM = measure of the difference between two attractors quantifying the differences between two movement patterns	FKS ≤ 4 = no fatigue FKS > 4 = fatigue		Multiple Sclerosis MS (n = 40) Healthy subjects (n = 20)	S=60 Age range 18 – 65 years (SD 7 – 8.6 years)	Able to walk on a treadmill without aids or assistance

		▪ δD = difference between the two associated deviations of the state vector away from the attractor representing the change in movement variation					Mean EDSS 3.4 (SD 1.3)
Sehle et al. 2014	Walking test on a treadmill until complete exhaustion or for a maximum of 60 minutes	Fatigue index Kliniken Schmieder FKS δF = δM x δD *(see above: Sehle et al. 2014)*	FKS ≤ 4 = no fatigue FKS > 4 = fatigue		Stroke patients (n = 10) Multiple Sclerosis MS (n = 40) Healthy subjects (n = 20)	S=70 Mean age MS 45 years (SD 7 years) Mean age stroke 51 years (SD 8.3 years) Mean age healthy subjects 43 years (SD 8.6 years)	Reduced walking capacity Able to walk on a treadmill without aids or assistance

Part two: Research protocol

1 Introduction

The focus in this paper is on fatigue: one of the most common symptoms in Multiple Sclerosis, which nearly half of the patients describe as their most disabling feature (Ben-Zacharia et al. 2011). Multiple Sclerosis is an autoimmune disorder characterized by inflammation and destruction of mostly the white matter of the Central Nervous System myelin. The damage to the central nervous system leads to a wide range of different physical and cognitive (mental processes) symptoms.

Not only fatigue, but also difficulty walking is often rated as the most challenging aspect of living with Multiple Sclerosis (McLoughlin et al. 2016). From the beginning of the disease, decreased walking capacity and physical activity levels are present (Motl et al. 2005; Dlugonski et al. 2013 & Gijbels et al. 2010). During their disease, almost 80% of all the PwMS experience walking difficulties (Ben-Zacharia et al. 2011). Consequently, patients have a reduced quality of life (McLoughlin et al. 2016).

Also in older adults perceived fatigability is a common complaint. Older adults may reduce their level of being physically active aiming to keep their feelings of fatigability in an acceptable range. Therefore, misleading conclusions could be made if the focus exclusively would be on fatigability, without the understanding of the activity context in which this fatigability occurs (Barbosa et al. 2016).

The concept ‘fatigability’ describes how fatigued an individual gets in relation to defined activities (Barbosa et al. 2016). This approach measures the change in fatigue level as a function of the change in intensity, duration or frequency of activity (Barbosa et al., Glynn et al. 2015).

A distinction is made between performance and perceived fatigability. Perceived fatigability reflects the self-reported change in tiredness, where the performance part refers to the objective change or decline during a performance: physic e.g. decreased walking speed or cognitive (Barbosa et al. 2016; Schnelle et al. 2012).

As a new concept, the assessment of fatigability is still not uniform (Barbosa et al. 2016). Therefore, the research question in this paper was: ‘How is motor fatigability objectively measured in walking on persons with neurological conditions?’. As the literature is scarce for neurological diseases, the focus in the literature study was extended to healthy people and all types of disorders.

Although the articles from the literature review offered different ways to objectively measure walking-related performance fatigability, a consistent method is still lacking due to differences in study population, terminology and definition of fatigability or variance in the walking task (e.g. speed, distance, protocol).

A golden standard for quantifying walking-related performance fatigability is lacking, but several good methods to assess this phenomena were provided based on different parameters such as walking speed, distance walked or both and heart rate or gait analysis characteristics.

Glynn et al. (2015), Leone et al. (2016), Simonsick et al. (2014), Qureshi et al. (2016) and Sehle et al. (2014) are a few studies out of the literature review which already provided a clear criterion to set the point from which an individual is objectively seen as fatigued.

Non of the studies in the literature review investigated psychometric properties of the method they used to assess walking-related performance fatigability.

Therefore, the aim of this research protocol was to investigate a few of the currently used methods which are based on both walking speed & total distance walked and on the other hand of the rating of perceived exertion. We will investigate these different perspectives (objective & subjective) in one walking task e.g. the 6-minute walk test.

A comparison will be made between more disabling persons with Multiple Sclerosis (PDDS-score > 3) and healthy individuals. Also some other variables e.g. age, gender, walking performance in daily life and severity of the disease will be investigated to see if there exists any correlation to walking-related performance fatigability.

At least, the experimental set-up which will take place in the next academic year (2017 – 2018), aims to find a criterion to objectively distinguish fatigued from non-fatigued individuals. Furthermore, the goal is to investigate test-retest reliability and sensitivity of the assessment that will be used to measure walking-related performance fatigability.

2 Aim of the study

This master thesis aims to investigate different aspects in the assessment of walking-related performance fatigability.

Firstly the focus will be on the comparison between healthy individuals and persons with Multiple Sclerosis. Also the objectively and subjectively assessment of walking-related performance fatigability (walking speed and total distance walked ↔ rate of perceived exertion) will be compared.

Secondly, the study aims to find a criterion on which walking-related performance fatigability can be set (e.g. a cut-off value that objectively distinguishes fatigued and non-fatigued individuals).

A third aim of this thesis would be to compare the objectively stated cut-off point with the subjective experience of the individual being fatigued. It is possible that a participant who indicates being abnormally fatigued, shows more a decrease in perceived fatigability during the walking task.

Not only walking speed and distance walked are parameters that could determine fatigability. Therefore, the study will investigate other important variables such as age, gender, type of Multiple Sclerosis (e.g. relapse-remitting, primary or secondary progressive), score on PDDS-scale, aerobic capacity, cognitive function and activity level in daily life, … which could have an impact on walking-related performance fatigability and state the clinical profile that eventually correlates with fatigability.

Finally, this study aims to examine the psychometric properties (test-retest reliability and validity) of the assessment method that will be used to objectively measure walking-related performance fatigability.

2.1 Research questions

As this master thesis has different aims related to the assessment of walking-related performance fatigability, a few research questions can be set up.

1) *Is the method used to objectively measure walking-related performance fatigability a good, reliable and valid way to assess this phenomenon?*
    - The method to assess fatigability is based on walking speed and total distance walked. The mean walking speed will be measured every minute of the walking assessment which will be the 6-minute walk test.
    - The assessment of fatigue will be repeated twice within 5 consecutive days. As such, between-day reliability of these assessments can be investigated.
    - Content validity or sensitivity will be investigated through the comparison of the objective and subjective outcome measures during walking relative to the self-assessment of the participant.

2) *Can there be set any similarity in the objective and subjective cut-off value when an individual states fatigability?*
   - The objective walking-based cut-off value still has to be obtained during the investigation.
   - For the subjective fatigue cut-off value the study will use a Rating of Perceived Exertion with the Borg Scale. High fatigability is seen as a score ≥ 10 (Simonsick et al. 2014).

3) *What is the influence of other parameters on this walking-related performance fatigability? Is there a significant impact of these variables?*
   These parameters are: age, gender, type of MS (e.g. relapse-remitting, primary or secondary progressive), PDDS-score, aerobic capacity expressed as VO_2max, heart rate (beats per minute) information processing speed (SDMT) and activity level & walking performance in daily life.
      - **Activity level:** not just related to walking but the general performance of all activities e.g. sports, hobbies, housekeeping, … measured through the IPAQ (Bethoux et al. 2011)
      - **Walking performance:** number of steps (walking) performed during the day assessed through pedometry/accelerometry.

4) *What is the difference between healthy individuals and persons with Multiple Sclerosis? This difference can be in all the assessed parameters such as walking speed, total distance walked, activity level in daily life, …*

2.2 Hypotheses

Based on the different aims and research questions mentioned above, a few hypotheses can be formulated.

First of all, a clear distinction can be made in walking-related performance fatigability between healthy individuals and patients with Multiple Sclerosis. During their disease, almost 80% of all the PwMS experience walking difficulties (Ben-Zacharia et al. 2011). For this reason, patients with MS will reach much sooner the moment of walking-related performance fatigability, in comparison to healthy individuals which may not even experience this during walking for 6 minutes.

A similar difference can be seen in the comparison of younger and older adults. Since older adults may reduce their level of being physically active aiming to keep their feelings of fatigability in an acceptable range (Barbosa et al. 2016), these participants will slow down earlier during the 6MWT. This would mean that walking-related performance fatigability would appear earlier to older than to younger adults. To investigate this, we will first investigate the research protocol in PwMS and afterwards, the research protocol will be applied in age and sex matched healthy controls.

Thirdly, there will be a difference in walking-related performance fatigability based on the activity level of participants and their walking performance in daily life. Participants which have a more active lifestyle and/or walk more during the day, won’t experience soon the feeling of being fatigued.

On the other hand, participants with a more sedentary lifestyle or patients with MS which are restricted in walking activities, will show more quickly walking-related performance fatigability during the 6MWT.

At least, PDDS-score also has an influence during the 6-minute walk test. Patients with Multiple Sclerosis with no to moderate disability which correspondents to an PDDS-score ranging from 0 – 2 won't reach soon the point of walking-related performance fatigability in comparison with MS-patients which have an PDDS-score ranging from 3 – 6 or have a more severe disability.

3 Methods

3.1 Research design

To investigate the research questions and hypotheses discussed above, an experimental longitudinal study design will be applied. All participants will be divided into two groups: a group consisting of healthy individuals and a group consisting of persons with Multiple Sclerosis.

Figure 1 provides an overview of the study design.

In total, the participants will come for 3 days to REVAL Rehabilitation Research Center at Diepenbeek (baseline assessment at the first day and two times a 6MWT spread over the other two days).

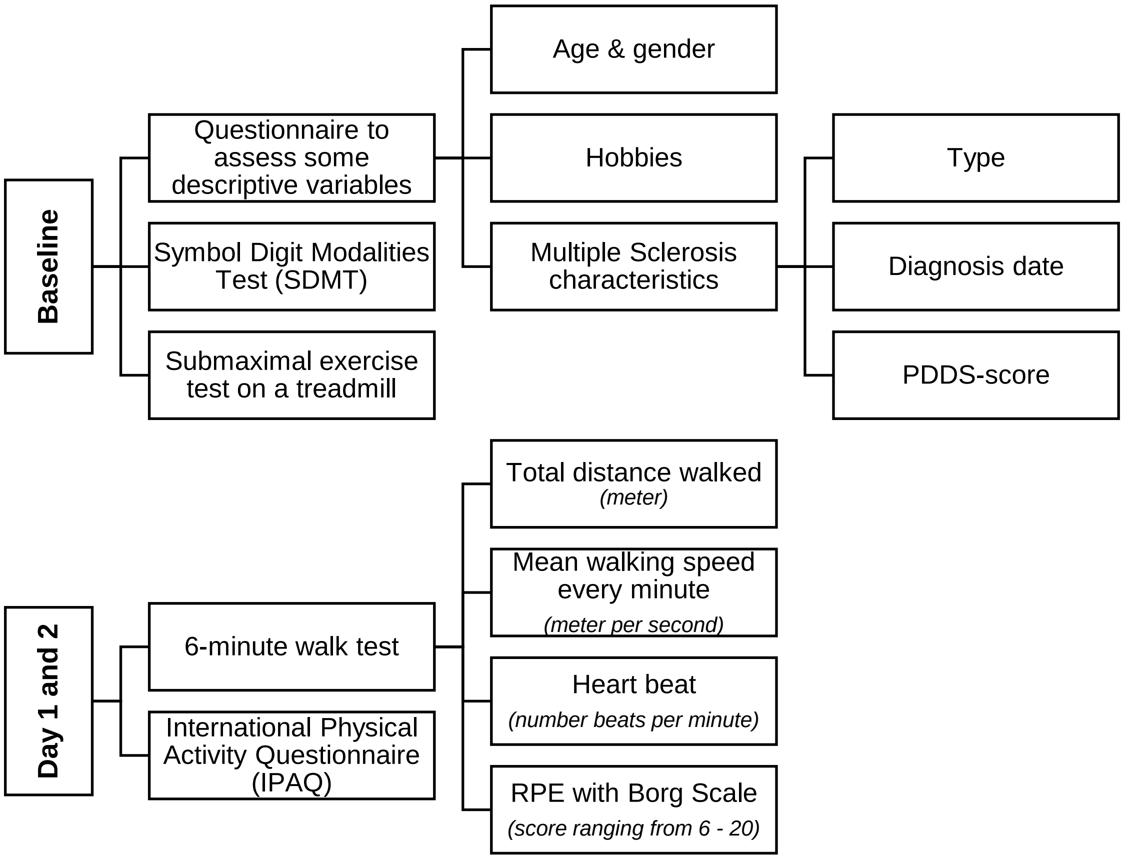

Figure 1 – Overview of the study design

At baseline, all participants will perform a submaximal exercise test to determine their basic aerobic capacity expressed as VO_2max. Through a short self-made questionnaire, a few descriptive variables will be assessed such as age, gender, activity level in daily life, PDDS-score and type of MS. These last two variables are only provided in the questionnaire for participants with Multiple Sclerosis. At least, all participants will receive a accelerometer to assess the basic walking performance in daily life.

In the following days, the participants will perform the 6-minute walk test at pre-set test moments to measure walking-related performance fatigue. During this task, the other parameters will be assessed: heart beats per minute, total distance walked, mean walking speed every minute and RPE with the Borg Scale. Every test-moment, the International Physical Activity Questionnaire (IPAQ) is questioned, to determine how many physical activities the participant performed during the past month. Information obtained through accelerometry, will be analysed at the end of the study.

On the basis of these parameters, two formulas can be used to calculate walking-related performance fatigability in an objective and subjective way:

$$\boldsymbol{Objective} = \frac{Mean\ walking\ speed\ minute\ n1\ /Mean\ walking\ speed\ minute\ n2}{Total\ distance\ walked}\ x\ 1000$$

$$\boldsymbol{Subjective} = \frac{Change\ in\ exertion: posttest - pretest}{Total\ distance\ walked}\ x\ 1000$$

3.2 Participants

3.2.1 Inclusion criteria

Since all participants will be split up into two groups, there are different inclusion criteria for both groups. Although the general inclusion criteria will be similar for all participants:

- Age between 18 – 70 years
- Willing to wear the accelerometer for 5 consecutive days
- Able to walk independently or with a walking aid if necessary for 6 minutes
- Good cognitive function (measured through the Symbol Digit Modalities Test)
- Have signed the informed consent documents

MS-patients must have a confirmed diagnosis of Multiple Sclerosis and have an Patient Determined Disease Steps (PDDS) score of 3.0 – 6.0 indicative of moderate disability.

3.2.2 Exclusion criteria

The healthy subjects participating in this study, are excluded if they have any neurological, cardiac, respiratory, metabolic, orthopedic or other medical condition that could influence their performance on the different parameters assessed.

Patients with MS will be excluded if they had an exacerbation or relapse within the last 3 months before the study starts; use medication prescribed for fatigue or mobility such as Amantadine, Modafinil or Fampridine; suffer from severe depression; have significant cardiac or respiratory disease or have arthritis, fibromyalgia, pain or other illness that severely limits their walking (based on McLoughlin et al. 2016).

3.2.3 Patient recruitment

MS-patients will be recruited from different centers: REVAL Rehabilitation Research Center, Hasselt; Rehabilitation and the MS Center Overpelt, Overpelt.

Through social media and on different locations, healthy participants will be recruited. This can be nearby the test locations, through family, friends and other contacts. Healthy controls will be age and gender matched for the MS-subjects.

3.3 Medical ethics

We will send a request to the Committee for Medical Ethics (CME) at the University of Hasselt and to the Rehabilitation and MS-Centre in Overpelt.

3.4 Experimental design and procedure

First, all participants fill in the questionnaire added in the appendix (document 1), to obtain some general information about age, gender, activity level in daily life, PDDS-score and type of MS.

At baseline all participants will perform a submaximal exercise test on a treadmill, to determine their aerobic capacity expressed as VO_2max. The performance of this test will take place in REVAL, Diepenbeek. We will use the Bruce protocol, where participants will walk 1.7 mph pace at 10% grade for the first 3 minutes. During the next 3 minutes grade will be increased by 2% and speed to 2.5 mph. Afterwards, the grade will be increased with 2% and the speed by either 0.8 or 0.9 mph until the patient is exhausted.

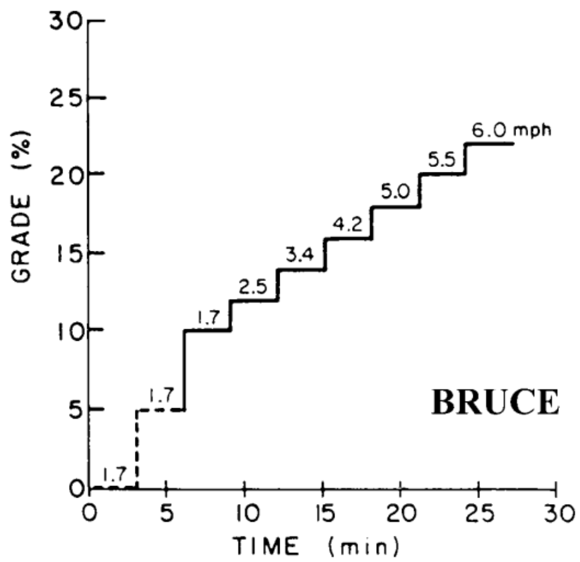

Figure 2 – Bruce protocol

At the end of the baseline assessment, all participants will receive an accelerometer (a SenseWear mini® armband; see Figure 3), to investigate their overall basic walking performance during the upcoming month (based on Krüger et al. 2017). Each test-moment, participants will be questioned about their overall physical activity level during that month using the Dutch-translated version of the International Physical Activity Questionnaire (see appendix – document 2).

Figure 3 – SenseWear mini® armband

The next day (test day 1) and a week later (test day 2) participants will perform the 6MWT, according to the protocol of Goldman et al. (2008) provided in the appendices. Subjects can use their assistive device and walk back and forth in a 30-m walkway, turning around cones at each end of the hall (Leone et al. 2016). During the test, the parameters which will be registered are: heart beats per minute, total distance walked, mean walking speed every minute and Rating of Perceived Exertion.

Heart beats per minute will be administered using a heart rate monitor. Rating of Perceived Exertion will be assessed during the six-minute walk test using the Borg RPE scale ranging from 6 – 20, where a score ≥ 10 indicates high fatigability (Simonsick et al. 2014; see document 4 in appendix). Total distance walked can be calculated with a hand counter (see figure 4).

Figure 4 – Hand counter

3.5 Outcome measures

3.5.1 Primary outcome measures

The main outcome measure in this study is the walking-related performance fatigability, which uses the mean walking speed each minute and total distance walked. The mean walking speed of each minute will be analysed relative to the mean walking speed at another minute. This outcome will then be divided by the total distance walked and multiplied by 100 to express walking-related performance fatigability as a percentage of slowing down during walking. A schematic representation of the formula that will be calculated for each participant is provided below:

$$\frac{Mean\ walking\ speed\ minute\ n1\ /Mean\ walking\ speed\ minute\ n2}{Total\ distance\ walked}\ x\ 1000$$

Since the study aims to compare this objectively measured walking-related performance fatigability with the subjective feeling of being fatigued, the other primary outcome measure is the point where the participant denotes a score ≥ 10 on the Borg Rating scale of Perceived Exertion. For this, the formula provided below (Murphy et al. 2017) will be calculated for each participant:

$$\frac{Change\ in\ exertion: posttest - pretest}{Total\ distance\ walked}\ x\ 1000$$

As a second form of assessing subjective walking-related performance fatigability, we will ask the participants if he or she thinks that he or she shows motor fatigability. Since there is no literature available on how this question should be asked, we will use the question: ‘Do you have the feeling that you showed motor fatigability during and after the 6MWT?’.

3.5.2 Secondary outcome measures

The secondary outcome measures that will be analysed in this study:

- Age in years
- Gender (men / women)
- MS-related characteristics
    - Type: relapse-remitting, primary or secondary progressive
    - PDDS-score ranging from 3.0 – 6.0
    - Diagnosis date: confirmed diagnosis of MS since … date
- Aerobic capacity expressed as VO_2max
- Heart beats per minute during 6MWT
- Activity level assessed through IPAQ
- Walking performance in daily life determined with accelerometry and expressed in the daily number of steps

3.6 Data-analysis

Firstly, we will investigate if the participants in each group (healthy controls and PwMS) are comparable. This can be checked by using:

- Test of normality (Goodness-of-fit): Shapiro-Wilk (N<100)
- Test to check if the variances are equal (homoscedasticity): O'Brien, Brown-Forsythe, Levene or Bartlett

A multiple Analysis Of Variance (ANOVA) will be investigated to compare the performance of the walking test between healthy individuals and patients with Multiple Sclerosis.

To compare the objectively and subjectively measured fatigability, a t-test one sample or not-parametric equivalent can be used.

For the investigation of the eventually influencing parameters on walking-related performance fatigability, a general linear model can be used: multiple linear regression. Here, fatigability will be the response (Y) variable and age, gender, type MS, PDDS-score, activity level and walking performance in daily life will be the predictor (X) variables.

To investigate the test-retest reliability of the assessment of walking-related performance fatigability, we will use an Intra-Class Correlation Coefficient. A two way random model will be used to calculate this coefficient. An ICC score of 0.75 or higher will indicate good test-retest reliability.

4 Time planning

At first, data-collection of baseline characteristics and assessment of walking-related performance fatigability during the 6MWT will be undertaken in patients with Multiple Sclerosis. This will take place during the first three months of the next academic year (September 2017 – December 2017).

Afterwards, during January 2018 – February 2018, data-collection of the baseline characteristics and the assessment of walking-related performance fatigability during the six-minute walk test will be performed in age and sex matched healthy individuals.

In the resting months of the academic year (March 2018 – June 2018), data will be extracted and processed. The plan afterwards is to write the manuscript about conclusions that can be made based on the experimental study.

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6 Appendices

Document 1 – Questionnaire to assess some descriptive variables

Algemene vragenlijst bij het onderzoek naar motorische vermoeibaarheid tijdens het wandelen

Leeftijd: ______

Geslacht:

☐ Man
☐ Vrouw

Hobby's: ____

Type Multiple Sclerose:

☐ Relapse-remitting
☐ Primary progressive
☐ Secondary progressive

Diagnose Multiple Sclerosis sinds ______

Score op de Patient Determined Disease Steps (PDDS-score):

☐ **0** = Ik heb mogelijkst enkele milde symptomen (meestal sensorisch van aard) die veroorzaakt worden door Multiple Sclerose. Deze symptomen beperken mijn activiteiten niet. Als ik een aanval krijg, keer ik terug naar normaal wanneer deze aanval voorbij is.

☐ **1** = Ik heb enkele opvallende symptomen van Multiple Sclerose, maar ze zijn ondergeschikt en hebben slechts een klein effect op mijn levensstijl.

☐ **2** = Ik heb geen enkele beperkingen in mijn wandelcapaciteit. Echter, ik heb wel significante problemen veroorzaakt door Multiple Sclerose die mijn dagelijkse activiteiten op andere manieren beperken.

☐ **3** = Multiple Sclerose bemoeilijkt mijn activiteiten, vooral het wandelen. Ik kan een volledige dag werken, maar activiteiten die fysieke inspanning vereisen zijn moeilijker dan dat ze zouden moeten zijn. Ik heb meestal geen kruk of ander hulpmiddel nodig om te wandelen, maar ik zou wel ondersteuning kunnen gebruiken wanneer ik een aanval krijg.

☐ **4** = Ik gebruik de hele of een deel van de tijd een wandelstok of één kruk of iets anders waarop ik kan steunen (bv. de muur of aan de arm) om te wandelen, vooral wanneer ik buiten wandel. Ik denk dat ik 7.62 meter kan wandelen in 20 seconden zonder het gebruik van een wandelstok of kruk. Ik heb altijd enige ondersteuning (wandelstok of kruk) nodig wanneer ik 3 blokken wil wandelen.

☐ **5** = Om 7.62 meter te wandelen, heb ik een wandelstok, kruk of steun van een person nodig. Ik kan rondwandelen binnenshuis of in andere gebouwen door de meubels vast te houden of de muren aan te raken ter ondersteuning. Ik gebruik mogelijks een scooter of rolstoel voor langere afstanden.

☐ **6** = Om 7.62 meter te wandelen heb ik 2 krukken / wandelstokken of een rollator nodig. Ik gebruik mogelijks een scooter of rolstoel voor langere afstanden.

Document 2 – Dutch version of the International Physical Activity Questionnaire

Internationale vragenlijst in verband met fysieke activiteiten

Wij willen onderzoeken welke lichaamsbeweging mensen doen in hun dagelijkse leven. Deze enquête maakt deel uit van een onderzoek dat in een groot aantal landen over de hele wereld wordt uitgevoerd. Aan de hand van uw antwoorden kunnen we ons actief-zijn vergelijken met dat in andere landen.

De vragen gaan over de fysieke activiteit die u in de laatste zeven dagen gedaan hebt. Er zitten vragen bij over de lichaamsbeweging op uw werk over uw verplaatsingsvermogen, over uw werk in huis en in de tuin, en over uw vrije tijd in verband met ontspanning, lichaamsbeweging en sport.

Uw antwoorden zijn belangrijk. Probeer op alle vragen te antwoorden, zelfs als u vindt dat u niet erg actief bent.

Dank voor uw medewerking

Een toelichting bij het beantwoorden van de volgende vragen:

- ZWARE fysieke activiteiten verwijzen naar activiteiten die een zware lichamelijke inspanning vereisen en waarbij u veel sneller en dieper ademt dan normaal.
- MATIGE fysieke activiteiten verwijzen naar activiteiten die een matige lichamelijke inspanning vereisen en waarbij u iets sneller en dieper ademt dan normaal.

Deel 1: Fysieke activiteiten tijdens uw werk

Deel 1 gaat over uw werk. Onder werk verstaan we: betaald werk, werk op de boerderij, vrijwilligerswerk, studiewerk en ander onbetaald werk dat u buitenshuis verricht heeft. Thuiswerk zoals huishoudelijk werk, tuinieren, klusjes en gezinstaken horen hier niet bij. Dat komt aan bod in deel 3.

1a Hebt u momenteel een baan of doet u onbetaald werk buitenshuis?

☐ Ja
☐ Nee → *(Ga naar Deel 2: Vervoer)*

De volgende vragen handelen over alle fysieke activiteiten die u gedaan heeft in de laatste zeven dagen als deel van uw betaald of onbetaald werk. De verplaatsing van en naar het werk hoort hier **niet** bij. Het gaat hier *alleen* om de fysieke activiteiten die u **gedurende minstens 10 minuten aan één stuk** gedaan heeft.

1b Op hoeveel dagen, in de laatste zeven dagen, heeft u **zware** fysieke activiteiten gedaan zoals zwaar tilwerk, spitten, bouwwerken of trappen oplopen *als deel van uw werk?*

________ dagen per week

☐ Geen → *(Ga naar vraag 1d)*

1c Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **zware** fysieke activiteiten *als deel van uw werk?*

____ uur ___ minuten /dag

1d Op hoeveel dagen, in de laatste zeven dagen, heeft u **matige** fysieke activiteiten gedaan zoals het dragen van lichte lasten *als deel van uw werk?*

________ dagen per week

☐ Geen → *(Ga naar vraag 1f)*

1e Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **matige** fysieke activiteiten *als deel van uw werk?*

____ uur ___ minuten /dag

1f Op hoeveel dagen, in de laatste zeven dagen, heeft u **gewandeld** gedurende minstens 10 minuten aan één stuk *als deel van uw werk*
Opgelet, de verplaatsing te voet van en naar het werk hoort hier **niet** bij !

________ dagen per week

☐ Geen → *(Ga naar Deel 2: Vervoer)*

1g Hoeveel tijd in totaal heeft u op zo'n dag **gewandeld** *als deel van uw werk?*

____ uur ___ minuten /dag

1h Indien u **gewandeld** heeft *als deel van uw werk*, in welk tempo was dat dan meestal?
Heeft u gewandeld u in:

☐ een **hoog** tempo?
☐ een **middelmatig** tempo?
☐ een **laag** tempo?

<u>Deel 2: Fysieke activiteiten die verband houden met vervoer</u>

Nu volgen enkele vragen over hoe u zich verplaatst heeft naar het werk, om boodschappen te doen, naar de film te gaan enzovoort.

2a Op hoeveel dagen, in de laatste zeven dagen, heeft u zich verplaatst met een motorvoertuig zoals de trein, de bus, de wagen of de tram?

________ dagen per week

 Geen → *(Ga naar vraag 2c)*

2b Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan verplaatsingen *met de wagen, de bus, de trein of een ander motorvoertuig?*

____ uur ___ minuten / dag

Denk nu **alleen** aan het *fietsen en het wandelen* dat u gedaan heeft om naar het werk te gaan, te winkelen of gewoon om ergens heen te gaan.

2c Op hoeveel dagen, in de laatste zeven dagen, heeft u **gefietst** gedurende minstens 10 minuten aan één stuk *om ergens heen te gaan?*

________ dagen per week.

 Geen → *(Ga naar vraag 2f)*

2d Hoeveel tijd in totaal heeft u op zo'n dag **gefietst** *om ergens heen te gaan*?

____ uur ___ minuten /dag

2e Als u *zich verplaatst heeft per **fiets**,* in welk tempo was dat dan meestal ?
Heeft u gefietst in:

 een **hoog** tempo
 een **middelmatig** tempo of
 een **laag** tempo

2f. Op hoeveel dagen, in de laatste zeven dagen, heeft u **gewandeld** gedurende minstens 10 minuten aan één stuk *om ergens heen te gaan?*

________ dagen per week

 Geen → *(Ga naar Deel 3: Huishoudelijk Werk, Klusjes en Gezinstaken)*

2g Hoeveel tijd in totaal heeft u op zo'n dag **gewandeld** *om ergens heen te gaan?*

____ uur ___ minuten /dag

2h Als u **gewandeld** heeft *om ergens heen te gaan,* in welk tempo was dat dan meestal?
Heeft u gewandeld in:

 een **hoog** tempo
 een **middelmatig** tempo of
 een **laag** tempo

Deel 3. Huishoudelijk werk, klusjes en gezinstaken

Dit deel gaat over de fysieke activiteiten die u in de laatste zeven dagen gedaan heeft *in en rond het huis,* bijvoorbeeld huishoudelijk werk, tuinieren, onderhoudswerk of voor het gezin zorgen. Nogmaals, denk *alleen* aan die fysieke activiteiten die u **gedurende minstens 10 minuten aan één stuk** verricht heeft.

3a Op hoeveel dagen, in de laatste zeven dagen, heeft u **zware** fysieke activiteiten gedaan zoals zwaar tilwerk, houthakken, sneeuwruimen of spitten **in de tuin of moestuin**?

________ dagen per week

☐ Geen → *(Ga naar vraag 3c)*

3b Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **zware** fysieke activiteiten *in de tuin of moestuin?*

____ uur ___ minuten /dag

3c Op hoeveel dagen, in de laatste zeven dagen, heeft u **matige** fysieke activiteiten gedaan zoals lichte lasten dragen, ruiten wassen, vegen of harken **in de tuin of moestuin**?

________ dagen per week

☐ Geen → *(Ga naar vraag 3e)*

3d Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **matige** fysieke activiteiten *in de tuin of moestuin?*

____ uur ___ minuten /dag

3e Op hoeveel dagen, in de laatste zeven dagen, heeft u **matige** fysieke activiteiten gedaan zoals lichte lasten dragen, ruiten wassen, vloeren schrobben of vegen **binnenshuis**?

________ dagen per week

☐ Geen → *(Ga naar Deel 4: Fysieke Activiteiten die verband houden met Sport, Ontspanning en Vrije Tijd)*

3f Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **matige** fysieke activiteiten *binnenshuis?*

____ uur ___ minuten /dag

Deel 4: Fysieke activiteiten die verband houden met sport, ontspanning en vrije tijd

Dit deel gaat over alle fysieke activiteiten die u de laatste zeven dagen gedaan heeft, maar dan uitsluitend als recreatie, sport, training of vrijetijdsbesteding. Nogmaals, denk *alleen* aan die fysieke activiteiten die u **gedurende minstens 10 minuten aan één stuk** verricht heeft. Gelieve **geen** activiteiten mee te rekenen die u reeds vermeld hebt.

4a Zonder het wandelen dat u reeds vermeld hebt, op hoeveel dagen, in de laatste zeven dagen, heeft u ge**wandeld** gedurende minstens 10 minuten aan één stuk *in uw vrije tijd?*

________ dagen per week

☐ Geen → *(Ga naar vraag 4d)*

4b Hoeveel tijd in totaal heeft u op zo'n dag **gewandeld** *in uw vrije tijd?*

____ uur ___ minuten /dag

4c Als u **gewandeld heeft** *in uw vrije tijd*, in welk tempo was dat dan meestal?
Heeft u gewandeld in:

☐ een **hoog** tempo
☐ een **middelmatig** tempo of
☐ een **laag** tempo

4d Op hoeveel dagen, in de laatste zeven dagen, heeft u **zware** fysieke activiteiten gedaan zoals bijvoorbeeld aerobics, lopen, snel fietsen, snel zwemmen of andere intense activiteiten, *in uw vrije tijd?*

________ dagen per week

☐ → Geen *(Ga naar vraag 4f)*

4e Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **zware** fysieke activiteiten *in uw vrije tijd?*

____ uur ___ minuten /dag

4f Op hoeveel dagen, in de laatste zeven dagen, heeft u **matige** fysieke activiteiten gedaan zoals bijvoorbeeld fietsen aan een middelmatig tempo, zwemmen aan een middelmatig tempo, tennis dubbelspel of andere activiteiten aan een matige intensiteit, *in uw vrije tijd?*

________ dagen per week

☐ Geen → *(Ga naar Deel 5: De tijd die u zittend doorbrengt)*

4g Hoeveel tijd in totaal heeft u op zo'n dag besteedt aan **matige** fysieke activiteiten *in uw vrije tijd?*

____ uur ___ minuten /dag

Deel 5: De tijd die u zittend doorbrengt

De laatste vragen gaan over de tijd die u de laatste zeven dagen zittend doorbracht op het werk, thuis, tijdens studiewerk of in uw vrije tijd. Hierbij hoort ook de tijd dat u achter een bureau zat, bezoek kreeg, zat te lezen, of naar televisie zat of lag te kijken.
De tijd die u zittend doorbracht in een motorvoertuig, die u reeds vermeld hebt, komt hier **niet** in aanmerking.

5a Hoeveel tijd heeft u gemiddeld *gezeten* op een **weekdag,** in de laatste zeven dagen?

____ uur ___ minuten /dag

5b Hoeveel tijd heeft u gemiddeld *gezeten* op een **weekenddag**, in de laatste zeven dagen?

____ uur ___ minuten /dag

Document 3 – Protocol 6-minute walk test (Goldmann et al. 2008)

“The object of this test is to walk as far as possible and as fast as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You should pivot briskly at this line (or around this cone) at each end of the hallway and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.” Demonstrate by walking one lap yourself. Walk and pivot at the line (or around the cone) briskly.

“Are you ready to do that? I am going to use this stop watch and clip board to keep track of the time and number of laps you complete. I will notify you of your time at 2 minutes and every minute after that. Remember that the object is to walk AS FAR AS and AS FAST AS POSSIBLE for 6 minutes, but don’t run or jog. Start now, or whenever you are ready.”

When the timer shows 4 minutes remaining, tell the patient the following: “Two minutes have passed. You have 4 minutes to go.”

When the timer shows 3 minutes remaining, tell the patient the following: “Three minutes have passed. You have three minutes to go.”

When the timer shows 2 minutes remaining, tell the patient the following: “Four minutes have passed. You have two minutes to go.”

When the timer shows only 1 minute remaining, tell the patient: “Five minutes have passed. You only have one minute left.”

Do not use other words of encouragement (or body language to speed up). If the patient stops walking during the test, say this: “You are doing well. You should keep walking if you are able.” Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely. When the timer is 15 seconds from completion, say this: “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.”

When the timer rings (or buzzes), say this: “Stop!” Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

Document 4 – Borg Rating scale of Perceived Exertion

6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
19/10/16	• ondertekenen contract • korte inleiding onderwerp	Promotor: Copromotor: Student(e): Student(e):
4/11/16	• brainstorm onderwerp • toelichting eerste stappen lit. search	Promotor: Copromotor: Student(e): Student(e):
5/12/16	• bespreken zoekstrategie • suggesties "	Promotor: Copromotor: Student(e): Student(e):
16/12/16	• overlopen zoekstrategie • toelichting volgende stappen MP	Promotor: Copromotor: Student(e): Student(e):
16/03/17	• overlopen screening T & A	Promotor: Copromotor: Student(e): Student(e):
15/05	• bespreken eerste draft • ideeën onderzoeksprotocol	Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
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Datum: **12/06/2017**