



Review

Digital Biomarkers in the Assessment of Mobility in Individuals with Multiple Sclerosis

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Abstract: The aim of this study was to investigate signal patterns and parameters of digital biomarkers in the assessment of mobility in individuals with multiple sclerosis, captured through motion sensors. This is an integrative literature review based on the PRISMA recommendations, which included studies that used wearable technology, such as accelerometers, wearable sensors or inertial sensors, and analyzed mobility/gait-related parameters, such as speed, step count, rhythm, balance, duration and intensity of activity. A total of 1602 studies were identified, of which only 21 were included in the final qualitative synthesis. The main digital biomarkers identified presented signal patterns and parameters captured through different wearable devices, including triaxial accelerometers, inertial sensors, smartphones or smartwatches. The studies employed different objective biomarker reference measures, such as walking speed and step count, and subjective biomarker reference measures, such as fatigue and quality of life assessment scales, for a comprehensive assessment of the participants' health and mobility. It was found that digital biomarkers play a fundamental role in any individual's health assessment and protocols. However, it is essential to understand these signals and standardize the choice of the best method to capture signals of high quantity and quality, especially for individuals affected by some neurological pathology.

Keywords: multiple sclerosis; mobility limitation; digital biomarkers



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1. Introduction

Multiple sclerosis is a chronic neurological disease that affects the central nervous system, presenting a variety of symptoms, including fatigue, mobility problems, cognitive behavior and sensory disturbances, which significantly reduce the quality of life of individuals affected by this condition [1]. Its etiology is complex and poorly understood, leading to theories and factors being investigated, such as genetic predisposition, environmental factors, abnormal immune response, chronic inflammation and a dysfunctional blood–brain barrier [2].

The global prevalence of multiple sclerosis has increased over the years, with around 2.8 million people affected worldwide, according to the World Health Organization in 2023 [3], representing a significant increase from the estimate of 2.2 million in 2016 [4]. In Brazil, approximately 40,000 individuals face this disease, with a higher incidence among those aged between 20 and 40, predominantly affecting females [1]. Statistics indicate that women account for at least twice as many cases (69%) as men [5].

One of the most pressing challenges faced by people with multiple sclerosis is reduced mobility, which has a significant impact on their independence and the execution of daily activities [6]. Approximately 85% to 90% of individuals with this disease face the inability to walk safely and independently, resulting in significant cases with needs of assistive devices such as canes, walkers or wheelchairs as the disease progresses [7]. This is due to difficulty in walking, fatigue, weakness, spasticity and the lack of coordination, all of which are common in this population and significantly impairs the performance of daily tasks by these people [6].

The assessment of mobility in people with multiple sclerosis provides valuable information for health professionals, allowing them to monitor the progression of the disease and to develop strategies for delaying it [8]. Motor rehabilitation exercises, which help to reduce spasticity, pain and fatigue, are essential in the functional recovery of motor disabilities in these individuals, allowing residual capacities to be strengthened and favoring activities of daily living [9].

In this context, wearable technologies, such as smartphones, smartwatches, accelerometers, pedometers and gyroscopes, comprise motion sensors that have been widely used to assess physical activity, walking, gait, balance and postural control in people with multiple sclerosis [10]. These devices have the ability to monitor and capture data in an individualized way at a higher resolution in different environments, including in clinical tests, those carried out in the laboratory, and in free living conditions when the individual is carrying out daily activities, capturing step count, turning and walking speed, and risk of falls, as well as other mobility-related variables [11].

Among different motion sensors currently available in the market, accelerometers have been instrumental in providing objective data on free-living mobility in different groups of the people. Accelerometers are technologies designed to detect and quantify changes in the speed or direction of movement of an object/individual or system [12]. Digital biomarkers, on the other hand, are objective indicators or measures designed to intervene in a particular area, such as physiological, pathological or pharmacological processes [13]. These digital biomarkers can be built from data from various sensors, not just accelerometers, and can involve more complex analysis and algorithms to extract useful information about a person's health, such as the analysis of an individual's gait [13].

Thus, digital biomarkers are able to identify signals and provide valuable information about health, including the progression of mobility limitations in multiple sclerosis, an immune-mediated and chronic inflammatory disease. Digital biomarkers may be valuable for significantly aiding, treating, delaying or helping stopping the disease progression and, consequently, enabling a better quality of life for this population. Therefore, the aim of this study was to investigate the signal patterns and parameters of digital biomarkers in the assessment of mobility in individuals with multiple sclerosis.

2. Materials and Methods

This study is an integrative literature review, based on the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [14]. This research approach was chosen because it allows for a comprehensive and integrated view of the knowledge available on a given subject through other existing research methodologies [15].

2.1. Eligibility Criteria

We included studies that addressed the use of digital biomarkers in the assessment of mobility in individuals with multiple sclerosis and that were written in English, Portuguese or Spanish. The choice to include studies in these three languages was based on considerations of the relevance and accessibility of the research sources, due to their wide dissemination in international scientific literature and their accessibility for the researchers involved in this study. In addition, articles published in the last 10 years were selected to ensure that the evidence incorporated into this review is contemporary and reflects the most recent approaches in the field of mobility assessment in individuals with multiple sclerosis, and that they were published in peer-reviewed scientific journals. Literature reviews, theses, dissertations, letters to the editor and course completion papers were excluded.

2.2. Search Strategy

The search strategy was developed around the following guiding question: "What signal patterns and parameters are used as objective and subjective biomarkers in the assessment of mobility in individuals with multiple sclerosis?". The databases selected were

Embase, PubMed and BVS, and search terms related to the guiding question, validated descriptors in Health Sciences (DeCS/MeSH) were used and combined using Boolean operators: (Multiple Sclerosis OR Disseminated Sclerosis OR Chronic Progressive Multiple Sclerosis) AND (Digital Biomarkers OR Biomarker OR Biological Biomarkers) AND (Mobility Limitation OR Walking Difficulty OR Occupational Mobility). During the searches, it was necessary to add terms that were not validated in the Health Sciences in order to better retrieve the studies for the purpose of this review, such as (Accelerometer OR Accelerometer OR accelerometer). The searches took place during the month of August 2023.

2.3. Article Selection Process

The Rayyan web application was used in the process of selecting and excluding articles and identifying duplicates. The search, selection and screening process were carried out independently by two researchers (RSDQ) and (JHA), and a third author (JES) participated in cases where there were disagreements. The other selected studies, although not directly included in the main discussion, were used to complement the arguments and clarifications presented in this review. For the outcomes analyzed, the following data were extracted from the articles: authors and year of publication, title, objectives, sample, digital biomarkers used and results. We used the mean number of individuals with multiple sclerosis, age and biomarkers reported in the articles to characterize the sample.

3. Results

A total of 1602 studies were identified from the databases (Pubmed, 1284; Embase, 182; VHL, 136), from which 6 articles were subtracted because they were duplicates, leaving 1596 articles to be screened. After screening, 1543 articles were excluded by reading the title and abstract, leaving 53 studies eligible for full reading. After this stage, 32 studies were excluded because they did not meet the inclusion and exclusion criteria, and 21 studies were included in the final qualitative synthesis. The selection process is described in the PRISMA flow diagram (Figure 1).

3.1. Characteristics of the Studies

A total of 1256 individuals with multiple sclerosis were evaluated. The mean age \pm standard deviation by information provided of the participants with multiple sclerosis was 50.6 ± 10.5 years. All the studies used wearable technology, such as accelerometers, body-worn sensors or inertial sensors, and mentioned the collection of objective data on gait parameters, such as speed, step count, pace, balance, the duration of physical activity and exercise intensity. In addition, the studies used clinical tests and questionnaires, which are often used in studies to assess gait and mobility in this population, in order to correlate data from wearable sensors with the information from objective and subjective biomarker reference methods. Table 1 shows the articles included in the integrative review.

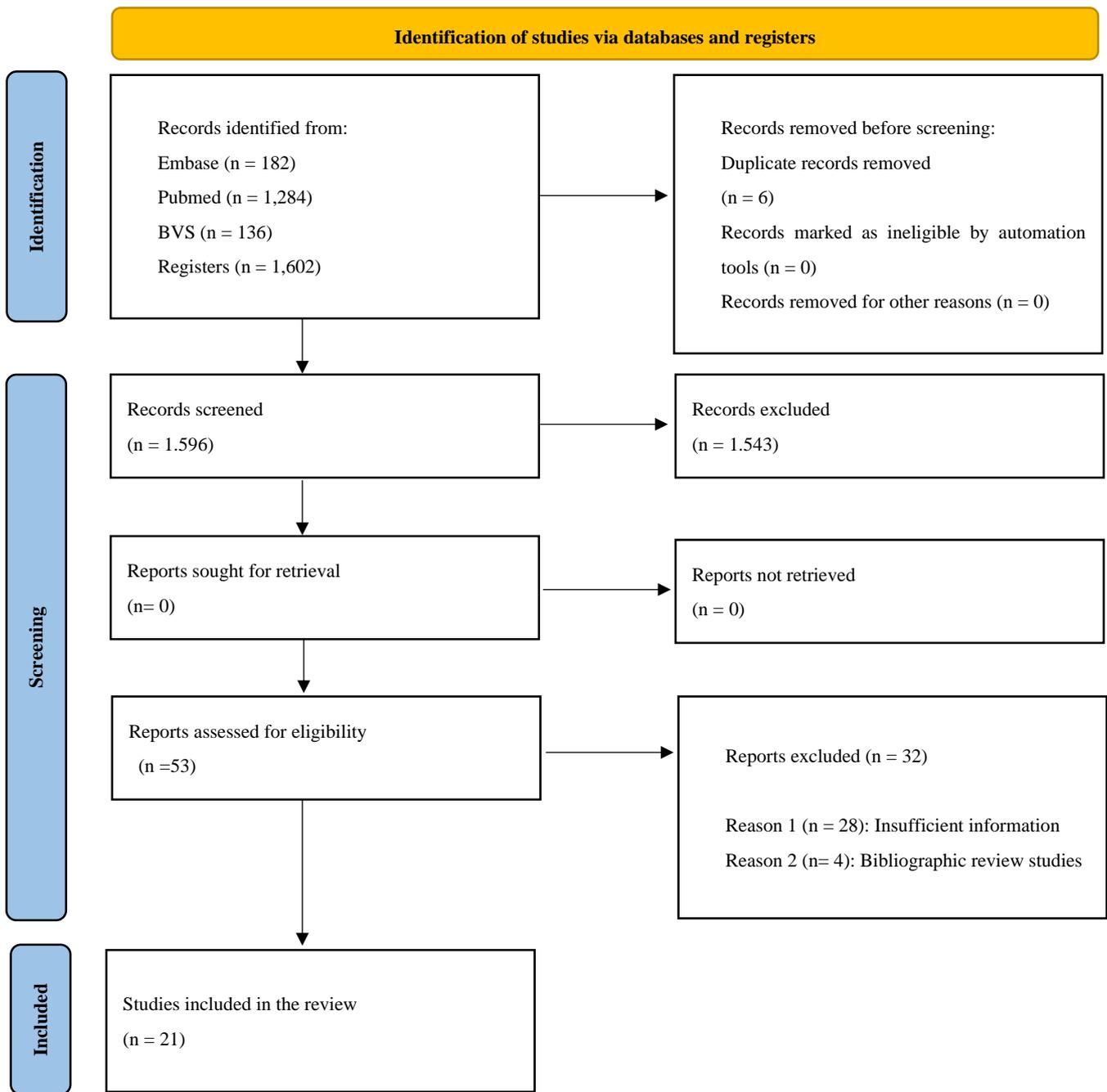


Figure 1. PRISMA flow diagram.

Table 1. Information extracted from the articles that make up the integrative review.

Title	Objectives	Sample	Digital Biomarkers	Results
Chest-Based Wearables and Individualized Distributions for Assessing Postural Sway in Persons with Multiple Sclerosis [16]	To validate postural sway measurements from a chest accelerometer.	16 people (4 M, 12 F, mean \pm standard deviation age 50.6 ± 10.5 years) with multiple sclerosis.	Wearable accelerometer on the chest and sacrum using BioStamp nPoint [®] sensors (Medidata) to capture movement patterns and postural sway, and frequency and intensity of falls, fatigue, rhythm and balance.	Chest sway measurements can differentiate between standing and falling tasks and are significantly related to patient-reported measures of balance confidence, fatigue and walking difficulty.
Assessing real-world gait with digital technology? Validation, insights and recommendations from the Mobilise-D consortium [17]	To evaluate digital mobility in six cohorts via gait data for gait sequencing.	60 participants, distributed in different groups. 20 were healthy elderly, 20 had Parkinson's disease and another 20 had multiple sclerosis.	McRoberts Dynaport MM+ wearable device (100 Hz sampling frequency; triaxial acceleration range: ± 8 g, resolution: 1 mg; triaxial gyroscope range: ± 2000 degrees per second (dps), resolution: 70 mdps), attached to the back and used in tests, such as the 6 Minute Walk, to capture movement patterns, gait index, cadence (count of steps per minute), rhythm and balance.	The choice of algorithm for estimating gait sequence detection and cadence should be cohort-specific (e.g., slow walkers and those with gait impairments). The short walking distance and slow walking speed worsened the performance of the algorithms.
Evaluation of unsupervised 30-s chair stand test performance assessed by wearable sensors to predict fall status in multiple sclerosis [18]	To evaluate the unsupervised 30-Second Chair Stand Test (30CST) in multiple sclerosis via accelerometer and compare it with the supervised 30CST.	37 people with multiple sclerosis.	MC10 BioStamp triaxial accelerometer (250 Hz, ± 16 G) recorded from ten inertial sensors (MC10, Inc., Lexington, MA, USA) adhered to the skin and smartphone with MC10 Link App to capture the sit-to-stand and stand-to-sit transition time, with the aim of detecting the risk of falls and standing time.	Individuals with a history of falls (Group F) ($n = 21$) and those with no history of falls (Group NF) ($n = 16$) showed statistically significant differences in age and 30CST performance ($p = 0.013$, $d = 0.88$).
The Sit-to-Stand Transition as a Biomarker for Impairment: Comparison of Instrumented 30-Second Chair Stand Test and Daily Life Transitions in multiple sclerosis [19]	To compare measurements from wearable sensors and the supervised/unsupervised 30-Second Chair Stand Test (30CST) to understand fall risk, sensory and pyramidal impairment.	37 people with multiple sclerosis.	Two inertial sensors (MC10, Inc., Lexington, MA, USA), one on the right thigh and one on the chest, which recorded data from the MC10 BioStamp triaxial accelerometer (250 Hz sampling rate, ± 16 G) and smartphone with MC10 Link App sensors to capture sit-stand and stand-sit transition time to detect falls risk and standing time.	Best fall risk discrimination: Chest acceleration of the supervised 30CST (Area under the curve (AUC) = 0.89)). Chest indicated sensory impairment, but different task in daily life. Discrimination of pyramidal impairment: chest acceleration in the supervised 30CST (AUC = 0.89). Highest AUC daily life: mean sit-to-lift time in fall classification (0.81).

Table 1. Cont.

Title	Objectives	Sample	Digital Biomarkers	Results
Practice Effects of Mobile Tests of Cognition, Dexterity, and Mobility on Patients with Multiple Sclerosis: Data Analysis of a Smartphone-Based Observational Study [20]	To examine the effects of short-term learning and long-term practice on six active tests of cognition, agility and mobility in a user-scheduled high-frequency smartphone test.	264 people with multiple sclerosis.	Data from the <i>Floodlight</i> Open app, which collects data from smartphone-based tests of people with multiple sclerosis, such as the 2-Minute Walk, Half Lap and Static Balance tests, to capture gait speed, gait reversal and static balance.	In the Half Lap ($n = 15,051$) and Static Balance ($n = 16,797$), only short-term learning effects were observed, which were interrupted after a maximum of 5 attempts. No short-term or long-term learning effects were observed in the 2-Minute Walk ($n = 14,393$).
Toward a Remote Assessment of Walking Bout and Speed: Application in Patients with Multiple Sclerosis [21]	To develop and validate a new gait speed estimation method based on machine learning to predict gait speed in clinical and home assessments using a sensor in the lumbar region.	35 people with multiple sclerosis.	Three Physilog 5 [®] inertial measurement units (IMU) (Physilog, Gait Up, Lausanne, Switzerland), one on the waist and two on the feet, i.e., one on each foot, with three axes, which included 3D accelerometer and gyroscope data recorded at a sampling rate of 128 Hz and smartphone to connect to the IMUs, used in the 10-Meter Walk Test to capture gait speed.	Compared to the silver standard multisensory reference, a bias close to zero and a gait speed accuracy of 0.15 m/s were achieved. In addition, the proposed machine learning-based gait detection method had a median specificity of 96.8%, sensitivity of 93.0%, an accuracy of 96.4% and an F1 score ($2 \times \text{true positive} / 2 \times \text{true positive} + \text{false positive} + \text{false negative}$) of 78.6% in detecting walking at home.
Automated Detection of Real-World Falls: Modeled from People with Multiple Sclerosis [22]	To describe the development of a context-sensitive fall detection system based on an inertial sensor and an imbalance-tolerant time-of-flight sensor that trains and evaluates real falls in patients with multiple sclerosis.	25 people with multiple sclerosis.	Body-worn triaxial accelerometer and a context-sensitive motion monitoring system that uses indoor wireless time-of-flight (ToF) beacons positioned around a house to track a person's movement and detect the risk of falls.	In a dataset obtained from 25 people with multiple sclerosis observed for 8 weeks in a free-living environment, 54 falls were observed and the system achieved a sensitivity of 92.14% and a false positive rate of 0.65 per day.
U-turn speed is a valid and reliable smartphone-based measure of multiple sclerosis-related gait and balance impairment [23]	To assess the feasibility of remote patient monitoring using digital technology in people with multiple sclerosis.	76 people with multiple sclerosis and 25 healthy controls.	Samsung Galaxy S7 smartphone (triaxial accelerometer and gyroscope sensors with a sample rate of 50 Hz) used to carry out tests, such as the Timed 25-Foot Walk (T25FW) and the 5 U-Turn Test (5UTT) to capture turning speed.	The minimum detectable change in the 5UTT return rate was low in multiple sclerosis patients (19.42%), and the accuracy of this measurement tool compared to existing measures of walking performance in the clinic was excellent.

Table 1. Cont.

Title	Objectives	Sample	Digital Biomarkers	Results
Metrics extracted from a single wearable sensor during sit-stand transitions relate to mobility impairment and fall risk in people with multiple sclerosis [24]	Obtain accelerometer-based metrics from a minimum number of sensors to characterize sitting and standing performance in people with multiple sclerosis during the 30-s chair stand test (30CST).	38 people with multiple sclerosis with an average age of 50.6 ± 12.1 .	MC10 BioStamp triaxial accelerometer (250 Hz sampling rate, ± 16 G) recorded from inertial sensors (MC10, Inc., Lexington, MA, USA) adhered to the skin in the region of the right thigh and chest used to perform tests, such as the 30CST Test, to capture balance and fatigue confidence, sit-stand transition time and stand-sit transition time to detect the risk of falls.	Acceleration-based scores were significantly correlated with several clinical indicators reflecting disease severity, balance confidence and fatigue. Logistic regression performed better for classifying fall conditions incorporating accelerometer features (74% accuracy, (Area Under the Curve (AUC) = 0.78)) compared to standard treatment (68% accuracy, AUC = 0.74) or patient-reported outcomes (71% accuracy, AUC = 0.75).
Does Multiple Sclerosis Differently Impact Physical Activity in Women and Men? A Quantitative Study Based on Wearable Accelerometers [25]	To investigate possible differences between women and men with multiple sclerosis in the amount and intensity of physical activity performed during a week.	45 people with multiple sclerosis (23 F, 22 M, average age 50.3) and 41 unaffected individuals of the same age and gender.	ActiGraph model GT3X triaxial accelerometer (Acticorp Co., Pensacola, FL, USA) used 24 h a day for 7 days to detect patterns of physical activity and sedentary behavior, the number of daily steps and vector magnitude count.	Women's physical activity patterns were characterized by greater sedentary behavior and decreased light activity compared to men, with similar levels of moderate and vigorous physical activity.
A wearable sensor identifies alterations in community ambulation in multiple sclerosis: contributors to real-world gait quality and physical activity [26]	To evaluate community walking and physical activity in patients with multiple sclerosis and healthy controls, and to compare laboratory walking with community walking.	104 subjects, 44 people with multiple sclerosis and 60 healthy controls.	Opal triaxial accelerometer (APDM Wearable Technologies, Portland, OR, USA) worn on the lower back in tests, such as the Timed 25-Foot Walk (T35FW), to detect changes in ambulation due to gait speed and step variability.	During the community walk, people with multiple sclerosis took fewer steps and walked more slowly, with greater asymmetry and greater step variability, compared to healthy controls ($p < 0.001$). Greater impairment is associated with reduced step count and reduced community walking speed.
Deterioration of specific aspects of gait during the instrumented 6 min walk test among people with multiple sclerosis [27]	To identify gait characteristics that worsen during sustained walking and to investigate their clinical correlation with walking fatigue in patients with multiple sclerosis.	58 people with multiple sclerosis.	Opal triaxial accelerometer (APDM Wearable Technologies Portland, OR, USA) worn on the lower back in tests, such as the 6-Minute Walk (6 MWT), to detect gait pace, rhythm, variability, asymmetry, complexity, fatigue and the risk of falls.	Individuals with moderate impairment ($n = 24$) walked worse than the group with mild impairment ($n = 34$) in most gait domains. A group x fatigue interaction effect was observed for gait rhythm and complexity. These rates decreased over time in the moderate impairment group, but not in the mild impairment group.

Table 1. Cont.

Title	Objectives	Sample	Digital Biomarkers	Results
Adherence and Satisfaction of Smartphone- and Smartwatch-Based Remote Active Testing and Passive Monitoring in People with Multiple Sclerosis: Nonrandomized Interventional Feasibility Study [28]	To assess the feasibility of remote active testing and passive monitoring using smartphones and smartwatch technology in people with multiple sclerosis with regard to adherence to and satisfaction with the <i>FloodLight</i> test battery.	People with multiple sclerosis (20 to 57 years; Expanded Disability Status Scale 0–5.5; $n = 76$) and healthy controls ($n = 25$).	<i>FloodLight</i> study, which combines continuous sensor data capture with smartphones and smartwatches, used in tests, such as the Timed 25-Foot Walk Test (T25FW), to detect gait speed and turnaround time.	People with multiple sclerosis had 70% (16.68/24 weeks) adherence in the active trials and 79% (18.89/24 weeks) in the passive surveillance. The average satisfaction score was 73.7 out of 100. Neither adherence nor satisfaction were related to any specific characteristics of the population. More than 80% (61/72) of multiple sclerosis patients had at least an acceptable effect on activities of daily living as assessed by the battery of tests.
Objective sensor-based gait measures reflect motor impairment in multiple sclerosis patients: Reliability and clinical validation of a wearable sensor device [29]	To investigate whether sensor-based gait analysis can detect gait disturbances in patients with multiple sclerosis.	102 people with multiple sclerosis and 22 healthy controls.	Triaxial accelerometer and gyroscope, recorded from SHIMMER 3 sensors (Shimmer Research Ltd., Dublin, Ireland), attached to both shoes, when performing tests, such as the 25-Foot Walk Test (25FWT), to detect average stride length, gait speed, toe-off angle, support time and swing time.	Subgroup analysis between healthy controls and people with multiple sclerosis (EDSS ≤ 3.5 and EDSS 4.0–7.0) revealed significant differences in several gait metrics, especially in fast walking speed. For example, the stride length in fast walking was 33.6 cm, while in self-selected walking, it was 16.3 cm.
Quantifying neurologic disease using biosensor measurements in-clinic and in free-living settings in multiple sclerosis [30]	To evaluate the feasibility and correlation of wearable biosensors with traditional clinical measures of disability both in the clinic and in free living in patients with multiple sclerosis.	25 people with multiple sclerosis.	Biosensors to detect support time, angular angle/velocity of turning, average speed of turning, balance, postural sway and mobility posture.	Feasibility, adherence and expansion between biosensors and traditional clinical measures (Expanded Disability Status Scale (EDSS) and MS Functional Composite-4 (MSFC-4)) were evaluated. Biosensor features correlated with EDSS and MSFC-4 scores at visit 2, including mobility stance time (−0.546), turning angle (0.437) and maximum angular velocity (0.653).

Table 1. Cont.

Title	Objectives	Sample	Digital Biomarkers	Results
Free-Living Physical Activity Monitoring in Adult US Patients with Multiple Sclerosis Using a Consumer Wearable Device [31]	To advance the literature on the usefulness of free-living physical activity screening from secondary analyses of a pilot study in patients with multiple sclerosis.	114 people with multiple sclerosis (mean age 52 years, female (75%), relapsing-remitting type (79%).	Online network of patients with chronic diseases, PatientLikeMe-FitbitOne, and wearable device, used to detect the number of daily steps and the inability to move.	23-day study: average of 20.1 days of data (87% adherence), 4393 steps/day. Multiple Sclerosis Rating Scale (MSRS) pre-study mean: 32.72% with gait disturbances. Step count reliability: interclass correlation coefficient (ICC) 0.55 (daily), 0.7 (2 days) 0.9 (7 days). Disease severity (MSRS) was an independent predictor of step count after controlling for covariates ($p < 0.001$).
Wearable technology reveals gait compensations, unstable walking patterns and fatigue in people with multiple sclerosis [32]	To quantify the patterns of head and pelvic movement that occur in Pulse Width Modulation-impaired patients and determine how these secondary gait compensations impact gait stability.	12 healthy participants and 12 people with multiple sclerosis.	Two Opal triaxial accelerometers (APDM, Wearable Technologies, Portland, OR, USA, 128 Hz sampling frequency), one fixed to the head and the other to the pelvis, used to perform tests, such as the 6-Minute Walk Test (6 MWT), to detect gait variability, mobility index (reduced mobility), risk of falls, gait asymmetry, fatigue and gait compensation measures.	People with multiple sclerosis vs. healthy controls: greater vertical asymmetry in cephalic and pelvic movements (Cohen's $d = 1.85$ and 1.60). In patients with multiple sclerosis, increased compensatory movement related to: decreased amplitude of active ankle movement ($r = -0.71$), greater EDSS ($r = 0.58$), unstable gait ($r = -0.76$), decreased range of motion ($r = -0.71$) and increased volatility ($r = 0.83$).
Monitoring gait in multiple sclerosis with novel wearable motion sensors [33]	To investigate the precision and accuracy of a new wearable device, BioStampRC, as a measure of gait of people with multiple sclerosis with various gait functions.	45 people with multiple sclerosis (Mild multiple sclerosis = 15, Moderate multiple sclerosis = 15, Severe multiple sclerosis = 15) and 15 healthy control subjects.	BioStampRC wireless Inertial Sensormounted on the skin, MTx (Xsens, Enschede, The Netherlands) on the legs and ActGraph model GT3X triaxial accelerometer (Acticorp Co., Pensacola, FL, USA,) on the hip, used to perform tests, such as the 25-Foot Walk Test (T25FW), 6-Minute Walk Test (6 MWT) and Timed Up and Go (TUG), to detect the number of steps, speed and length of gait.	Average accuracy \pm precision for BioStampRC: 2 ± 2 steps error, 6 ± 9 ms error for stride time, 6 ± 7 ms error for step time (0.6–2.6% relative error). Lower accuracy \pm precision in swing time (25 ± 19 ms error, $5 \pm 4\%$ relative error). GT3X with lower accuracy \pm precision ($8 \pm 14\%$ relative error) in estimating number of steps. MTx and BioStampRC detected significant differences in gait in multiple sclerosis patients of different levels of disability ($p < 0.01$).

Table 1. Cont.

Title	Objectives	Sample	Digital Biomarkers	Results
Mobility measures differentiate falls risk status in persons with multiple sclerosis: An exploratory study [34]	To examine differences in mobility metrics, postural control and cognition in people with multiple sclerosis with distinct fall risk status; and to investigate predictors of participation in fall risk groups using discriminant analysis.	47 people with multiple sclerosis.	ActiGraph accelerometer model GT3X (Acticorp Co., Pensacola, FL, USA), used to perform tests, such as the 25-Foot Walk Test (T25FW), 6-Minute Walk Test (6 MWT), Timed Up and Go (TUG), Multiple Sclerosis Walking Scale 12 (MSWS-12) and Six-Spot Step Test (SSST), to detect the number of steps per day and the risk of falls.	The fall risk group showed significantly worse ($p < 0.05$) mobility measures (MSWS-12, 6 MWT and steps/day) compared to the normal fall risk group. Discriminant analysis of MSWS-12 and 6 MWT as significant predictors ($p < 0.05$) for the fall risk group, explaining 55% of the variance.
Body-worn sensors capture variability, but not decline, of gait and balance measures in multiple sclerosis over 18 months [35]	To determine whether body-worn sensors detected any decline in gait and balance measures in people with multiple sclerosis over time.	27 people with multiple sclerosis (13 mildly disabled; self-rated Expanded Disability Status Scale 0 to 3.5; 14 moderately disabled; self-rated expanded disability status scale 4.0 to 5.5).	Six body-worn MTx sensors (Xsens, Enschede, The Netherlands), each including a three-dimensional gyroscope and triaxial accelerometer sampling at 50 Hz, used in tests, such as the Timed 25-Foot Walk Test (T25FW), the Multiple Sclerosis Walk Scale 12 (MSWS12) and the Activities of Balance Confidence Scale (ABC), to detect gait variability.	Although no parameter worsened over time, the multiple sclerosis cohort with moderate disability performed worse than the cohort with mild disability, which, in turn, was worse than the controls on measures of walking and balance. In addition, the cohort with moderate disability had greater variation between visits than the other cohorts ($p < 0.05$, Bonferroni corrected).
Accelerometry as a measure of walking behavior in multiple sclerosis [36]	To validate accelerometer output based on associations with Expanded Disability Status Scale (EDSS), PDDS-Patient Determined Disease Steps Scale (PDDS), Multiple Sclerosis Walking Scale 12 (MSWS-12), Timed 25-Foot Walk Test (T25FW), 6-Minute Walk Test (6 MWT), O2 cost and gait parameters.	256 people with multiple sclerosis.	ActiGraph accelerometer model GT3X (Health One Technology, Fort Walton Beach, FL, USA), used when carrying out tests such as the T35FW and the 6 MWT, to detect spatial and temporal gait parameters, such as walking speed, cadence-number of steps per minute, stride length and stride time.	Accelerometer output was significantly correlated with EDSS ($\rho = -0.522$), PDDS ($\rho = -0.551$), MSWS-12 ($\rho = -0.617$), T25FW ($\rho = -0.595$) and 6 MWT ($\rho = 0.630$) scores.) performance and O2 cost of walking ($\rho = -0.457$). Regarding gait parameters, accelerometer output was significantly correlated with speed ($\rho = 0.420$), cadence ($\rho = 0.349$), step time ($\rho = -0.353$), step length ($\rho = 0.395$), double support ($\rho = -0.424$) and single support ($\rho = 0.400$).

3.2. Characteristics of the Instruments Used

A variety of technologies were identified in the selected studies, including smartphones and specific accelerometers to analyzing movement patterns, balance and fall risk in individuals with multiple sclerosis. Four studies used the ActiGraph model GT3X triaxial accelerometer (Acticorp Co., Pensacola, FL, USA), which was employed for various tests, as well as used in the free-living, with each study having its own objective, including detecting

the number of steps per day or per minute (cadence), walking speed, time, stride length and variability, and the risk of falls [25,33,34,36]. Three studies used the MC10's BioStamp triaxial accelerometer (MC10, Inc., Cambridge, MA, USA) [18,19,24], while three other studies used the Opal triaxial accelerometer (APDM Wearable Technologies, Portland, OR, USA) [26,27,32]. The skin-mounted MTx (Xsens, Enschede, The Netherlands) was reported in two studies [33,35] as well as the FloodLight Open study, which collects data from tests based on smartphones and smartwatches [20,28]. The BioStamp nPoint® wearable accelerometer placed on the chest and sacrum was also used in one study (Medidata, New York, NY, USA) [16].

The McRoberts Dynaport MM wearable device was reported in only one study, with a sampling frequency of 100 Hz, triaxial acceleration range of ± 8 g and resolution of 1 mg, and triaxial gyroscope range of ± 2000 degrees per second (dps) and resolution: 70 mdps [17]. One study used a skin-mounted BioStampRC wireless inertial sensor, in which the triaxial accelerometer used has a sampling rate of 250 Hz, ± 16 G [33]. Another study used the online network of patients with chronic diseases, PatientLikeMe by FitbitOne, a wearable device that records the number of daily steps [31] and only one study used the Physilog 5® inertial measurement unit (IMU) (Physilog, Gait Up, Lausanne, Switzerland), one on the waist and two on the feet, which included 3D accelerometer and gyroscope data recorded at a sampling rate of 128 Hz and a smartphone to connect to the IMUs [21]. The Samsung Galaxy S7 smartphone with triaxial accelerometer and gyroscope sensors with a sampling rate of 50 Hz was also used in one study [23].

One study did not cite the triaxial accelerometer used, but reported it being worn on the body along with a context-sensitive motion tracking system that uses internal wireless time-of-flight (ToF) beacons positioned around a house to track a person's movement [22]. One study reported the use of SHIMMER 3 sensors (Shimmer Research Ltd., Dublin, Ireland), attached to both shoes [29] and another study only cited the use of biosensor data, but did not specify the equipment [30].

3.3. Objective Biomarkers Reference Methods

Walking speed, step count and gait index were the most commonly used objective biomarkers reference methods. The 25-Foot Walk test (T25FW) was reported in 8 studies [20,23,26,28,29,33,34,36]. Other authors have used the 6-Minute Walk (6MW) test [17,27,32,33,36], the 10-Meter Walk test [21], the 2-Minute Walk, half-turn and static balance test for mobility assessment [20]. Of note, sensor data collected during the Get Up and Walk test (TUG) served as a parameter to identify walking speed, movement patterns, frequency and intensity of falls, gait index, the duration of physical activity, the intensity of activity, pace and balance in four studies [23,29,33,34]. Two studies [17] used the duration of physical activity, the intensity of activity, gait index, frequency and intensity of falls as biomarkers of mobility. Besides assessment of low extremity function, sensor data from the 30CST (30-s chair stand test) [19,24] was used for assessment of movement patterns and weight load distribution.

3.4. Subjective Biomarkers Reference Methods

A total of 12 subjective biomarkers were used as reference methods for mobility across the aforementioned studies, including questionnaires, scales, interviews or self-reports, with the aim of obtaining information on the individual perception of symptoms, quality of life and emotional well-being of individuals with multiple sclerosis. The most commonly used questionnaires were the Expanded Disability Status Scale (EDSS), reported in 16 studies [16,17,19,21–23,25,26,28–30,32–36], and the Modified Fatigue Impact Scale (MFIS), reported in 10 articles [16,18,19,23,24,26–29,31], followed by the Multiple Sclerosis Walking Scale-12 (MSWS-12) reported in 8 studies [16,27,29,31,33–36].

The Activity Specific Balance Confidence Scale (ABC) was identified in five studies [16,18,19,24,35]. The Patient Determined Disease Steps Scale (PDSS) was reported in four studies [16,28,33,36]. The Patient Health Questionnaire-9 (PHQ-9) only

appeared in two articles [28,31], similar to the 36-Item Short Form Survey Instrument (SF-36) [29,31] and the Berg Balance Scale [20,28]. Only one study used the Fatigue Scale for Motor and Cognitive Functions (FSMC) [28], while another used the Disease Assessment Scale Part III [16] and the Kansas City-12 Cardiomyopathy Questionnaire [16]. The self-reported fatigue and balance confidence questionnaire was used in [18].

4. Discussion

The main objective of this review was to investigate which signal patterns and parameters are used as digital biomarkers in the assessment of mobility in individuals with multiple sclerosis. The results revealed that wearable sensor data were associated with a wide variety of objective and subjective biomarkers used as reference methods in the studies reviewed, highlighting the complexity of assessing mobility in this population.

The wearable devices used in the studies included ActiGraph, BioStamp, Opal triaxial accelerometers [25,33,34,36], BioStamp nPoint[®] chest- and sacrum- worn accelerometer [16], McRoberts Dynaport MM wearable device [17], BioStampRC Wireless Skin-Mounted Inertial Sensor [33], Samsung Galaxy S7 smartphone with Triaxial Motion and Gyroscope Sensors [20,28], as well as SHIMMER 3 Sensors (Shimmer Research Ltd., Dublin, Ireland) [29], biosensors [30], and the FitbitOne online network for patients with chronic diseases [31]. These devices were employed in the studies in order to collect information on physical activity and mobility in patients with multiple sclerosis, specifically in relation to walking speed, step count and gait index. Thus, the aforementioned wearable devices have been helpful in measuring motor and movement patterns, providing important information for assessing gait and mobility in this population.

The most commonly reported objective biomarkers reference methods in the selected studies were walking speed, step count, gait index and gait-related intervals. Walking speed, assessed using the Timed 25-Foot Walk Test (T25FW) [20,23,26,28,29,33,34,36], and the 6-Minute Walk Test (6 MWT) [17,27,32,33,36], were considered key indicators of motor function in patients with multiple sclerosis. Step counting provides a detailed overview of daily physical activity [31], but the gait index and other related parameters provide details about the nature of this movement, disease progression, assessing the effectiveness of therapeutic interventions and enabling changes to treatment plans, making these tools essential for monitoring patients and making more accurate clinical decisions [37,38].

In addition to objective biomarkers reference methods, the studies reviewed also employed a series of subjective biomarkers reference methods, including scales and questionnaires to assess symptoms, quality of life and emotional well-being. The Expanded Disability Status Scale (EDSS) [16,17,19,21–23,25,26,28–30,32–36], the Modified Fatigue Impact Scale (MFIS) [16,18,19,23,24,26–29,31], and the Multiple Sclerosis Walking Scale-12 (MSWS-12) [16,27,29,31,33–36] stand out as widely used tools. These instruments provide crucial information on how the patient's daily life is impacted by the disease and their physical activity, allowing for a more in-depth understanding of their state of health, helping to personalize their treatment plans and promote a better quality of life.

This variety of biomarkers reference methods emphasizes the need to assess many facets of functionality and movement. However, it is essential to emphasize that the choice of biomarkers must be made carefully, taking into account clinical relevance and the ability to provide accurate and useful information to improve the quality of life of individuals with multiple sclerosis.

The first accelerometers had limitations, with a limited battery life and data storage capacity, low sensitivity and connectivity, as well as a low sampling rate, which is the number of times the acceleration is detected per second, with most old devices allowing sampling rates of up to 10 Hz [39]. Modern accelerometers present higher sampling rates, are small in size and record acceleration in three different axes and can be positioned on various parts of the body, the most common locations being the hip, wrist and thigh [40].

Sampling rates play a critical role in collecting objective data in studies using wearable technology, such as accelerometers. These rates can significantly affect the accuracy, resolu-

tion and clinical usefulness of the results, especially when assessing mobility in patients with multiple sclerosis. Therefore, a sensible conclusion would be to choose a sampling rate of 90 Hz when using the methods provided by the manufacturer and a rate of 100 Hz when performing filtering and signal processing independently [41].

Using the raw acceleration data, which provides information on the direction and magnitude of the acceleration in each of these axes, with 1 g representing the force of Earth's gravity, and the sampling rate, which in most current accelerometers is between 30 and 100 Hz, the measurement range and resolution are configured and adjusted according to the objective of each study [40]. In the articles analyzed in this review, for example, a variety of sampling rates were used, the most commonly used being 250 Hz [18,19,24], followed by 128 Hz [21,32] and 50 Hz [23,35], with the least commonly used being 100 Hz [17]. Of note, in several studies [16,20,22,25–31,33,34,36], the sampling rate used was not specified.

If the accelerometer has a low sampling rate, such as 10 Hz, it will take an acceleration reading every 1/10th of a second (or every 0.1 s), and during accelerations of more than 4 m/s, accuracy is compromised [42]. An average sampling rate could be 100 Hz, which means that the accelerometer will take 100 acceleration measurements per second, every 1/100th of a second (or every 0.01 s) [17]. A high sampling rate, such as 1000 Hz, will take 1000 acceleration measurements per second, or one every 1/1000th of a second (or every 0.001 s) [43]. The choice of sampling rate depends on the objectives of the study or application. Higher sampling rates can capture fine and precise details of movement but will also result in a larger volume of data, as well as high battery consumption [44]. On the other hand, lower sampling rates can save battery power and storage space, but may lose important information about fast movements [45].

Higher sampling rates, such as 250 Hz, allow for the detection of subtle changes in mobility, as well as helping to capture rapid movement data, such as jerky movements or spasms. In some of the studies analyzed in this review [18,19,24], a sampling rate of 250 Hz was used in order to capture data on sitting and standing and standing and sitting, which are rapid movements and can detect the risk of falls, for example. This ability to capture rapid events is essential for accurately assessing mobility and identifying signs that can help delay or prevent the progression of multiple sclerosis. This is very important in patients with this disease, as small changes in motor function can be clinically relevant.

The wearable technology most used to identify objective markers and even correlate them with subjective biomarkers were triaxial accelerometers, such as the ActiGraph GT3X [25,33,34,36], the MC10's BioStamp [18,19,24], the Opal [26,27,32], the skin-mounted MTx (Xsens, Enschede, The Netherlands) [33,35], and the BioStamp nPoint[®] from Medidata [16].

Choosing the right accelerometer for a study depends on a number of factors, including the research objectives, the characteristics of the target population, the type of data the study wishes to collect and the location and positioning of the participants. In addition, factors such as the sampling rate, the duration of data collection, compatibility with software and analysis platforms and budget constraints are very important to consider, since the sampling rate, the loading time, the reading of the data into programs and the value vary according to the model.

Among the brands available on the market, the accelerometers from ActiGraph, based in Pensacola, Florida, USA, are the most widely adopted by researchers, accounting for more than 50% of published studies [39]. This evaluation focused exclusively on the latest generation of ActiGraph devices, i.e., the GT3X, GT3X+ and wGT3X-BT [40]. In the studies analyzed in this review, triaxial accelerometers were the most commonly reported model, and they were attached to different devices. The information presented in above about the brand most used in the studies was confirmed in this review, since most of them used the GT3X model (Acticorp Co., Pensacola, FL, USA) [25,33,34,36], which is an ActiGraph brand device, usually worn on the hip or wrist.

Gait impairment is highly prevalent in people with multiple sclerosis, as the decline in neural control affects motor functions and, consequently, gait, including gait variability and asymmetry. This variability and asymmetry, both in stride time and stride speed, are considered digital biomarkers of mobility [46].

Advances in digital health technology and ongoing refinements of diagnostic criteria have enabled earlier diagnosis and treatment, and attempts are being made to further refine definitions of disease phenotypes. The prognosis of multiple sclerosis varies substantially between patients on an individual basis. Along with clinical judgment, a combination of digital, imaging and laboratory biomarkers can be useful for predicting the clinical course and optimizing treatment in individuals with multiple sclerosis. Future research will allow for the development of new and more accurate biomarkers for categorizing and prognosticating multiple sclerosis, which will allow personalized treatments to be carried out in time to prevent the disease from progressing.

We recommend a continued focus on developing new devices for validating digital biomarkers that can better reflect the complex changes in mobility associated with these conditions. It is important that future studies strive to establish clear guidelines and criteria for the selection and use of these biomarkers, considering not only their sensitivity and accuracy, but also their clinical practicality. It is therefore important to establish clear criteria for the selection and use of digital biomarkers, considering not only their sensitivity and accuracy, but also their clinical practicality. One possibility is the integration of digital biomarkers into accessible and easy-to-use devices, such as triaxial accelerometers incorporated into smartphones or smartwatches. These devices offer the promising ability of collecting accurate and precise data on free-living mobility of patients with multiple sclerosis, including walking speed, number of steps, movement patterns and balance.

In the future, it will be worth investing in advanced digital monitoring technologies, such as wearable devices equipped with high-precision sensors and artificial intelligence, to analyze the complex mobility patterns of multiple sclerosis patients. In addition, the development of integrated mobile applications and online platforms that allow patients to record data about their daily movements easily and accurately could be a valuable tool. Ongoing research and improvements in data analysis algorithms can help identify relevant patterns, detect changes in patients' conditions and provide early intervention. This innovative approach has the potential to revolutionize mobility monitoring in patients with multiple sclerosis, improving quality of life and promoting disease management.

Limitations and Future Considerations

The main limitation of this review is related to the selection of the included studies. Although we followed strict inclusion and exclusion criteria, there is a possibility that some relevant studies were not identified or were inadvertently excluded. This may result in a partial view of the digital biomarkers used to assess mobility in patients with multiple sclerosis. Future research could focus on validating and assessing the reliability of digital biomarkers used in the assessment of mobility in patients with multiple sclerosis. This involves conducting studies that compare the data obtained by digital devices with reference measures, such as traditional clinical tests. Longitudinal studies that follow patients over time can provide valuable information about the progression of multiple sclerosis and how digital biomarkers can detect changes in mobility throughout the course of the disease.

Digital biomarkers are emerging as an innovative tool in mobility assessment, and artificial intelligence plays an important role in advancing this field. By harnessing the capabilities of artificial intelligence, we can not only improve the accuracy and sensitivity of mobility assessments but also open the door to personalized treatment strategies. Artificial intelligence can help analyze large amounts of mobility data, identify subtle patterns and predict health risks. Telehealth can also benefit from these advances, as remote monitoring of patient mobility can become more efficient and beneficial, improving the overall quality of care. Although the limitations of this study are acknowledged, the future of mobility

assessment in patients with multiple sclerosis looks promising thanks to digital biomarkers and artificial intelligence. This technology has the potential to transform the approach to understanding and improving mobility, providing a more holistic and data-driven view of patient care. In the future, more research and validation will be needed to exploit the full potential of these tools for the benefit of patients and healthcare providers.

5. Conclusions

Our results indicate that the main accelerometer signal patterns and parameters for assessing mobility impairment in individuals with multiple sclerosis have been captured through wearable triaxial accelerometers, inertial measurement units, smartphones or smartwatches. Subjective parameters, on the other hand, have been reported using validated scales and questionnaires, resources that allow us to assess the individual's compromised mobility, but in a less precise way. Digital biomarkers play a fundamental role in health assessment and protocols for any individual. However, it is important to understand these signals and seek standardization in choosing the best method to capture the greatest quantity and best quality of signals, especially for individuals affected by some neurological pathology. This will allow us to make progress in understanding, treating and preventing the progression and severity of multiple sclerosis, especially when it comes to mobility impairment in this population.

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