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Wearable inertial sensors provide reliable biomarkers of disease severity in multiple sclerosis: a systematic review and meta-analysis

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Wearable inertial sensors provide reliable biomarkers of disease severity in multiple sclerosis: a systematic review and meta-analysis

Abstract

Background. Gait impairment is a hallmark of multiple sclerosis (MS). InertiaLocoGraphy, the quantification of gait with inertial measurement units (IMUs), has been found useful to detect early changes in gait in MS. Still, the potential use of IMUs as a reliable biomarker of disease severity in MS remains unknown.

Objective. This systematic review and meta-analysis of observational studies aimed to describe IMU protocols used to assess gait in MS patients and calculate the effect sizes of IMU features associated with disease severity scale measures.

Methods. We searched MEDLINE, Cochrane Central, EMBASE and grey literature to identify articles published before May 2, 2018 that measured gait in MS patients by using IMUs and correlated IMU parameters with disease severity scale measures. We excluded from the meta-analysis articles that did not provide enough data to evaluate the association between IMU parameters and disease severity scale measures. The study was registered with the International Prospective Register of Systematic Reviews on May 2, 2018 (Registration: CRD42018092651) and the protocol was published in *Systematic Reviews* on January 8, 2019.

Results. We included 36 articles in the systematic review and pooled 12 for the meta-analysis. The risk of bias was moderate, with only 2 articles (none included in the meta-analysis) showing a bias score < 50%. Among protocols tested, 2 were predominant (the Timed Up and Go test and 6-min walk test). Speed, step length and step time with IMUs were significantly correlated with

the Expanded Disability Status Scale (EDSS) score, and speed and step length were significantly correlated with the Multiple Sclerosis Walking Scale-12 score.

Conclusion. IMU measurement has the potential to increase the sensitivity of clinical and performance tests to identify evolution in gait alteration in MS. Kinematic parameters easily accessible with IMUs, such as speed, step length and step duration, can help follow up disease severity in MS individuals with low to medium EDSS score (1.0–4.5).

Keywords: multiple sclerosis, gait analysis, gait quantification, gait disorders, wearable inertial sensors, inertial measurement unit, accelerometer

Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with varying clinical presentation and progression. Gait impairment is a hallmark of MS, and lower-limb function is considered the most important body disability across the disease spectrum [1]. Thus, objective gait assessment both in routine clinic care and in clinical research trials is needed to improve follow-up of gait and balance in people with MS.

Mobility in MS patients is one of the disabilities measured by the Expanded Disability Status Scale (EDSS), which has been criticized for its lack of sensitivity to change [2–4] and its high interrater variability [5]. The Multiple Sclerosis Severity Score (MSSS) is another scale whose score is obtained by normalizing the EDSS score for disease duration [6]. Both scales are practical and easy to use in routine clinical practice, but in some cases, more sensitive and analytical evaluations are needed [4,7,8]. Patient-reported outcomes, subjective by definition, are also useful to inform disease severity and the Multiple Sclerosis Walking Scale-12 (MSWS) is a

12-item measure of the impact of MS on walking [9], which was found to be less precise than a gait test and accelerometric data [10]. The Multiple Sclerosis Impact Scale (MSIS-29) is a 29-item measure of the impact of MS on day-to-day life in the previous 2 weeks but does not primarily focus on gait [11]. Gait speed is measured by using stopwatch-timed tests such as the Timed 25-foot Walk Test (T25FW), which has been criticized for being highly variable [12,13]. Finally, the Multiple Sclerosis Functional Composite (MSFC), which is used frequently, involves 3 tests, including the T25FW, expressed as a single score along a continuous scale [14]. However, the test is prone to practice effects [15] and day-to-day variability [12,13].

Inertial measurement units (IMUs) are small, light, integrated systems that measure linear and angular motion usually with a triad of accelerometers and a triad of gyroscopes, often associated with a magnetometer. Motion capture systems based on these wearable sensors have become widely used for the biomechanical analysis of human movement. InertiaLocoGraphy (ILG), the quantification of gait with IMUs, was first reported 70 years ago [16] and has now been implemented in a wide range of neurological and non-neurological diseases [17,18]. The tool can be used both at the hospital, mainly for short tests, and at home for more long-term physiological gait assessment [19]. Automatic detection of steps and U-turns are now available [20–24], which allows for online processing of signals and computation of a large amount of features describing gait speed and quality [19]. Hence, the clinician has a direct and reproducible access to a great number of objective gait indicators. These indicators have proved useful to analyze gait and extract biomarkers of functional impairment observed during chronic neurological disease progression [19] such as Parkinson disease [25–28], spinocerebellar ataxia [29,30], post-stroke hemiparesis [29,31] or idiopathic normal pressure hydrocephalus [32].

However, the potential for using IMUs as biomarkers of disease severity in MS remains to be tested. Indeed, IMUs have been found useful to detect early changes in MS undetectable with previously mentioned assessments [33]. Still, whether IMU analysis helps in evaluating disease severity remains unknown because no review has comprehensively assessed whether features obtained from IMUs could be used as biomarkers of MS severity. The association between features from IMUs and MS progression would be worth exploring.

Here we report the largest and most comprehensive systematic review and meta-analysis of observational studies to describe IMU protocols used to assess gait in MS patients and calculate the effect sizes of IMU features associated with disease severity scale measures.

Materials and Methods

The literature search and analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [34] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [35] guidelines.

Search strategy and selection criteria

The search strategy is explained in our published protocol, available at the International Prospective Register of Systematic Reviews (Registration: CRD42018092651) and *Systematic Reviews* [36]. We searched MEDLINE via PubMed, Cochrane Central, and EMBASE electronic databases to identify articles published before May 2, 2018 that measured gait by using inertial sensors in people with MS. In addition, the grey literature was searched in Google Scholar, OpenGrey.eu, GreyLit.org, WorldCat, World Health Organization Clinical Trials Search Portal, ClinicalTrials.gov and the European Union Clinical Trials Register. All reference lists and bibliographies of included studies were also reviewed for relevant articles.

Inclusion and exclusion criteria are described in the protocol [36]. Randomized controlled trials, non-randomized controlled trials and observational studies were eligible for inclusion. Inclusion criteria were adults with a clinical diagnosis of MS and gait measured by using inertial sensors (accelerometer and/or gyroscope). We excluded articles of studies that did not include people with MS (POPULATION criterion), quantified other activities such as standing or running or assessed general physical activities using only step count or walking bout length (GAIT criterion), or used sensors other than IMUs (IMU criterion). We excluded from the meta-analysis articles that did not provide sufficient data for pooling results even though authors were contacted for missing information (see 1.6.1). Data were considered sufficient with one of the 3 following situations: correlation between gait parameters and EDSS or MSSS, MSWS, MSFC, MSIS-29 or T25FW scores reported or obtained from the main author; raw values of gait parameters and EDSS, MSSS, MSWS, MSFC, MSIS-29 or T25FW scores reported or obtained from the main author for every patient; raw values for gait parameters reported or obtained from the main author for groups of patients, with groups drawn from their EDSS, MSSS, MSWS, MSFC, MSIS-29 or T25FW values (REPORTING criterion). As we considered during the design of the study and detailed in the protocol, we added an AMBULATORY criterion to exclude articles that measured gait only at home, because the protocols were heterogeneous (hence exclusion from the systematic review) and we could not find more than 3 studies assessing ambulatory gait and for which a common effect size could be drawn (hence exclusion from the meta-analysis).

Data analysis

The primary outcome was the correlation of ILG parameters with EDSS score. Secondary outcomes were the correlation of ILG IMU parameters with scores for other severity scales or

tests (MSSS, MSWS, MSIS-29, stopwatch-timed T25FW, MSFC). Scales or tests for which data for at least one parameter could not be retrieved for at least 2 articles from different authors are only commented on. Assessment of fall risk was too rare and highly variable across studies to be added as an additional objective.

Articles were reviewed independently by 2 review authors (AVJ and FQ). The data extraction method is described in the protocol [36]. The risk of bias assessment relied on a 20-item quality checklist for longitudinal studies that we adapted from Hubble et al. [37] (the checklist can be found in the supplemental section of the protocol [36]). Risk of bias assessment was performed independently by 2 review authors (AVJ and FQ), each blinded to the score given by the other. These authors later discussed discrepancies ($\approx 5\%$ of scores) until they agreed on the final score. To visualize possible publication bias, we used funnel plots, which represent the estimated effect size (plotted on the horizontal axis) versus its standard error mean (plotted on the vertical axis). A symmetric inverted funnel shape favors no publication bias.

Statistical analysis

Extracted data were pooled to derive effect sizes of correlations of IMU features with severity scale scores. To summarize, when a given feature was reported in at least 3 studies from different authors, correlation coefficients (r) were transformed by using the Fisher z transformation [$z = \text{atanh}(r)$] and the analysis was performed using this index with 95% confidence interval excluding the null value considered significant. This process allowed for the use of tests for normal distribution. Then, the summary values were converted back to Pearson coefficient correlations for presentation [$r = \tanh(z)$] [38]. Because only one interventional study was included, the GRADE criteria were not used [39]. A fixed-effects model was chosen when

heterogeneity, as measured by the I^2 , the percentage of total variation across studies that is due to heterogeneity rather than chance, was low to moderate ($I^2 < 50\%$) [40]; otherwise, a random-effects model was used.

For significant correlations found between a given kinematic parameter and a severity scale, we performed an individual participant analysis using full data included in articles as well as data provided by authors.

Statistical analysis involved using R v3.5.1. Effect sizes were computed based on the recommendations from the Cochrane Collaboration handbook and Cochrane Review Manager v5.3). MATLAB® R2018 was used to create the forest plots for the meta-analysis.

Results

Study characteristics

Our systematic search of the literature identified 103 records after duplicates were removed. No study was identified by exploration of grey literature. Eleven records were excluded on the basis of the abstract. Finally, articles for 36 studies (including 1480 patients), published between 2009 and 2018, met our inclusion criteria (Fig. 1). Five studies (14%) were longitudinal studies, and the remainder were cross-sectional. Study characteristics and references for all 36 included trials are in Table 1. Study populations, protocols and outcomes are in Supplemental Tables 1 and 2. The meta-analysis included articles for 12 studies (44% of all articles included in the systematic review) including 524 patients (median of 44 patients per study [interquartile range (IQR) 24–54]). The mean (SD) age of all participants was 47 (7) years for papers included in the systematic review, and 48 (6) years for those included in the meta-analysis. The mean (SD) proportion of female participants was 70% (15%) and 71% (11%) for all papers and those in the meta-analysis. At inclusion, the mean (SD) disease duration was 10.8 (4.3) and 12.3 (0.5) years for all

participants and those in the meta-analysis. In total, 87% had relapsing-remitting disease, both when considering all articles and articles included in the meta-analysis. The mean (SD) EDSS score was 3.2 (1.5) and 3.5 (1.7), respectively.

Risk of bias assessment

Detailed evaluation of risk of bias is in Supplemental Table 3 and mean scores are in Figure 2. Overall, the risk of bias was moderate, with a Gaussian-shape curve for mean scores (Shapiro-Wilk normality test: $p = 0.3$) and a median score of 70% (IQR 60–74). Two articles (for which data could not be used in the meta-analysis) had a risk of bias score $< 50\%$, and 18/36 articles (8/16 articles included in the meta-analysis) had a score $> 70\%$. Funnel plots were drawn for all features that were included in the meta-analysis: speed (V , in m/s), step length (SteL, in m), step time (SteT, in s), swing time (swT, in % of step time), stance time (stT, in % of step time) and double stance time (dstT, in % of stride time) (Supplemental Table 4). Visual inspection of funnel plots (Fig. 3) revealed little evidence of publication bias for correlations of these kinematic parameters with the EDSS score but larger publication bias for their correlation with the MSWS score.

Description of protocols

Protocols used to assess gait were various (Fig. 4). Regarding floor type and sequence of steps, 2 protocols were predominant: the Timed Up and Go (TUG) test is a 6-min walk test with a U-turn and sit-to-stand transition depending on the authors, and the 6-min walking test (6MWT) involves a 6-min walk, mostly on unlevelled floor in the articles included. Most of the time, speed was left to the convenience of the patient, but both protocols (TUG test, 6MWT) were also performed at the fastest speed in some studies (2/6 for the TUG test and 8/12 for the 6MWT). The most widely chosen IMU position was the lower back (68% of all 36 articles and 75% of the

12 meta-analysis articles) (Fig. 5A and Table 2). The lower back was the only position selected in 39% of all articles and 17% of meta-analysis articles. However, 39% and 42% of articles in the systematic review and meta-analysis, respectively, recorded from more than one IMU, with a maximum of 7 sensors. Other positions included the sternum (21% of all articles and 42% of meta-analysis articles), shanks (18% and 25%), wrists (18% and 25%), ankles (16% and 17%), hip (13% and 17%) and, more anecdotally, thighs, head and lower front (in 5%, 5% and 3% and 0%, 0% and 17%, respectively).

Many types of IMUs were tested, but 2 were predominant: XSens® MtW (22% of all articles and none in the meta-analysis) and Actigraph® (19% of all articles and 17% of meta-analysis articles) (Fig. 5B). Nearly half of the articles did not specify the sampling frequency of sensors used (44% of all articles and 50% of meta-analysis articles). The IMUs mainly had a 50–128 Hz sampling frequency.

Pooled meta-analysis

All scales and tests referred to in the secondary outcomes were reported at least once in one of the 36 included articles. However, only the EDSS and MSWS scores were reported in a sufficient number of articles to calculate a pooled correlation effect size. Risk of falls or previous falls was assessed in 4/36 articles, but methods were too heterogeneous to allow a comparison because they reported number of previous falls (1 study) or different risk assessment scores (3 studies). Data for 6 kinematic parameters were sufficient to calculate a correlation effect size with the EDSS and MSWS. V, SteL, SteT, swT, stT and dstT were all analyzed in terms of the EDSS or MSWS score in at least 3 studies. For correlation with the EDSS score, a random-effects model was used for all kinematic parameters except V, stT and swT, for which I^2 was 49%, 0% and 4%, respectively. Heterogeneity was high for dstT ($I^2 = 64%$), moderate for V ($I^2 =$

49%), and low for the other kinematic parameters (SteL: $I^2 = 8\%$; SteT: $I^2 = 0\%$; stT: $I^2 = 0\%$; swT: $I^2 = 4\%$). Only V, SteL and SteT showed significant correlation with the EDSS score (overall Pearson coefficient -0.60 [-0.67 ; -0.53], -0.46 [-0.61 ; -0.40] and 0.32 [0.14 ; 0.40], respectively; Fig. 6A). For correlation with the MSWS score, a random-effects model was used for V, SteL and SteT. Heterogeneity was high for V ($I^2 = 83\%$) and SteT ($I^2 = 64\%$), moderate for SteL ($I^2 = 38\%$), and low for the other kinematic parameters (stT: $I^2 = 0\%$; swT: $I^2 = 0\%$; dstT: $I^2 = 0\%$). Only V and SteL showed significant correlation with the MSWS score (overall Pearson coefficient -0.64 [-0.77 ; -0.54] and -0.37 [-0.65 ; -0.16]; Fig. 6B). For both V and SteT, all findings were consistent for the direction of the correlation (decreasing speed and increasing SteT with increasing disease severity) except for one study [41]. Removing this study highly decreased the heterogeneity for V (correlation with EDSS score: $I^2 = 0\%$; correlation with MSWS score: $I^2 = 0\%$) and SteT (correlation with EDSS score: $I^2 = 0\%$; correlation with MSWS score: $I^2 = 33\%$) but not dstT (correlation with EDSS score: $I^2 = 82\%$). After this removal, the overall correlation effect of V with EDSS and MSWS scores changed from -0.58 [-0.66 ; -0.51] to -0.64 [-0.69 ; -0.56] and -0.67 [-0.77 ; -0.54] to -0.77 [-0.85 ; -0.67]. The overall correlation effect of SteT with the EDSS score changed from 0.32 [0.14 ; 0.40] to 0.39 [0.18 ; 0.44].

Individual meta-analysis

Individual participant correlation data with the EDSS score could be retrieved for 6 studies. Three datasets were sent by the authors [42–44], one dataset was directly accessible within the publication [45] and 2 other datasets were accessible only as group mean and standard deviations with the group of increasing EDSS score [46,47]. We reconstituted these 2 datasets by generating a normal distribution of mean and standard deviation within groups. We could not retrieve individual participant correlation data with the MSWS score. Individual participant data for

correlation of V, SteL and SteT with the EDSS score are in Figure 7. The inter-individual variability of measures for SteL and SteT greatly increased with high EDSS score (> 6) versus low EDSS score. A score test for non-constant error variance (NCV test), used to reveal some evidence for a non-constant variance of the residuals [48], showed that the data were indeed highly heteroskedastic for SteL and SteT (NCV test: SteL: $p=0.010$ and SteT: $p<0.0001$), with no heteroskedasticity found for the correlation of V with the EDSS score (NCV test: $p = 0.087$).

Discussion

Identifying changes in disease state throughout the course of MS is essential for optimal care [49]. Current clinical and performance tests (EDSS, MSSS, MSWS, MSIS-29, MSFC, T25FW) allow for identifying advanced alterations in gait in MS but lack sensitivity to detect subtle gait dysfunction or progression. Indeed, these scales associate different components, both clinical symptoms and functional capacities, which do not all concern gait. Therefore, they cannot be as sensitive to detect gait alteration as a specific index of gait. However, they provide a general view of the impact of the disease on the patient's various functions, with the key advantage to adapt to the different clinical forms of associated deficiencies. IMUs are small wearable sensors that can be easily used in clinical practice to quantify gait in MS patients. Nevertheless, whether these outcomes are clinically relevant is uncertain because no study has evaluated their correlation with disease severity across different settings.

This systematic review and meta-analysis provides insight into the potential of using IMUs as a marker of disease evolution. We included 36 articles evaluating IMU parameters with different protocols and correlating parameters with performance outcomes in our systematic review and pooled 12 for the meta-analysis. The risk of bias was moderate, with only 2 articles

(none in the meta-analysis) showing a risk of bias score < 50%. Among protocols tested, 2 were predominant (TUG test and 6MWT). The position of the IMUs is crucial for sensitivity of human kinematic observation, especially for tests like the TUG. Most studies placed their sensor on the lower back of the participant (L3-L4 vertebrae), which was also the preferred position for other gait pathologies, as found in a previous review [19]. Besides, this position was found reliable for inter-session measurements in healthy participants [50,51]. Other sensors were frequently associated and placed on the shanks or ankles. Therefore, we propose that gait assessment using IMUs include a short test with a turn as well as a long test such as the 6MWT when possible, as previously recommended [52,53]. We also suggest attaching the IMU to the lower back (L3-L4 vertebrae) and to add IMUs on the lower parts of both lower limbs when possible.

Speed, step length and step time were significantly correlated with the EDSS score, and speed and step length were significantly correlated with the MSWS score. Video motion systems can be considered gold standards for gait analysis. By using this bench-marking technology, earlier studies found similar gait patterns (lower speed, shorter strides, higher step time) in MS patients with low EDSS score (0–2.0) [7,54]. What is more, several studies using this gold standard found similar correlations of velocity, step length and step time with the EDSS score [55,56]. However, intra-individual changes in these gait parameters measured by video motion was not associated with a change in EDSS score, as was found in a 12-month prospective study by Galea et al. [4] or a 6-month prospective study by Rodgers et al [56]. IMUs have been validated against such systems in patients with MS [57,58]. Therefore, quantitative gait analysis using IMUs has the potential to increase the sensitivity of clinical and performance tests to identify evolution in gait in MS.

Kinematic parameters easily accessible with IMUs, such as speed, step length and step duration, can help follow up disease severity for people with MS and low to medium EDSS score (1.0–4.5). Indeed, an EDSS score of 1.0 was found associated with altered gait, which argues for a systemic assessment of their gait even at these very low EDSS scores [42]. Very little data were available for patients with EDSS score 5.0 to 5.5 and analyzed parameters showed high variability for EDSS score ≥ 6.0 as shown by the test for heteroskedasticity and Figure 7. Besides, to the best of our knowledge, no automated step-detection method proved robust enough to be applied to patients with EDSS score ≥ 6.0 [44,59]. Therefore, complementary systems such as walkways or footswitches are added to assess such patients, or manual painstaking step detection is performed, which hinders the use of such analysis in routine clinical workup. However, the improvement of algorithms may soon overcome such limitations.

Patient characteristics were comparable in terms of age, sex ratio, disease type, disease duration and EDSS score in articles included in the systematic review and in both the systematic review and meta-analysis. Except for speed, step time and double stance time, heterogeneity for other parameters was low, which supports our conclusions. High heterogeneity found for speed and step time was regularly $< 50\%$ when removing the study by Craig et al. [41], which was opposite to the other studies. High heterogeneity for correlation of step time with EDSS score might be explained by the difficulty in computing this parameter, which requires a precise definition of toe-off and heel strike during a step. The remaining heterogeneity can also be due in part to the diversity of protocols and algorithms used to sequence steps from the signals of the IMUs. Elevated inter-individual variability of step time and step length for high EDSS score argues against their use as independent markers of severity in people with severe disease. However, low inter-individual variability of speed — even at high EDSS score — provides

arguments for using speed or a combination of step time and step length, which are related to speed. This combination is worth exploring to evaluate whether different phenotypes affect the pattern of evolution of step time and step length.

We acknowledge several other limitations to this study. Although PRISMA guidelines were adhered to and the methodology was strictly followed, completely accounting for the limitations of included studies is impossible. Because MS patients present variable symptoms, populations vary across studies. Similar to a recent meta-analysis evaluating gait alteration in MS [60], we found that included studies involved mainly individuals with low mean (SD) EDSS score (3.2 [1.5]), which may limit the sensitivity as well as the external validity of the findings. Another limitation lies in the fact that we did not review correlations of gait features with disease severity for various evolution states in a given patient. Therefore, we cannot directly conclude that parameters that we found associated with the EDSS or MSWS score in this review can be used as a severity marker in a given patient. Such assumption would require postulating that individual-based correlations can be interpolated from population-based correlations, which must be verified. For this aim, longitudinal studies only should be included, which seems impossible at this time because of their small number in the literature. Furthermore, articles included in this study were too few to perform a sensitivity analysis on protocols (floor type [ground vs treadmill], sequence of steps [ambulatory vs clinical setting and U-turn vs no U-turn], speed instruction [convenient vs fastest]) on the computed gait features and their correlation with disease severity. The quantitative synthesis of the effect of sensitizing conditions (e.g., fatigue, dual-tasking, eyes-closed walk, narrow-step width, and obstacle negotiation) on the altered gait parameters identified by this review should also be investigated to enhance the assessment and follow up on the treatment of gait in individuals with MS. Eventually, the study focused on

general disease severity without evaluating how it would depend on the participant's functional status regarding known impairments such as spasticity, cerebellar status, sensitivity deficit or motor deficiency. Such group analysis would have required more papers and more information per paper. Similarly, we could not assess therapeutic efficiency. Indeed, too little data on treatment interventions are available for now. However; video motion analysis was used for that aim, and both velocity and stride length proved sensitive to change induced by muscular strengthening [61]. Because personalized gait profiles may inform patient-tailored exercise programs [62,63], the use of IMUs should be developed within the framework of precision medicine and evaluated in individual longitudinal follow-up.

Conclusions

IMUs are very simple wearable sensors that are quick and easy to use, which supports their routine use during the medical check-up in people with MS. Simple kinematic IMU parameters, such as speed, step length and step duration, can help in following up disease severity in people with MS and low to medium EDSS score (1.0–4.5) and hold great promise as biomarkers of gait severity in MS. With the development of more precise algorithms for gait event detection, more elaborate features exist, which should be tested in more studies to evaluate their potential as biomarkers for the evolution of disease severity in MS. Individual follow-up from long-term prospective studies is also needed to test how these parameters evolve for individuals.

Author contributions. AV conceived the study and the statistical analysis and wrote the manuscript. FQ conceived the study. PPV conceived the study and wrote the manuscript. DR

conceived the study and wrote the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflict of interest. None declared.

FIGURE LEGENDS

Figure 1. Flow of articles included in the systematic review and meta-analysis.

Figure 2. Histogram of results for quality assessment (%).

Figure 3. Funnel plots for correlation of inertial measurement unit (IMU) kinetic parameters with (A) Expanded Disability Status Scale (EDSS) score and (B) Multiple Sclerosis Walking Scale-12 (MSWS) score. Speed (V, in m/s), step length (SteL, in m), step time (SteT, in s), swing time (swT, in % of step time), stance time (stT, in % of step time) and double stance time (dstT, in % of stride time).

Figure 4. Protocols used in (A) all 36 articles included in the systematic review and (B) the 12 articles included in the meta-analysis. Striped green: treadmill walking; dark green: unlevelled surface without U-turn; emerald green: unlevelled surface with U-turn; light green: stand up from a chair and unlevelled surface with U-turn.

Figure 5. Description of sensor placement and types: (A) Sensor position in all 36 articles in the systematic review (left panel) and the 12 articles in the meta-analysis (right panel). Size and numbers in the circles represent the number of studies using the sensors attached to the underlying body parts. Lines joining several circles represent associations of sensors used in studies. The thickness of the lines represents the number of studies using this association. When a sensor was attached to a foot, ankle or thigh unilaterally, we added one study point on the right

side and none on the left side. (B) Sensor brand as a function of frequency in all 36 articles (left panel) and the 12 articles in the meta-analysis (right panel). The size of the term represents the number of studies using this brand and frequency.

Figure 6. Forest plots for correlation of IMU parameters with (A) EDSS score and (B) MSWS score.

Figure 7. Participant meta-analysis for correlation of EDSS score with main kinematic parameters: (A) speed (V), (B) step length (SteL), and (C) step time (SteT). Red lines: linear regression lines.

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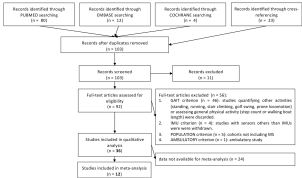
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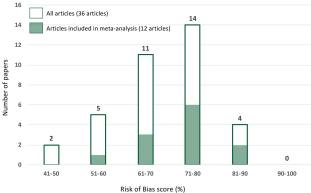
Identification

Screening

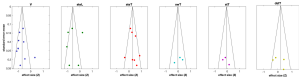
Eligibility

Included

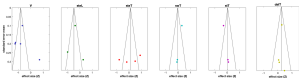


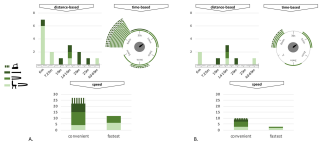


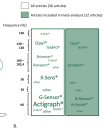
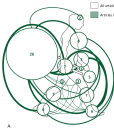
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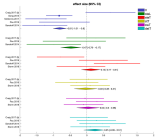
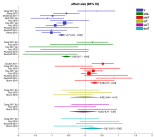


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A.

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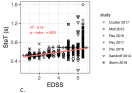


Table 1. Summary of risk of bias scores for included studies.

	REPORTING	EXTERNAL VALIDITY	INTERNAL VALIDITY	POWER	TOTAL SCORE	INCLUSION IN META-ANALYSIS
Braendvik, 2016	100%	25%	67%	40%	70%	no
Coulter, 2017	83%	25%	83%	80%	74%	yes
Craig, 2017 (a)	83%	0%	83%	80%	70%	no
Craig, 2017 (b)	92%	25%	83%	0%	63%	yes
Engelhard, 2016	83%	0%	50%	100%	67%	no
Fanchamps, 2012	83%	25%	50%	0%	52%	no
Fazio, 2013	67%	0%	75%	40%	54%	no
Gong, 2015	100%	25%	67%	60%	73%	yes
Gong, 2016	58%	50%	42%	60%	54%	no
Greene, 2014	82%	25%	80%	20%	60%	no
Greene, 2015	79%	25%	50%	80%	65%	no
Hale, 2007	83%	25%	33%	0%	48%	no
Hilfiker, 2013	82%	25%	80%	0%	56%	no

Huisinga, 2013	75%	25%	67%	0%	52%	no
Huisinga, 2014	83%	25%	83%	80%	74%	no
Lorefice, 2017	75%	25%	67%	100%	70%	no
McGinnis, 2017	82%	25%	50%	60%	62%	yes
Moon, 2015	92%	25%	83%	0%	63%	no
Moon, 2017	92%	25%	83%	100%	81%	no
Motl, 2009	100%	25%	83%	40%	74%	no
Motl, 2011	100%	25%	75%	40%	72%	no
Motl, 2012 (a)	100%	25%	92%	100%	87%	yes
Motl, 2012 (b)	83%	25%	83%	100%	78%	no
Motta, 2016	83%	25%	67%	100%	74%	no
Pau, 2016	79%	25%	75%	100%	74%	yes
Pau, 2018	83%	25%	50%	100%	70%	yes
Pau, 2017 (a)	92%	25%	67%	100%	78%	yes
Pau, 2017 (b)	75%	25%	83%	100%	74%	no
Psarakis, 2018	100%	25%	83%	0%	67%	yes

Qureshi, 2016	32%	25%	75%	60%	44%	no
Sandroff, 2014 (a)	83%	75%	100%	100%	89%	no
Sandroff, 2014 (b)	92%	75%	67%	100%	85%	yes
Spain, 2012	75%	25%	58%	60%	61%	no
Spain, 2014	100%	25%	83%	60%	78%	no
Storm, 2018	75%	25%	67%	0%	52%	yes
Vaney, 2012	64%	50%	80%	100%	72%	yes

“Reporting” assesses the clarity of the reporting (hypothesis, outcomes, protocol, gait analysis, patients’ characteristics, distributions of principal confounders, main findings, random variability in the data and probability values). “External validity” evaluates the generalizability regarding the population and the sensor used. “Internal validity” estimates the suitability of the analysis and outcomes (transparency on data dredging, appropriate statistical tests, accuracy of the outcomes) and the risk of selection bias (same population for all groups, same period for recruitment in all groups, adjustment for confounding). “Power” gauges the power to detect a clinically important effect on the primary outcome of this meta-analysis (power to find a significant correlation between **inertial measurement units** and **Expanded Disability Status Scale** score considering an overall effect of -0.58 as we found in the meta-analysis). For detailed scores item per item, see Supplemental table 1. For the exact description of the items, please refer to the supplemental data published with the protocol [36].

Table 2. Sensor positions used in articles in terms of percentage of total number of studies.

	ALL 36 ARTICLES	12 ARTICLES INCLUDED IN THE META-ANALYSIS
head	5%	0%
sternum	21%	42%
wrist	18%	25%
lower front	3%	0%
lower back	68%	75%
hip	13%	17%
thigh	5%	17%
shank	18%	25%
ankle	16%	17%