Postural control deficits in people with multiple sclerosis: A systematic review and meta-analysis

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Highlights

- People with MS have deficits in postural control compared to healthy controls
- These deficits are considerable regardless of task complexity or sensory condition
- A lack of standardisation of reporting exists for assessment of postural control

Abstract

Background: Multiple sclerosis (MS) is a neurological condition that can affect the postural stability of the individual and predispose falls in this population.

Methods: A systematic literature search identified case-control studies investigating differences in postural control across a diversity of task conditions, with the exception of gait, between people with MS and healthy controls. Meta-analysis was conducted where a variable was presented by four or more studies.

Results: Forty-three studies of people with a mean Expanded Disability Status Scale (EDSS) of 1.0 to 6.0 were included. Seven conditions of assessment and 105 individual measurement variables relating to postural control were included. Quiet stance was the only condition (11 studies) possessing sufficient data to contribute to meta-analysis in terms of centre of pressure path length (SMD=1.04, 95% CI {0.86-1.22}, p<0.001), medio-lateral velocity (SMD=1.35, 95% CI {0.77-1.92}, p<0.001) and 95% confidence ellipse (SMD=0.83 95% CI {0.59-1.08}, p<0.001). Results indicate that regardless of task complexity or sensory condition, people with MS display considerable deficits in postural control in comparison to healthy controls.

Conclusions: The large number of variables and lack of standardisation of reporting makes data synthesis challenging, however, people with MS display considerable deficits in postural control compared to healthy controls regardless of task condition or complexity.

Keywords; Multiple Sclerosis, Accidental Falls, Postural Balance

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory-mediated disease resulting in demyelination of the central nervous system which is often progressive in nature [1]. Currently it is estimated that the global prevalence of MS is 33 per 100,000 with a total of 2.3 million people with MS (pwMS) worldwide and a notably high incidence in young adults [2]. The heterogeneous pathological and clinical presentation of MS predisposes deterioration of motor, sensory and/or cognitive function [3]. Such impairments lead to symptoms such as gait deficits [4], postural instability [5] and predispose falls in this population.

Falls are increasingly being recognised as a significant consequence of MS with 56% of individuals experiencing a fall in any three-month period[6]. Much like the clinical presentation of the disease itself, risk factors for falls in pwMS are diverse [7]. The potential physical [8], psychological [9] and social [10] impact associated with falls in pwMS have led to falls prevention becoming a rapidly developing research area in rehabilitation for pwMS [11].

Postural control is an encompassing term referring to the ability of the body to pre-empt or react to conditions threatening stability and maintain or adjust body position to prevent a fall [12]. Rather than an automatic response, the ability to maintain or change posture is a complex process embodying a diversity of sensorimotor processes [13]. Notably, the disease pathology associated with diseases such as MS predispose postural instability and falls [5]. The identification and quantification of postural control deficiencies in pwMS is pertinent to the development of theory based interventions for falls. A recent meta-analysis quantified the deficits in postural control during gait in pwMS in comparison to healthy counterparts [4], to date no such comparison has been conducted for stationary or reactive postural control

conditions. These forms of postural control are crucial for the maintenance of stability and the prevention of falls across functional and compensatory tasks.

As such, this systematic review and meta-analysis aimed to identify and quantify deficits in postural control across task conditions for pwMS in comparison to healthy controls to inform the development of falls prevention interventions for this population.

Methods

Study Design

This study is a systematic review and meta-analysis of case-control studies. The recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group statement [14] were followed throughout this study to strengthen and standardise the conduct and reporting.

Search Strategy

A literature search was conducted during May 2016 by the primary author (LC) through the following databases; Ebsco (Academic Search Complete, AMED, CINAHL, Medline, PsychArticles, PsychInfo, SportDiscus, Biomedical Reference Collection), Scopus and Web of Science. Suitable keywords and MeSH headings were generated through discussions amongst the study authors and the following were utilised for the search; "multiple sclerosis OR multiple sclerosis sufferers OR multiple sclerosis patients OR adults with multiple sclerosis" AND "balance OR dynamic balance OR postural control OR postural stability OR postural balance OR postural equilibrium OR postural sway OR postural instability OR posturogra* OR somatosensory impairment OR Sensory changes OR dynamic stability OR dynamic control OR postural impairment OR perturbation OR functional activities OR cent*

of mass OR cent* of pressure". The literature search was supplemented by examining reference lists of returned articles and through Google Scholar searches.

Study Identification

Only case-control studies in which an outcome of postural control was investigated in both pwMS and healthy controls were included. To meet the inclusion criteria for this review studies must have identified an examination of postural control between pwMS and healthy controls within their study aims, objectives or hypotheses. Outcomes of interest included examination of postural control during quiet stance, feedback or feedforward activities. No restrictions were placed on year or language of publications. Studies examining postural control during gait, the effects of an intervention or examining a case population other than pwMS were excluded.

The title and abstracts of the retrieved articles were screened for relevance based on the pre-identified criteria for inclusion. Three authors (LC, SC and JS) independently assessed all retrieved full-text articles for inclusion. Where disagreement over eligibility for inclusion of articles occurred, the authors deliberated until a consensus was reached. Study authors were contacted to provide additional information on study status where abstracts were returned without the availability of a full text or in cases where all relevant data was not reported in the article. Where multiple studies contained the same outcomes of interest from the same patient cohorts, only one study was included in this systematic review.

Data Extraction

Information relating to population demographics, assessment apparatus, procedures, outcome variables and units of measurement were extracted and study summary tables generated.. Means and standard deviations for each relevant variable relating to postural control were

extracted. Data relating to variables of interest were extracted based on condition of assessment.

Quality Assessment

Quality of included studies was assessed using the Newcastle Ottawa Scale for case-control studies [15]. This scale possesses three sections, namely; Selection of populations, Comparability of populations and Ascertainment of exposure. Stars are given for each criteria fulfilled with a maximum of four stars for section one, two stars for section two and three stars for section three with a total of nine stars possible across all criteria. Given the checklist nature of the Newcastle Ottawa Scale, the provision of mean scores is not appropriate. Five researchers independently assessed the quality of included studies (LC, SC, RG, GQ, BC). Where disagreement occurred, the three authors deliberated until a consensus was reached.

Statistical Analysis

Where the same variable under the same condition of assessment was presented in four or more studies, statistical analysis to examine differences between pwMS and healthy controls was conducted using the Cochrane Review Manager software (Version 5.3). Standardised mean differences and 95% confidence intervals were employed to examine differences in continuous variables. The SMD expresses the size of the exposure effect in each study relative to the variability observed in that study. The SMD equates to the Hedges' g effect size. In general, ≤ 0.20 is a small effect size, 0.50 is a moderate effect size and ≥ 0.80 is a large effect size [16]. I^2 statistics were examined and where this statistic was found to indicate moderate or substantial heterogeneity (>30%) the authors employed a random-effects modelling approach for meta-analysis in favour of the less conservative fixed-effects modelling approach.

Where standard errors were included by studies, these were converted to standard deviations by multiplying the standard error by the square root of the total sample size per population [17]. Where multiple subgroups of each population were reported (e.g. ataxic or spastic), the means and standard deviations of each subgroup were combined to provide a singular mean and standard deviation through the formulae presented in online Appendix 1 [17].

Results

Study Identification

Figure 1. provides detailed information relating to study identification and selection for inclusion. A total of 31,624 articles were generated through the initial search of relevant databases. Following the removal of duplicates, the titles and abstracts of 23,883 articles were screened for eligibility. The full texts of 153 articles were examined for eligibility by the authors. One hundred and nine studies did not meet the predefined criteria for inclusion. Sandroff et al.[18, 19] reported the same outcome of interest across the same study populations therefore only findings from the former study were included to avoid duplication. As such, 43 studies [18, 20-62] satisfied the eligibility criteria and were included in the systematic review.

Study Characteristics

A detailed summary of included studies is provided in online Appendix 2. The number of pwMS included by studies ranged from eight to 124, with a total of 1271 participants across all studies. The number of healthy controls included by studies ranged from 10 to 45, with a total of 858 participants across all studies. The mean age reported by included studies ranged from 27 to 63 years for pwMS and 26 to 63 years for healthy controls. The ratio of males to

females for the 40 studies reporting data on gender was 1:2.65 for pwMS and 1:2.62 for healthy controls. The mean Expanded Disability Status Scale (EDSS) for participants with MS was reported by 38 studies and ranged from one to six. The mean disease duration of MS ranged from eight to 24 years across the 32 studies who reported this characteristic.

Seven assessment conditions were identified by the authors across the 43 included studies; Quiet stance with eyes open, quiet stance with eyes closed, compliant surface with eyes open, compliant surface with eyes closed, leaning towards limits of stability, perturbed stance and clinical measures. These assessment conditions will be used to guide the reporting of results.

Figure 2. provides details relating to number of studies and variables explored for each assessment condition. Collectively, the 43 included studies examined 105 individual measurement variables relating to postural control.

Thirteen authors were contacted to provide data of whom eight replied and five provided data.

Quality Assessment

A detailed overview of the methodological quality of the included studies is provided in Table 1. The overall methodological quality of the included studies was varied with total scores ranging from three to nine stars out of a possible nine stars. Only one study [18] satisfied the criteria of non-response rate reporting under the exposure category, while only five studies [18, 24, 43, 48, 49] provided adequate information relating to case population selection, highlighting a particular concern regarding the possibility of selection bias.

Meta-analysis

Only the condition of quiet stance possessed sufficient data to enable meta-analysis. Data from eleven studies [18, 20, 24, 25, 37, 39, 45, 48, 49, 54, 59] were meta-analysed for three variables of interest.

COP Path Length

Seven studies[20, 24, 25, 39, 48, 49, 59] examined COP path length between pwMS and healthy control populations in a quiet stance condition. As presented in Figure 3. pwMS (n=393) exhibit significantly longer COP path length than healthy controls (n=209) (FEM, SMD= 1.04, 95% CI {0.86, 1.22}, P<0.001, I^2=25%).

COP Velocity

Four studies[25, 37, 39, 48] examined the velocity of COP in the medio-lateral plane between pwMS (n=165) and healthy controls (n=86). As shown in Figure 4. pwMS exhibited a significantly higher COP velocity than healthy controls in a quiet stance condition (REM, SMD= 1.35, 95% CI {0.77, 1.92}, P<0.001, I^2=60%). There was insufficient data to enable quantitative synthesis of this variable in the anteroposterior plane.

95% Confidence Ellipse

Four studies[18, 45, 48, 54] investigated sway area as indicated by 95% confidence ellipses under a quiet stance condition. As shown in Figure 5. pwMS (n=170) displayed significantly larger 95% confidence ellipses than healthy controls (n=120) (FEM, SMD= 0.83, 95% CI {0.59, 1.08}, P<0.001, I^2=0%).

Narrative Synthesis

Quiet stance

Excluding variables which have been quantitatively synthesised, 22 studies [20, 22, 25, 26, 28, 29, 34, 36, 37, 39, 43, 45, 46, 48, 50-52, 54, 56-58, 62] investigated postural control in a quiet stance condition and collectively examined 43 variables relevant to this review. Across these studies 16 utilised a force platform, three utilised motion capture systems, two used a neurocom balance master and one employed a combination of force plate and motion capture systems.

In terms of COP displacement, the eight studies investigating measurements relating to this variable showed the absolute values of pwMS to have higher raw displacement, larger variability and higher root mean square values in comparison to healthy controls, albeit not all reached statistical significance [20, 26, 28, 29, 34, 37, 48, 51].

A similar trend was seen in terms of COP velocity in which higher raw values, greater standard deviations and higher root mean square measurements were reported by eight studies in terms of absolute values for pwMS, again however some results did not reach statistical significance [25, 29, 34, 37, 45, 48, 52, 54].

Nonlinear measurements of postural sway including approximate entropy, sample entropy, lyapunov exponent, complexity index and power bands were similarly variable in terms of

statistical significance however absolute values consistently indicated greater instability in pwMS compared to healthy controls[20, 22, 34, 37, 39, 46, 52].

Measures including time to contact boundaries [25, 57], loading asymmetry [28, 57], trunk sway [58], centre of gravity measures [36, 50, 62] and sway path [43] were shown to be significantly altered in pwMS in comparison to healthy controls.

Quiet stance with eyes closed

Sixteen studies [22, 25, 29, 34, 36, 37, 39, 43, 45, 46, 48, 56-59, 62] examined postural control during quiet stance with participants' eyes closed, a total of 31 variables were reported for this condition across studies. Ten employed a force platform for assessment while three utilised motion capture systems, two utilised neurocom balance master measures and one used a combination of force plate and motion capture systems

Measurements of COP displacement included raw values in the anteroposterior and mediolateral planes, root mean square and path length. The majority of studies found significantly larger values for pwMS across all measurements of COP displacement in comparison to healthy controls[29, 34, 37, 48, 59].

In terms of COP velocity, data was presented as raw values, root mean square and standard deviation and significant differences were found across all measures indicating higher velocity in pwMS in comparison to healthy controls [29, 37, 39, 45, 48].

Furthermore statistically significant results including lower time to contact boundaries [25, 57], larger COP area [45, 48, 59], larger loading asymmetry [57], greater trunk sway [58], larger centre of gravity movement [36, 62], greater sway acceleration, greater sway jerk [56] and larger sway path [43] were shown in pwMS

Four studies employed nonlinear measures of postural sway during this condition and despite varying in magnitude, pwMS consistently showed results indicative of instability in comparison to healthy controls. These measurements were reoccurrence quantification analysis, complexity index, approximate entropy, lyapunov exponent and frequency bands of power[22, 34, 39, 46].

Compliant surface with eyes open

Four studies [25, 36, 53, 58] investigated participants' control when standing on a compliant surface with eyes open and reported a total of 52 variables. Two studies utilised motion capture systems, one used a force platform and one used a neurocom balance master.

Measures of postural sway during stance on a compliant surface through the use of body worn sensors were shown to be significantly higher in pwMS in comparison to healthy controls were shown in terms trunk measurements [58] and across 15 of 46 variables investigated by Solomon *et al.* [53]. Time to contact boundaries was shown to be significantly shorter in pwMS than healthy controls by Cattaneo *et al.* [25]. Centre of gravity velocity was found to be significantly higher in pwMS by Kanekar and Aruin [36].

Compliant surface with eyes closed

Seven studies [25, 30, 36, 45, 46, 53, 58] examined postural control while standing on a compliant surface with participants' eyes closed with a total of 60 variables being reported across studies. Three studies employed force platforms to assess this condition, two utilised motion capture systems and two used a neurocom balance master.

Measurements of postural sway through the use of body worn sensors was found to be significant higher in pwMS than healthy controls in terms of trunk variables[58] and across 22 of 46 variables assessed by Solomon *et al.* [53]. COP measurements investigated by two

studies utilising force platforms were found to significantly different between groups in terms of a shorter time to contact, higher velocity and larger area cover in pwMS [25, 45]. Centre of gravity velocity was found to be significantly higher in pwMS by two studies [30, 36]. One study employed nonlinear measurements of COP with no significant differences reported between pwMS and healthy controls [46].

Leaning towards limits of stability

Eight studies [22, 29, 33, 35, 36, 38, 41, 57] investigated the condition of leaning towards limits of stability with 16 variables reported. Five studies utilised force platforms to investigate this condition while three utilised the neurocom balance master.

The limits of stability (LOS) test through the use of the neurocom balance master was employed by three studies in this review. Significant differences between pwMS and healthy controls across all measurements with pwMS exhibiting significantly longer reaction times, higher movement velocities and lower endpoint excursion, maximum excursion and directional control values [33, 36, 41].

Measurements relating to COP displacement and velocity were shown to be significantly altered in pwMS compared to healthy controls by the majority of studies investigating variables relating to these measurements [29, 35, 38, 57]. In terms of nonlinear measures, only Busa *et al.* [22] adopted such a measurement approach and noted pwMS to have a significantly lower COP complexity index than healthy controls. These findings were similar irrespective of direction of lean employed.

Perturbed Stance

In terms of perturbed stance, ten studies investigating 22 variables were included by this review. Of these, seven studies utilised an external form of perturbation including load

releasing [40, 60], surface oscillation or translation [23, 31, 35, 47] and pendulum impact [21]. The remaining three studies investigated perturbed stance through participant generated means of arm movement [27], bending from the mid-section [26] or rapid shoulder movements [41]. One study solely investigated electromyography (EMG) activity while five studies utilised force platform data and four utilised motion capture measurements.

Significant differences were reported in terms of COP and COM displacement measures with pwMS exhibiting larger displacements following perturbation across the majority of included studies [35, 41, 47, 60] while similarities were shown in terms of capacity for postural adaptation [31]. Furthermore Cattaneo *et al.* [26] found pwMS to have significantly greater sway during perturbation and to take a significantly longer time than healthy controls to restore normative sway following. Altered EMG activity was reported across all studies investigating these variables representing deficits in anticipatory and compensatory postural responses to perturbations in pwMS [21, 23, 27, 40, 41, 60].

Clinical Measures

Nine studies [25, 32, 33, 36, 38, 42, 44, 55, 62]included in this review utilised a clinical measure of postural control. These measures included the Berg balance test [25, 33, 36, 38, 62], functional reach [32, 42, 55], adaptation test [62], pastor test [32, 55], physiological profile assessment [44] and duration of time able to hold steady stance [32, 55], tandem stance [32, 55], and stride stance [32, 55]. The majority of studies presented significantly poorer results in pwMS in comparison to healthy controls across these clinical measures of postural control.

Discussion

This systematic review and meta-analysis aimed to identify and quantify the effects of MS on postural control. The methodological quality of the 43 included studies was varied. The key findings of this research highlight that, irrespective of sensory state or task complexity, pwMS display large deficits in postural control compared to their healthy counterparts. Despite relative homogeneity between studies in terms of apparatus, conditions and protocols, the diversity of measurement variables reported by included studies limited quantitative synthesis and restricted definitive conclusions being drawn.

A total of 105 variables relating to postural control were examined across the included studies, the majority using posturography. Advancements in posturography have been valuable in enabling reliable and objective assessments of postural control [63]; however, these advancements have added a significant difficulty with a seemingly infinite number of measurement variables at the disposal of the researcher with little agreement surrounding the key outcomes for extraction [64]. This review highlights the necessity of the development of a core measurement set for postural control. Such development would greatly facilitate the identification of elements of postural control that are reliable for the identification of fallers and potential focuses for rehabilitation.

Our findings highlight that during static, challenged and reactive conditions of postural control, pwMS display considerable deficits in comparison to healthy controls. The presence of such deficits in the ability to maintain posture within a controlled lab-based assessment will be further heightened when placed in a real world environment when the necessity of navigating novel environments and increased cognitive load is presented [65]. This suggests that a wide range of balance conditions, possessing real-world challenges, should be incorporated into interventions to improve balance for pwMS.

The identification of whether such deficits in postural control are protective or predictive of falls in pwMS is an important consideration in terms of assessment and intervention for falls in this population. A recent systematic review and meta-analysis examining the diagnostic accuracy of clinical balance measures suggests differences between fallers and non-fallers but poor predictive validity of measures overall [66]. Interestingly, Prosperini *et al.* [48] highlight COP path length during quiet stance to have acceptable diagnostic accuracy in terms of future falls for pwMS, with longer COP path length associated with falls. These data suggest that instrumented tests of postural control show promise and may be associated with and predictive of falling in people with MS. A number of prospective cohort studies confirm this and suggest that postural sway, particularly with a visual challenge or when leaning towards limits of stability, to be predictive of future falls in pwMS [67-69].

The findings have a number of clinical and research implications. Firstly, the deficits in postural control in pwMS compared to their healthy counterparts are considerable despite the relatively low EDSS and young age of participants within the included studies. This finding highlights the importance of early assessment and intervention for balance dysfunction in MS. Secondly, the deficits in postural control across all task conditions investigated by this review adds further weight to the position that falls within this population are likely multifaceted in nature with pwMS experiencing difficulty with the majority of postural demands. As such, both balance assessment and intervention for falls prevention in pwMS should be treated with an individualised approach with interventions targeting deficits identified from a comprehensive assessment to a suitably challenging degree [70]. In terms of research implications, the heterogeneity of measurements relating to postural control for pwMS highlights a considerable lack of standardisation. Such lack of consistency requires addressment particularly for the strength of future replication studies.

The results should be interpreted with consideration of this review's strengths and limitations. This is the first systematic review to explore deficits in postural control in pwMS compared to healthy controls. The MOOSE guidelines [14] were followed throughout the conduct and reporting of this study. Furthermore, the identification of relevant studies and the methodological quality of the included studies was conducted based on pre-established criteria and checklists with the authors blinded from each other's responses until deliberation was performed. However, the heterogeneity of measurements within the included studies limit definitive conclusions through the use of a quantitative synthesis and further the relatively low EDSS levels investigated by the included studies may further limit the generalisability of the findings of this review overall.

In terms of future research, there is a need to identify a core set of variables relating to postural control. An agreement of such a core set would strengthen and enhance the synthesis of future research relating to postural control in MS. The exploration of postural control deficits in pwMS with higher EDSS and more advanced disease is needed, particularly given the associations between such factors and a higher risk of falls [7]. Finally, there is a need to further explore the relationship between postural control deficits and the likelihood of falls in pwMS. The identification of deficits and the detection of whether these deficits are protective or predictive of falls is imperative to the development of future falls prevention interventions for this population. Furthermore, such investigations should be conducted using prospective falls monitoring methods [71].

Conclusion

PwMS display considerable deficits in postural control compared to healthy controls regardless of task condition or complexity. A significant lack of standardisation exists

regarding the reporting of variables measuring postural control for pwMS and there is a timely need for agreement in terms of core measurements for extraction and reporting.

Conflict of Interest

The authors declare no conflict of interest.

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Figure 1. Flow diagram of search results and identification of relevant studies

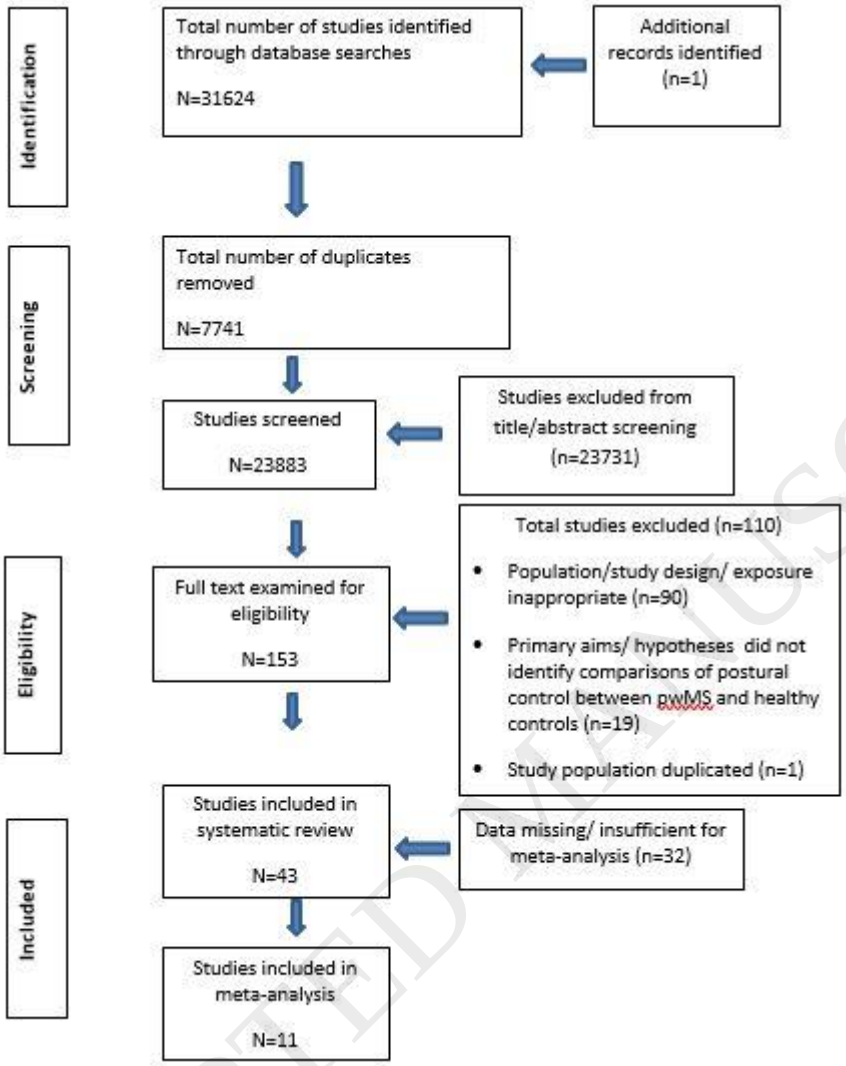

Figure 2. Flow diagram of number of studies and measurement variables per task condition assessed

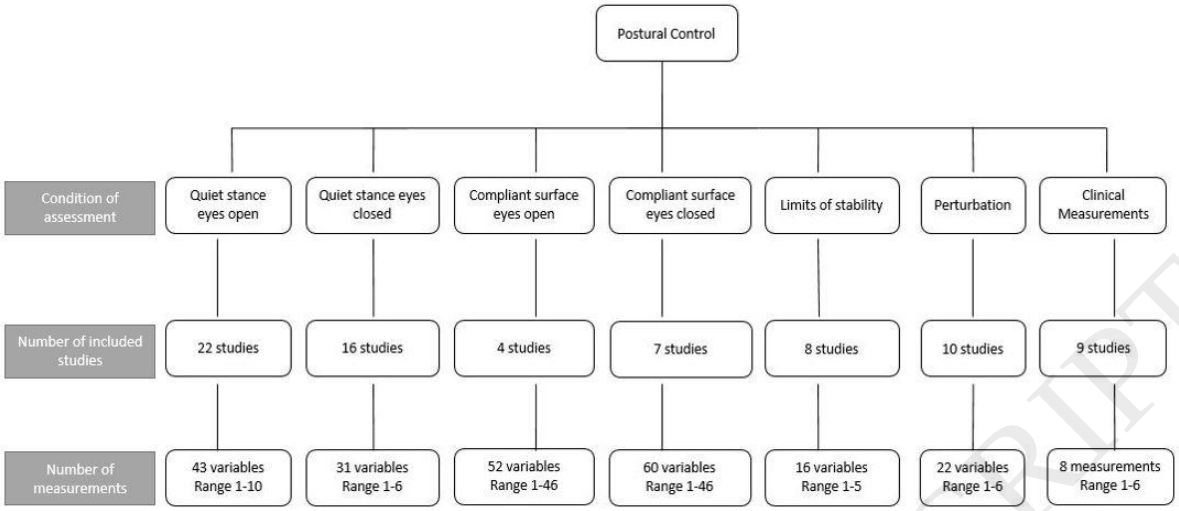

Figure 3. Standardised mean difference in COP path length

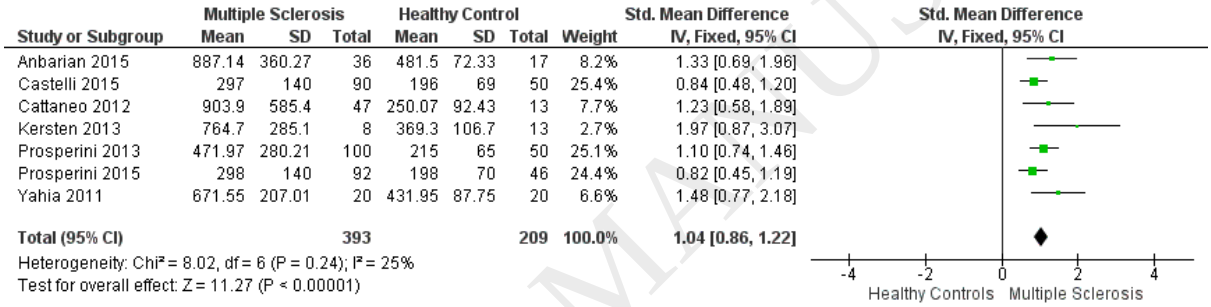

Figure 4. Standardised mean difference in COP velocity in the mediolateral plane

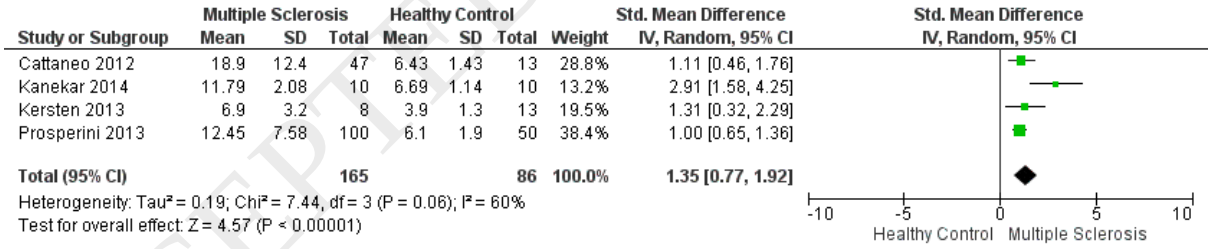

Figure 5. Standardised mean difference in 95% confidence ellipse

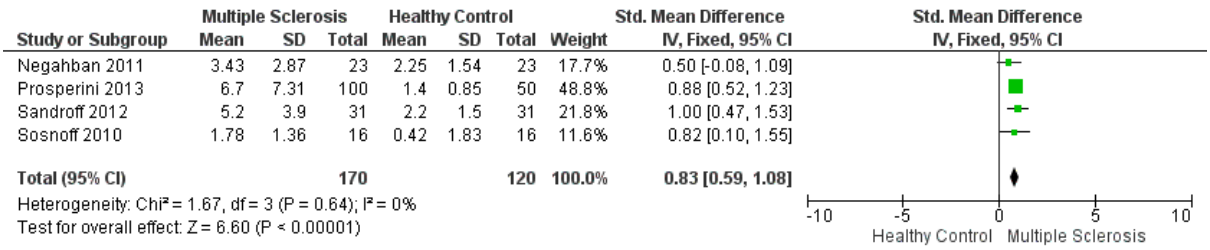

Table 1

	Selection				Comparability		Exposure			Total
	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 1	Criteria 2	Criteria 1	Criteria 2	Criteria 3	
Anbarian 2015	*		*	*			*	*		5
Aruin 2015	*			*	*		*	*		5
Busa 2016	*				*	*	*	*		5
Cameron 2008	*			*	*		*	*		5
Castelli 2015	*	*		*	*	*	*	*		7
Cattaneo 2011	*			*			*	*		4
Cattaneo 2014	*			*			*	*		4
Chua 2014				*			*	*		3
Chung 2008	*		*	*	*	*	*	*		7
Denommé 2014	*			*			*	*		4
Fjeldstad 2009	*		*	*		*	*	*		6
Fjeldstad 2011	*		*	*			*	*		5
Fling 2015	*		*	*			*	*		5
Frzovic 2000	*				*		*	*		4
Ganesan 2015	*			*	*	*	*	*		6
Huisinga 2012	*		*	*		*	*	*		6

Jacobs 2012	*			*	*	*	*	*		6
Kanekar 2013	*			*	*	*	*	*		6
Kanekar 2014	*			*	*		*	*		5
Karst 2005	*		*	*	*		*			5
Kersten 2013	*		*	*			*	*		5
Krishnan 2012	*			*	*		*	*		5
Krishnan 2012 (b)	*			*	*		*	*		5
Martin 2006	*		*	*	*		*	*		6
Mehravar 2013	*			*	*	*	*	*		6
McLoughlin 2015	*	*	*		*	*	*	*		7
Moon 2015	*		*	*	*		*	*		6
Negahban 2011	*			*	*	*	*	*		6
Negahban 2013	*			*	*	*	*	*		6
Peterson 2016	*		*	*		*	*	*		6
Prosperini 2013	*	*	*	*	*		*	*		7
Prosperini 2015	*	*	*	*	*	*	*	*		8
Rougier 2007				*			*	*		3
Sandroff 2012	*	*	*	*	*	*	*	*	*	9
Shin 2011	*			*	*		*	*		5
Skurvydas 2014	*		*	*			*	*		5
Soloman 2015	*			*	*		*	*		5

Sosnoff 2010	*			*	*		*	*		5
Soyeur 2006	*			*	*	*	*	*		6
Spain 2012	*		*	*	*		*	*		6
Van Emmerik 2010	*			*	*	*	*	*		6
Wolfsegger 2013	*			*			*	*		4
Yahia 2011	*		*	*	*		*	*		6