Correlates of dual-task performance in people with Multiple Sclerosis: a systematic review

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Abstract

Background: Gait, balance, and cognitive disorders are common in people with Multiple Sclerosis (MS). In addition, people with MS have impaired ability to concurrently perform gait/balance and cognitive tasks due to cognitive-motor interference (CMI). Clinical features of MS may affect CMI; however, the relationship between CMI and clinical features of MS remains unclear.

Research Question: Are clinical features of MS associated with CMI?

Methods: A systematic review was conducted, and four databases (CINAHL, MEDLINE, ProQuest, and Web of Science) were searched up to March 2019 using a combination of keywords related to MS and dual-tasking/CMI. Cross-sectional or longitudinal studies that reported the association between CMI and clinical features of MS were included in the review. The correlation coefficient for the relationship between CMI and clinical features of MS were extracted and the results were categorized according to the clinical feature measured.

Results: 13 studies were included in this review, of which nine investigated the association between CMI and disability and cognition, and four investigated the association between CMI and other clinical features of MS. While some studies reported that disability and cognition were negatively associated with CMI, the evidence was inconsistent regarding the magnitude and presence of these relationships. In addition, the relationship between CMI and other clinical features (balance, falls risk, fatigue, anxiety, depression, pain, spasticity) remains unclear.

Significance: This review presents evidence from a small number of studies that suggests disability and cognition are negatively associated with CMI in people with MS, indicating that greater disability and cognitive dysfunction may be associated with lower dual-task performance. These findings highlight the potential importance of disability and cognition in the measurement and rehabilitation of people with dual-task impairments. However, further research is required to confirm these findings and determine the relationship between CMI and other clinical features of MS.

Key words: Multiple Sclerosis; dual-tasking; cognitive-motor interference; clinical features; gait; cognition

Introduction

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system that is characterised by brain volume loss, impaired nerve conduction, and dysfunction of neural pathways [1]. Consequently, cognitive and motor impairments are common in people with MS, with up to 65% demonstrating signs of impaired cognition [2]. Similarly people with MS demonstrate a decline in gait velocity and walking performance [3-6] and a reduction in balance [7-9] compared to healthy controls, which is indicative of motor impairment.

The performance of motor tasks such as gait and balance is complex and requires the integration of higher-level cognitive input in order to plan, control, and modulate movement [10]. Accordingly, the execution of safe and efficient functional movement requires the ability to concurrently perform motor and/or cognitive tasks, which is referred to as dual-tasking [10,11]. A decrement in motor and/or cognitive task performance whilst simultaneously undertaking another task is defined as cognitive-motor interference (CMI) and can be quantified through calculating dual-task cost (DTC) – that is the difference when comparing single and dual task performance on a specified outcome relative to single task performance [12]. CMI can lead to balance and gait disturbances and increase the risk of falling, which limits physical function and the ability to perform activities of daily living [11].

People with MS have impaired ability to integrate cognitive and motor tasks, as previous systematic reviews have reported that simultaneous performance of motor and cognitive tasks in patients with MS caused a significant decrease in gait speed, changes to kinematic parameters of gait, and increase in postural sway compared to single task performance alone [12-14]. In addition, some studies report that people with MS demonstrate a larger magnitude of CMI (i.e. a larger reduction in dual-task performance) in comparison to healthy controls; although this finding is not consistently reported as some studies report no difference in CMI between people with MS and healthy controls [14]. However, while the presence and magnitude of CMI has been established in MS populations, it remains unclear which, if any, clinical features (for example, disability, cognition, and fatigue) are associated with dual-task performance.

Investigating the relationship between CMI and clinical features of MS is important for understanding the mechanisms underlying dual-task performance and determining appropriate rehabilitation strategies. For example, although the mechanisms underlying CMI are unknown, it is thought that motor impairments may increase the cognitive demands required to execute functional movements, and the simultaneous performance of tasks may exceed cognitive processing capacity [15]. In addition, the presence of cognitive impairments may reduce the processing capacity required for the completion of dual-tasks [16]. Therefore, the severity of motor and/or cognitive impairment may influence the magnitude of CMI. Furthermore, other clinical features, such as fatigue, are associated with both cognitive and motor outcomes [17-19], and may also influence dual-task performance. Accordingly, this systematic review aims to investigate the association between CMI and clinical features of MS.

Methods

Eligibility criteria

The following criteria were used to screen studies for eligibility: 1) observational studies (with either a cross-sectional or prospective design) or randomised controlled trials; 2) include adult participants with a diagnosis of MS; 3) require participants to concurrently perform a standardised motor task (e.g. walking, balance, or upper-limb tasks) and cognitive task; 4) objectively measure DTC; 5) report the association between DTC and a clinical feature of MS using baseline values. Only full-text articles published in English were included in this review.

Search strategy

In line with the protocol registered on the PROSPERO database (number: CRD42019130177), the following four databases were searched from inception to August 2019: CINAHL (via EBSCOhost), MEDLINE (via Ovid), ProQuest (Health & Medical Collection, Nursing & Allied Health Database, ProQuest Central, PsychInfo) and Web of Science Core Collections. Search strategies included keywords related to MS and dual-tasking/CMI (Supplementary table 1). In addition, reference lists of included articles were hand searched to identify any additional articles.

Study selection

All articles identified through database searching were exported to Covidence systematic review software, and duplicates were removed prior to screening. Titles and abstracts were initially screened against the eligibility criteria by one reviewer (CO). Subsequently, two reviewers (CO, SR) independently screened full texts of the remaining articles for eligibility, and disagreements were resolved through consensus in consultation with a third reviewer if required (LP).

Quality assessment

The Joanna Briggs Institute Appraisal Checklist for Analytical Cross-sectional Studies (2017) was used to assess the methodological quality of all included studies. Quality assessment was completed independently by two reviewers (SR, LP), and a third reviewer (CO) was consulted to resolve any discrepancies that arose.

Data extraction

Data extraction was completed independently by one reviewer (CO) and verified by another (SR). Study details (author, year of publication, study design), participant demographics (total number, age, gender, EDSS, MS-type), the outcome measure used to assess clinical features of MS, the motor and cognitive task, and measure of DTC were extracted from each study. Motor tasks were classified as walking, balance, or upper-limb tasks according to the original description of the task by the study authors. Cognitive tasks were classified as mental tracking, verbal fluency, discrimination and decision making, or working memory tasks according to the definitions reported in a previous systematic review [20]. The correlation coefficient relating to the association between DTC and clinical features of MS at baseline was also extracted. When studies reported multiple outcomes related to DTC (e.g. different spatiotemporal parameters of gait), individual correlation coefficients were extracted for each outcome.

Data synthesis

The results of all studies were analysed by narrative synthesis. Results were grouped according to the clinical feature measured, and the association between DTC and each clinical feature was compared to other studies which reported the same clinical feature to determine the consistency of the results. In addition, results were compared across studies that used different measures to assess DTC. The association between DTC and each clinical feature was determined using the correlation coefficients and was classified by direction and statistical significance. Correlation coefficients <0.3 were interpreted as a weak association, ≥ 0.3 to <0.7 as a moderate association, and ≥ 0.7 as a strong association [21]. Confidence intervals were calculated for each correlation coefficient in order to determine the reliability of the results.

Results

From searching the electronic databases 555 articles were identified after removing duplicates, of which 492 were excluded during title and abstract screening (Figure 1). The full-texts of 63 articles were assessed and 50 were excluded because the correlation between DTC and clinical features of MS was not reported (n=29), DTC was not objectively defined (n=11), a standardised motor task was not included (n=4), outcome measures of clinical features were not included (n=2), the study included a non-MS sample (n=2), or the study did not include a dual-task (n=2). Therefore, 13 articles were included in this systematic review [22-34] (Table 1). Of these articles, all reported the results of cross-sectional analyses – four of which used baseline data collected from on-going intervention trials for increasing physical activity [27], improving cognition [30], and preventing falls [33,34].

Figure 1 near here

Table 1 near here

Participants

A total of 669 participants were included in the studies in this review, and sample sizes ranged from 13 to 96. Participants were mostly female (74%) and had relapsing-remitting MS (79%), and the mean age of participants ranged from 39.0 to 61.6 years. All studies used the Expanded Disability Status Scale to measure disability, with mean and median scores ranging from 2.4 to 2.7 and 2.5 to 6.0 respectively indicating that most participants had mild to moderate disability and did not require a walking aid.

Dual-task protocol

Motor tasks

Of the studies included in this review, nine used walking tasks to measure motor performance during dual-task conditions [23-27,30,31,32,34]. Walking tasks mainly involved walking at a self-selected pace over instrumented walkways (between distances of 4.6-16m [23, 25-27,31,32,34] or for a duration of 90s [24]); however, one study used the timed 25-ft walk test (T25FWT) as a measure of walking performance [30]. The remaining four studies used balance tasks to measure motor performance [22,28,29,33].

Cognitive tasks

The cognitive tasks used in the studies in this review included: mental tracking (n=6) [22,23,25,26,30,34], verbal fluency (n=4) [27,31-33], working memory (n=2) [22,24], and discrimination and decision making tasks (n=2) [28,29].

Quantification of dual-task cost

Most studies included in this review quantified DTC according to the percentage change in task performance between single and dual-task conditions using the equation: DTC=100*(single task performance – dual-task performance)/single task performance) [22-25, 27, 31-34]. Although four studies quantified DTC using a different equation: DTC=100*(dual-task performance – single-task performance)/single task performance) [26, 28-30]. Accordingly, the direction of DTC in relation to CMI varied between studies depending on the equation used.

All studies used a motor task performance outcome to quantify DTC, and only four quantified DTC using both motor and cognitive task performance outcomes [22-24,34]. The most commonly used motor performance outcome to quantify DTC was the difference in gait velocity between single and dual-task conditions [23-27,30,31,32,34]. Five studies also defined DTC using other spatiotemporal parameters of gait such as cadence, double-limb support time, swing time, and step length [24-27,32], whereas four studies used the difference in net postural sway between single and dual-task conditions during balance tasks to quantify DTC [22,28,29,33]. Studies that defined DTC using a cognitive outcome measure reported the difference in accuracy on mental tracking and working memory tasks between single and dual task conditions [22-24,34].

Study quality

The total number of items on the Joanna Briggs Institute Appraisal Checklist that were adequately addressed by studies ranged from 4-6 (Table 2). Only six studies adequately reported the study subjects and setting in detail [22,24,26,28,29,31], whereas five described the criteria used to confirm MS diagnosis [22-25,28]. Only one study identified and adjusted for confounding variables, as the study by Wajda et al. [34] controlled for EDSS and education level in the statistical analysis.

Table 2 near here

Association between dual-task cost and clinical features of MS

Disability

Nine studies investigated the association between DTC and disability (measured by EDSS and self-reported EDSS) (Table 3). Of these studies, Motl et al. [27] reported that self-reported EDSS was weakly associated with DTC quantified by gait velocity (r = 0.249, p<0.05) and step length (r = 0.238, p<0.01) while performing a verbal fluency task, indicating that higher levels of disability were associated with a greater decrement in gait velocity and step length whilst dual-tasking. In addition, Butchard-MacDonald et al. [22] reported that EDSS was weak-moderately correlated with DTC when measured using postural sway on an unstable surface on a Biodex unit whilst performing a working memory and mental tracking task (r = 0.360, p = 0.036), suggesting that higher levels of disability are associated with reduced balance performance in dual-task conditions. However, the study by Butchard-Macdonald et al. [22] reported wide confidence intervals for each correlation coefficient and did not find any association between disability and other DTC outcomes. Furthermore, all remaining studies reported that disability was not significantly associated with DTC measured using walking [24-26], balance [28,29,33], or cognitive outcomes [22,23]. Therefore the relationship between DTC and disability is unclear.

Table 3 near here

Cognition

Nine studies reported the association between DTC and cognition (Table 3), using the Symbol Digits Modalities Test (SDMT) [27,28,30,31,33], Montreal Cognitive Assessment (MoCA) [23,25], Addenbrooke's Cognitive Examination [22], MS Neuropsychological Screening Questionnaire [30], and the Stroop test [29]. Cognition was found to be significantly associated with DTC measured by spatiotemporal parameters of gait in the study by Motl et al. [27], as a weak-moderate correlation was reported between SDMT scores and DTC of gait velocity (r = -0.315, p<0.01) and step length (r = -0.371, p<0.01) when performing a verbal fluency task. In addition, Prosperini et al. [28] reported that SDMT scores were weakly correlated with DTC of postural sway measured when performing static standing and a discrimination and decision making task (r = -0.241, p = 0.021). Therefore, these studies suggest that lower levels of cognitive function are associated with greater decrements in motor performance (walking and balance) during dual-tasks. However, although Kirkland et al. [25] reported a moderate correlation between MoCA scores and DTC of double limb support time when performing a mental tracking task (r = 0.54, p <0.05), no significant association was reported between cognition and DTC of other spatiotemporal parameters of gait. Furthermore, the remaining studies reported no association between cognition and DTC of walking [30,31] and balance [22,29]. Accordingly, due to the inconsistent findings and heterogeneous methods used by studies, the relationship between cognition and DTC is unclear as it is unknown whether specific cognitive domains are only associated with DTC under specific dual-task conditions.

Mobility

Mobility was measured in five studies using the Timed 25-ft Walk Test (T25FWT) [28,31], gait velocity [23,25], and the 6-Minute Walk Test (6MWT) [27]. Of these studies, Motl et al. [27] reported a significant association between mobility (6MWT) and DTC measured by gait velocity ($r = -0.411$, $p<0.01$) and step length ($r = -0.450$, $p<0.01$) when performing a verbal fluency task (Table 3). Additionally, Sosnoff et al. reported a weak significant association between T25FWT and DTC of gait velocity while also performing a verbal fluency task ($r = 0.27$, $p<0.005$) [31]. Therefore, these studies suggest that reduced levels of mobility may be associated with increased dual-tasking impairments. However, as all other studies reported no association between measures of mobility and DTC measured using walking [25], balance [28], and cognitive outcomes [23], the relationship between DTC and mobility is unclear.

Balance and falls risk

Balance was assessed by three studies in this review using the Berg Balance Scale [33], postural sway [29], and the Activities-specific Balance Confidence Scale [33,34]. Only the study by Wajda et al. [34] reported a significant moderate association between balance and DTC of cognitive (mental tracking task) performance ($r = -0.651$, $p<0.01$), whereas the other two studies reported no association between DTC and objectively measured balance outcomes [29,33] (Table 3). In addition, two studies investigated the association between falls risk (assessed by the Physiological Profile Assessment) and DTC [32,33]. The study by Wajda et al. [32] reported that falls risk was moderately associated with decrements in gait velocity ($r = 0.39$, $p = 0.03$) and stride length ($r = 0.39$, $p =0.03$) in dual-task conditions when performing a verbal fluency task, whereas the study by Wajda et al. [33] reported no association between falls risk and DTC of balance when also performing a verbal fluency task.

Fatigue

Four studies reported the association between DTC and fatigue, which was measured using the Modified Fatigue Impact Scale [22,28,33] and Fatigue Severity Scale [27]. Fatigue was not found to be significantly associated with DTC when measured using walking [27], balance [22,28,33], or cognitive outcomes [22] (Table 3). Of these studies, two reported a non-significant weak association between MFIS and decrements in balance when performing a working memory and mental tracking task ($r = 0.273$, $p>0.05$) [22] and verbal fluency task ($r = 0.24$, $p>0.05$) [33], whereas the other two studies reported no association between fatigue and DTC [27,28].

Anxiety and depression

Anxiety and depression was measured in two studies using the Hospital Anxiety and Depression Scale (HADS) [22,27]. Butchard-MacDonald et al. [22] found that both HADS anxiety and depression subscales were moderately correlated with DTC of postural sway when standing on a stable surface and performing working memory and mental tracking task ($r = 0.527$, $p<0.001$ and $r = 0.451$, $p = 0.007$ respectively) (Table 3). Conversely, Motl et al. [27] reported that neither anxiety nor depression were associated with changes in spatiotemporal gait parameters while performing a verbal fluency task. Although due to differences in the motor/cognitive tasks performed and methods used to quantify DTC, it is unclear whether variance in study design influenced the magnitude of the relationship between DTC and anxiety/depression.

Dual-tasking

The study by Wajda et al. [34] investigated whether concurrent decrements in walking and cognitive performance whilst dual-tasking were associated; however this study reported no association between these outcomes (Table 3). In addition, the study by Butchard-MacDonald et al. [22] reported that self-reported dual-task ability was not significantly associated with either DTC when measured using balance or cognitive outcome measures.

Pain and spasticity

The study by Motl et al. [27] investigated the association between McGill Pain Questionnaire scores and DTC of walking while performing a verbal fluency task, and another study by Wajda et al. [33] investigated the association between spasticity (measured using the Modified Ashworth scale) and DTC of balance while performing a verbal fluency task. Neither study reported a significant association between these outcomes [27,33] (Table 3).

Discussion

This systematic review identified 13 studies which investigated the association between DTC and clinical features of MS. Although some studies reported that disability and cognition may be weak-moderately associated with DTC in MS populations, the relationship between these variables is complex as the overall evidence was inconsistent regarding the presence and magnitude of any association with several studies reporting no significant associations with DTC. Therefore, it remains unclear whether these outcomes and other clinical features (including balance, falls risk, fatigue, anxiety, depression, pain, and spasticity) are indeed associated with DTC in MS populations.

Two of the nine studies that investigated the association between DTC and disability reported that DTC demonstrated a weak-moderate positive correlation with disability when DTC was measured using walking and balance tasks [22,27]. This evidence suggests that people with higher levels of disability may demonstrate greater decrements in walking and balance performance during dual-task conditions. However, the findings from studies included in this review were inconsistent with many studies reporting non-significant associations between DTC and disability. Therefore, it remains unclear whether DTC and disability are indeed associated in people with MS, and further research is required to understand the relationship between these variables to inform the assessment and management of dual-task impairments.

Of the studies to investigate the association between DTC and disability, all used EDSS which mainly quantifies disability according to walking performance [35]. However, it remains unclear whether other walking related outcome measures (such as 6MWT, T25FWT, and gait velocity) are associated DTC, with only two of the five studies identified by this review reporting a significant association between mobility outcomes and DTC. The inconsistent relationship between DTC and disability/mobility measures may be related to the studies in this review mostly including participants with low levels of walking impairments, as less cognitive demand may be required to perform mobility tasks in people with minimal levels of disability [15]. Furthermore, the variability in dual-task protocols and quantification of DTC may have also influenced the strength of the reported correlations. For example, the cognitive task performed while dual-tasking may influence the magnitude of change in walking/balance performance depending upon the attentional demand of each task [36]; therefore, studies that selected cognitive tasks with greater attentional demands may report larger decrements in dual-task performance. Similarly, motor tasks with greater complexity (e.g. dynamic walking tasks compared to static standing tasks) may also increase the magnitude of DTC due to varying levels of motor and/or cognitive demand. As no combinations of motor/cognitive tasks were found to be consistently associated with the clinical features included in this review, further research is required to determine the influence of motor and cognitive task selection on DTC as this may moderate the relationship between CMI and clinical features of MS.

Due to the cross-sectional nature of the studies included in this review, the direction of causality between DTC and disability/mobility is unclear. However, the possible relationship between these variables is likely to be bi-directional as a greater magnitude of CMI (indicated through greater DTC) may lead to disability/mobility impairment due to the important role of dual-tasking during every-day functional tasks [10,11]; conversely, greater levels of disability and mobility impairment may cause CMI in people with MS. The possible association between disability and CMI may be explained by the capacity sharing model which proposes that cognitive capacity is limited and when the performance of two or more tasks exceeds the available cognitive capacity then CMI will occur [36]. Consequently, as mobility impairments increase the cognitive (attentional) demands required to execute motor tasks [15], the simultaneous performance of cognitive and motor tasks may exceed cognitive processing capacity in those with higher levels of disability. However, further research is required to determine if disability is associated with DTC and whether it is a causal mechanism of CMI in people with MS.

In addition to disability, the relationship between dual-task performance and cognitive function has also been investigated in MS populations. DTC was reported to be moderately correlated with cognition in four studies [23,25,27,28], with the direction of correlation indicating that greater levels of cognitive impairment were associated with greater DTC on walking, balance, and cognitive outcomes. Similar findings have also been reported in other progressive neurological conditions such as Alzheimer's disease and Parkinson's disease [37,38]. The relationship between DTC and cognition may also be explained by the capacity sharing model of CMI, with cognitive dysfunction limiting the available processing capacity required to execute dual-tasks [16,36]. However, as the relationship between DTC and cognition was inconsistent in MS populations, further research is required to investigate the strength and direction of association between these variables. Perhaps the inconsistent findings reported in this review could be related to the variance in cognitive domains that were assessed, as five different cognitive outcome measures were used across the nine studies – although no outcome measure was found to be consistently associated with DTC. In addition, there was significant heterogeneity in the dual-task protocols used which may influence the magnitude of CMI and resultant association with cognition depending on the motor and cognitive task selected [36].

Although DTC has been demonstrated to predict falls in older adults [39,40], only two studies included in this review investigated the association between DTC and falls risk, and falls risk was found to be moderately correlated only when DTC was measured using a walking and verbal fluency task [32] – no association was found when DTC was measured using a balance and verbal fluency task [33]. As walking tasks place a greater demand on the postural control system compared to static standing balance tasks [41], changes in walking performance may be more sensitive to falls risk and may explain the association between DTC of walking and falls risk. Indeed, previous studies have demonstrated that dual-task related detriments in walking performance (e.g. decrease in gait speed and stride length) can distinguish between fallers and non-fallers among stroke survivors [42,43] and older adults [39,40]. However, due to the limited available evidence identified through this review, further research is required to investigate the association between these outcomes and determine whether falls are associated with CMI in MS populations.

As this review identified a limited number of studies which investigated the association between DTC and other clinical features of MS (fatigue, pain, spasticity, anxiety and depression), it is not possible to reach any conclusions regarding the relationship between these variables. Understanding the relationship between DTC and outcomes such as fatigue may hold significance for the management of CMI, as fatigue is related to both physical [18] and cognitive function [17] and could consequently influence dual-task performance. In addition, as those with greater depression have often have higher levels of cognitive impairment [44,45], and a higher level of spasticity is associated with greater mobility and physical dysfunction [46], the association between these variables should be explored in future research.

Limitations of the evidence

There are several important limitations that should be considered when interpreting the findings of this review. Firstly, there was significant heterogeneity in dual-task protocols and the methods used to measure DTC, as six different combinations of motor and cognitive tasks were used by the 13 included studies. This limited the interpretation of the evidence as it was not possible to perform a meta-analysis, and it remains unclear whether the selection of dual-task methods influenced the direction and magnitude of the reported correlation coefficients. In addition, most studies only quantified DTC using one outcome measure (i.e. one of the dual tasks) which does not truly reflects DTC – for example, if the dual task situation consists of concurrent motor and cognitive task then decrement in both tasks should be measured. [36]. Therefore, standardised methods of defining and measuring DTC should be used and reported by future studies when investigating dual-task performance in MS to improve the interpretation of findings. Secondly, few studies considered the influence of confounding variables when analysing the association between DTC and clinical features; as a result, it is unclear whether the clinical features investigated were independently associated with DTC or whether other clinical features of MS moderated the reported relationships. Furthermore, multiple correlations coefficients were reported by some studies for a single clinical feature, which introduces the chance of type I errors in the results. Lastly, due to the cross-sectional design of the studies included in this review, the direction of causality cannot be inferred from the results.

Conclusions

This systematic review highlights that, in a small number of studies, DTC is associated with disability, mobility, and cognition in people with MS, which suggests that higher levels of disability/mobility impairment and cognitive dysfunction may be associated with greater decrements in dual-task performance. However, this evidence is inconsistent and limited by the small number of studies and heterogeneity in the methods used to measure DTC. Furthermore, there is a lack of evidence investigating the association between DTC and other clinical features of MS such as fatigue and falls risk. Therefore, it remains unclear whether clinical features of MS are indeed associated with DTC. Accordingly, further research is required to investigate the association between DTC and clinical features of MS to inform the assessment and management of CMI and elucidate potential mechanisms influencing dual-task performance in people with MS.

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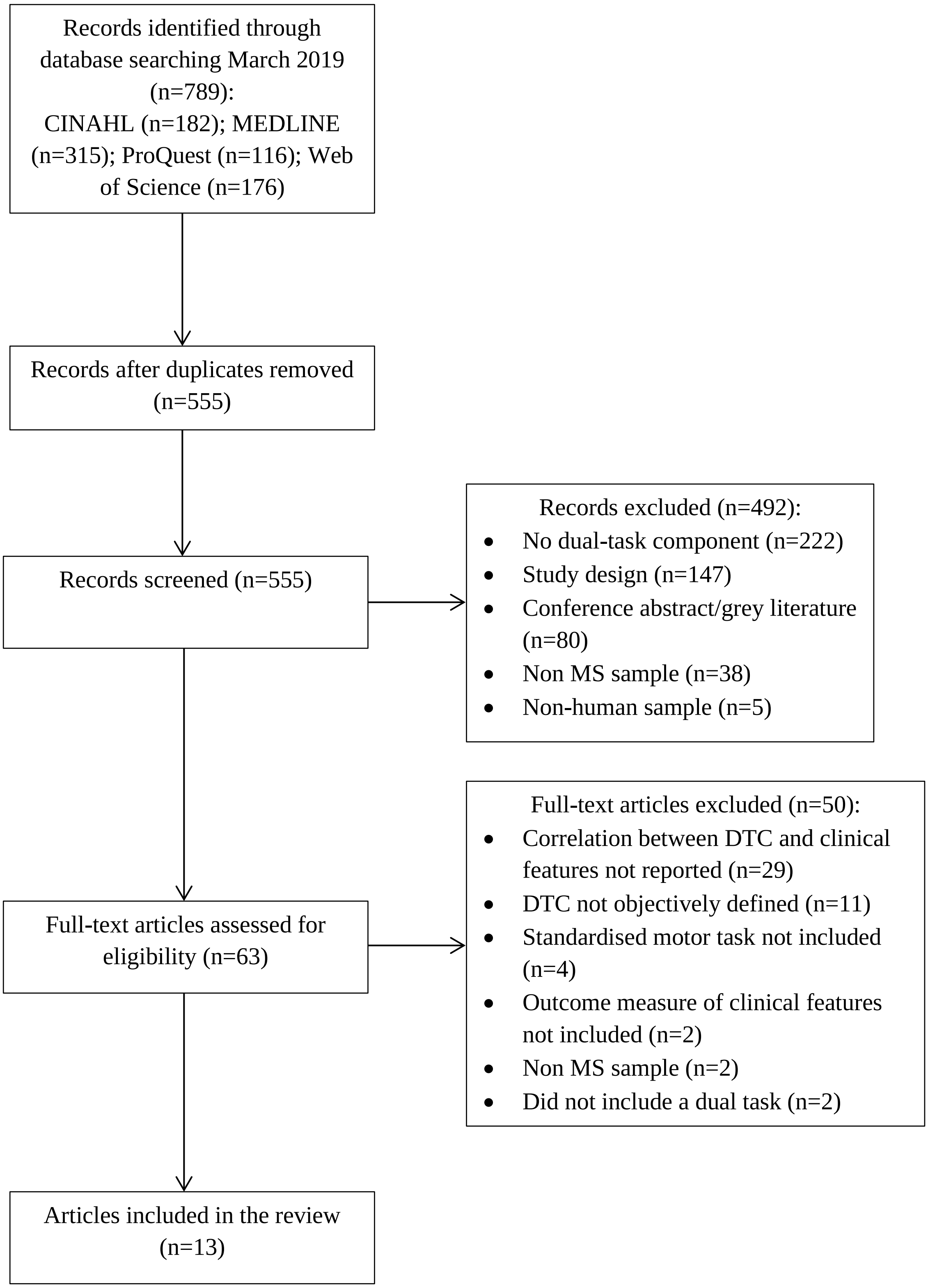

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

Table 1 Characteristics and results of included studies

Author, date, study design	**Participant demographics**	**Dual-task protocol**	**Secondary outcomes (clinical features)**
Butchard-MacDonald et al., 2018 [22] Cross-sectional	N = 34 (28 F/6 M) MS type: 100% RRMS Age (mean ± SD) = 43.1 ± 9.9 years EDSS (median (IQR)) = 4.0 (1.0) Disease duration: NR	Motor task *Domain*: Balance *Task*: Static standing on stable and unstable surfaces *Measurement*: Force platform analysis (BioSway, Biodex, USA) *DTC outcome:* Net postural sway Cognitive task *Domain*: Working memory; mental tracking *Task*: Reciting number sequences in reverse *DTC outcome:* Correct answers	Self-reported dual-tasking (DTQ), fatigue (MFIS), cognition (ACE-III), anxiety and depression (HADS), disability (EDSS)
Downer et al., 2016 [23] Cross-sectional	N = 13 (9 F/4 M) MS type: NR Age (mean ± SD): 43.9 ± 12.9 years EDSS (mean ± SD): 2.4 ± 2.5 Disease duration (mean ± SD) = 7.2 ± 8.0 years	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis (pressure sensitive walkway, Protokinetics Inc., USA) *DTC outcome:* Gait velocity (cm/s) Cognitive task *Domain*: Mental tracking *Task*: Serial-7 subtraction *DTC outcome:* Correct answers	Cognition (MoCA), disability (EDSS), gait velocity (cm/s)
Hamilton et al., 2009 [24] Cross-	N = 18 (16 F/2 M) MS type: 100% RRMS Age (mean ± SD) = 39.2 ± 8.2 years	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed for 90s	Disability (EDSS)

sectional	EDSS (mean ± SD) = 2.7 ± 1.6 Disease duration (median (95% CI)): 4 (1-7) years	*Measurement:* Spatiotemporal gait analysis (GAITRite System, CIR Systems Inc., USA) *DTC outcome:* gait velocity (cm/s); swing time (% gait cycle); double-limb support time (% gait cycle) Cognitive task *Domain*: Working memory *Task*: Titrated and fixed demand digit sequence recall *DTC outcome:* Correct answers	
Kirkland et al., 2015 [25] Cross-sectional	N = 20 (13 F/7 M) MS type: 75% RRMS, 25% SPMS Age: NR EDSS (range) = 0-6.5 Disease duration: NR	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis *(*16 m walkway, Protokinetics Inc., USA) *DTC outcome:* stride length (cm); stride width (cm); double-limb support time (% gait cycle); gait velocity (cm/s); cadence (steps/min) Cognitive task *Domain*: Mental tracking *Task*: Serial-7 subtraction; reciting alternate letters of the alphabet; reciting numbers beginning with 1 excluding those that contain number 3 or multiples of 3 *DTC outcome:* NR	Cognition (MoCA), disability (EDSS), gait velocity (cm/s)
Learmonth et al., 2014 [26] Cross-sectional	N = 61 (46 F/15 M) MS type: 77% RRMS, 13% SPMS, 10% PPMS Age (mean ± SD) = 50.8 ± 9.3 years EDSS (median (IQR)) = 4.0 (2.8). Disease duration (mean ± SD) = 12.4 ± 7.6 years	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis (GAITRite System, CIR Systems Inc., USA) *DTC outcome:* gait velocity (cm/s); cadence (steps/min); step time (s); step length (cm); swing time (% gait cycle); double-limb support time (% gait cycle)	Disability (EDSS)

		<u>Cognitive task</u> *Domain*: Mental tracking *Task*: Reciting alternate letters of alphabet *DTC outcome:* NR	
Motl et al., 2014 [27] Cross-sectional	N = 82 (63 F/19 M) MS type: 80% RRMS, 11% SPMS, 9% PPMS Age (mean ± SD) = 49.4 ± 9.1 years EDSS (median (IQR)) = 3.5 (3.0) Disease duration (mean ± SD) = 11.6 ± 8.2 years	<u>Motor task</u> *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis (GAITRite System, CIR Systems Inc., USA) *DTC outcome:* gait velocity (cm/s); cadence (steps/min); step length (cm) <u>Cognitive task</u> *Domain*: Verbal fluency *Task*: Word generation *DTC outcome:* NR	Mobility (6MWT), cognition (SDMT), fatigue (FSS), depression and anxiety (HADS), pain (SF-MPQ), disability (SR-EDSS)
Prosperini et al., 2015 [28] Cross-sectional	N = 92 (60 F/32 M) MS type: 73% RRMS, 27% Age (mean ± SD) = 39.0 ± 10.0 years EDSS (median (range)) = 2.5 (1-6) Disease duration (mean ± SD) = 11.8 ± 8.1 years	<u>Motor task</u> *Domain*: Balance *Task*: Static standing *Measurement:* Force platform analysis (ProKin, Tecnobody, Italy) *DTC outcome:* Net displacement of COP (mm) <u>Cognitive task</u> *Domain*: Discrimination and decision making *Task*: Stroop word-colour task *DTC outcome:* NR	Disability (EDSS), mobility (T25FWT), mobility (MSWS-12), fatigue (MFIS), cognition (SDMT)

Ruggieri et al., 2018 [29] Cross-sectional	N = 96 (64 F/32 M) MS type: NR Age (mean ± SD) = 41.8 ± 10.6 years EDSS (median (range)) = 3.0 (1-6) Disease duration (mean ± SD) = 13.3 ± 7.9 years	<u>Motor task</u> *Domain*: Balance *Task*: Static standing *Measurement:* Force platform analysis (ProKin, Tecnobody, Italy) *DTC outcome:* Postural sway (Net displacement of COP (mm)) <u>Cognitive task</u> *Domain*: Discrimination and decision making *Task*: Stroop word-colour task *DTC outcome:* NR	Disability (EDSS), cognition, (Stroop test), balance (postural sway)
Sandroff et al., 2015 [30] Cross-sectional	N = 28 (26 F/ 2 M) MS type:100% RRMS Age (mean ± SD): 44.0 ± 7.8 years EDSS (median (range)) = 3.0 (2-6) Disease duration (mean ± SD) = 10.0 ± 8.6 years	<u>Motor task</u> *Domain*: Walking *Task*: T25FWT *DTC outcome:* gait velocity (ft/s) <u>Cognitive task</u> *Domain*: Mental tracking *Task*: reciting alternate letters of the alphabet *DTC outcome:* NR	Cognition (SDMT & MSNSQ)

Sosnoff et al., 2014 [31] Cross-sectional	N = 96 (gender: NR) MS type: NR Age (mean ± SD) = 52.7±11.2 years EDSS (median (range)) = 4.5 (2-6.5) Disease duration: NR	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis (GAITRite System, CIR Systems Inc., USA) *DTC outcome:* gait velocity (units NR) Cognitive task *Domain*: Verbal fluency *Task*: Word generation *DTC outcome:* NR	Mobility (T25FWT), cognition (SDMT)
Wajda et al., 2013 [32] Cross-sectional	N = 33 (28 F/5 M) MS type: 70% RRMS, 15% SPMS, 15% PPMS Age (mean ± SD) = 60 ± 6.1 years EDSS (median (range)) = 6.0 (1-6) Disease duration (mean ± SD) = 15.9 ±9.1 years	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis (GAITRite System, CIR Systems Inc., USA) *DTC outcome:* gait velocity (cm/s); cadence (steps/min); stride length (cm) Cognitive task *Domain*: Verbal fluency *Task*: Word generation *DTC outcome:* NR	Fall risk (PPA)

Wajda et al., 2014 [33] Cross-sectional	N = 62 (46 F/16 M) MS type: NR Age (mean ± SD) = 60.9 ± 7.2 years EDSS (median (range)): 6.0 (1-7) Disease duration: NR	Motor task *Domain*: Balance *Task*: Static standing *Measurement:* Force platform analysis *DTC outcome:* Net displacement of COP (mm) Cognitive task *Domain*: Verbal fluency *Task*: Word generation *DTC outcome:* NR	Disability (SR-EDSS), falls risk (PPA), balance (Berg balance scale), fatigue (MFIS), cognition (SDMT), balance confidence (ABC), spasticity (Modified Ashworth scale)
Wajda et al., 2016 [34] Cross-sectional	N = 34 (24 F/10 M) MS type: 61% RRMS, 24% SPMS, 15% PPMS Age (mean ± SD) = 61.6 ± 8.7 years EDSS (median (IQR)) = 6.0 (2) Disease duration (mean ± SD) = 16.6 ± 8.3 years	Motor task *Domain*: Walking *Task*: Steady-state walking at self-selected speed *Measurement:* Spatiotemporal gait analysis (Zeno walkway, Protokinetics Inc., USA) *DTC outcome:* gait velocity (cm/s) Cognitive task *Domain*: Mental tracking *Task*: reciting alternate letters of the alphabet *DTC outcome:* Composite score of accuracy and frequency	DTC motor (% change in gait velocity), DTC cognitive (% change in composite score), balance confidence (ABC)

*Correlation coefficient not reported

Abbreviations: ABC, Activities-specific Balance Confidence scale; ACE-III, Addenbrooke's Cognitive Examination; COP, Centre of pressure; DTC, Dual-task cost; DTQ, Dual-Tasking Questionnaire; EDSS, Expanded Disability Status Scale; F, Female; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; M, Male; MFIS, Modified Fatigue Impact Scale; MoCA, Montreal Cognitive Assessment; MS, Multiple Sclerosis; NR, Not reported; PPA, Physiological Profile Assessment; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; SDMT, Symbol Digit Modalities Test; SF-MPQ: short-form, McGill Pain Questionnaire; SPMS, Secondary Progressive Multiple Sclerosis; SR-EDSS, self-reported Expanded Disability Status Scale; 6MWT, 6-minute walk test; T25FWT timed 25-ft walk test

Table 2 Joanna Briggs Institute Appraisal Checklist for Analytical Cross-sectional Studies

Study	1. Were the criteria for inclusion in the sample clearly defined?	2. Were the study subjects and the setting described in detail?	3. Was the exposure measured in a valid and reliable way?	4. Were objective, standard criteria used for measurement of the condition?	5. Were confounding factors identified?	6. Were strategies to deal with confounding factors stated?	7. Were the outcomes measured in a valid and reliable way?	8. Was appropriate statistical analysis used?
Butchard-MacDonald et al., 2018 (22)	Y	Y	Y	Y	N	N	Y	Y
Downer et al., 2016 [23]	Y	U	Y	Y	N	N	Y	Y
Hamilton et al., 2009 [24]	Y	Y	Y	Y	N	N	Y	Y
Kirkland et al., 2015 [25]	Y	N	Y	Y	N	N	U	Y
Learmonth et al., 2014 [26]	Y	Y	Y	U	N	N	Y	Y
Motl et al., 2014 [27]	Y	N	Y	U	N	N	Y	Y
Prosperini et al., 2015 [28]	Y	Y	Y	Y	N	N	U	Y
Ruggieri et al., 2018 [29]	Y	Y	Y	U	N	N	Y	Y
Sandroff et al., 2015 [30]	Y	N	Y	U	N	N	Y	Y
Sosnoff et al., 2014 [31]	Y	Y	Y	U	N	N	Y	Y
Wajda et al., 2013 [32]	Y	U	Y	U	N	N	Y	Y
Wajda et al., 2014 [33]	Y	N	Y	U	N	N	Y	Y
Wajda et al., 2016 [34]	Y	N	Y	U	Y	Y	Y	Y

Table 3 Results for each study presented according to the clinical feature measured

Clinical feature	Study	DTC outcome	Correlation coefficient (95% CI), p value
Disability (n=9)	Butchard-MacDonald et al., 2018 [22]	Balance (net postural sway - stable task)	-0.05 (-0.380, 0.295), p=0.789
		Balance (net postural sway - unstable task)	**0.360 (0.024, 0.622), p=0.036**
		Cognition (stable task)	-0.133 (-0.451, 0.215), p=0.455
		Cognition (unstable task)	0.256 (-0.090, 0.547), p=0.144
	Downer et al., 2013 [23]	Cognition	NR, p>0.05
	Hamilton et al., 2009 [24]	Walking (gait velocity)	0.008 (-0.461, 0.473), p=0.280
		Walking (swing time)	NR, p>0.05
		Walking (double-limb support time)	NR, p>0.05
	Kirkland et al., 2015 [25]	Walking (gait velocity)	NR, p>0.05
		Walking (cadence)	NR, p>0.05
		Walking (stride length)	NR, p>0.05
		Walking (stride width)	NR, p>0.05
		Walking (double-limb support time)	NR, p>0.05
	Learmonth et al., 2014 [26]	Walking (gait velocity)	-0.006 (-0.246, 0.257), p>0.05
		Walking (cadence)	0.024 (-0.229, 0.274), p>0.05
		Walking (step length)	0.032 (-0.222, 0.282), p >0.05
		Walking (step time)	-0.030 (-0.280, 0.224), p>0.05
		Walking (swing time)	-0.047 (-0.295, 0.207), p>0.05
		Walking (double-limb support time)	-0.116 (-0.357, 0.140), p>0.05
	Motl et al., 2014 [27]	Walking (gait velocity)	**0.249 (0.034, 0.442), p<0.05**
		Walking (cadence)	0.076 (-0.143, 0.288), p>0.05
		Walking (step length)	**0.283 (0.070, 0.471), p<0.01**
	Prosperini et al., 2015 [28]	Balance (net postural sway)	0.010 (-0.195, 0.214), p=0.926
	Ruggieri et al., 2018 [29]	Balance (net postural sway)	-0.130 (-0.322, 0.073), p>0.05
	Wajda et al., 2014 [33]	Balance (net postural sway)	0.030 (-0.221, 0.278), p>0.05
Cognition (n=9)	Butchard-MacDonald et al., 2018 [22]	Balance (net postural sway - stable task)	0.126 (-0.222, 0.445), p=0.478
		Balance (net postural sway - unstable task)	0.093 (-0.253, 0.418), p=0.600
		Cognition (stable task)	0.121 (-0.227, 0.441), p=0.494
		Cognition (unstable task)	-0.092 (-0.417, 0.254), p=0.606
	Downer et al., 2013 [23]	Cognition	**0.580 (0.042, 0.857), p=0.04**
	Kirkland et al., 2015 [25]	Walking (gait velocity)	NR, p>0.05
		Walking (cadence)	NR, p>0.05

		Walking (stride length)	NR, p>0.05
		Walking (stride width)	NR, p>0.05
		Walking (double-limb support time)	**0.540 (0.100, 0.782), p<0.05**
	Motl et al., 2014 [27]	Walking (gait velocity)	**-0.315 (-0.498, -0.105), p<0.01**
		Walking (cadence)	-0.100 (-0.310, 0.120), p>0.05
		Walking (step length)	**-0.371 (-0.544, -0.167), p<0.01**
	Prosperini et al., 2015 [28]	Balance (net postural sway)	**-0.241 (-0.425, -0.038), p=0.021**
	Ruggieri et al., 2018 [29]	Balance (net postural sway)	0.060 (-0.142, 0.257), p>0.05
	Sandroff et al., 2015 (SDMT) [30]	Walking (gait velocity)	-0.102 (-0.458, 0.282), p>0.05
	Sandroff et al., 2015 (MSNSQ) [30]	Walking (gait velocity)	-0.074 (-0.435, 0.308), p>0.05
	Sosnoff et al., 2014 [31]	Walking (gait velocity)	0.010 (-0.191, 0.210), p>0.05
	Wajda et al., 2014 [33]	Balance (net postural sway)	0.240 (-0.011, 0.462), p>0.05
Mobility (n=5)	Downer et al., 2013 [23]	Cognition	NR, p>0.05
	Kirkland et al., 2015 [25]	Walking (gait velocity)	NR, p>0.05
		Walking (cadence)	NR, p>0.05
		Walking (stride length)	NR, p>0.05
		Walking (stride width)	NR, p>0.05
		Walking (double-limb support time)	NR, p>0.05
	Motl et al., 2014 [27]	Walking (gait velocity)	**-0.411 (-0.576, -0.213), p<0.01**
		Walking (cadence)	-0.150 (-0.355, 0.069), p>0.05
		Walking (step length)	**-0.450 (-0.607, -0.258), p<0.01**
	Prosperini et al., 2015 (T25FWT) [28]	Balance (net postural sway)	-0.118 (-0.315, 0.089), p=0.261
	Prosperini et al., 2015 (MSWS) [28]	Balance (net postural sway)	-0.006 (-0.211 to 0.199), p=0.958
	Sosnoff et al., 2014 [31]	Walking (gait velocity)	**0.27 (0.073 to 0.446), p<0.05**
Fatigue (n=4)	Butchard-MacDonald et al., 2018 [22]	Balance (net postural sway - stable task)	0.273 (-0.072, 0.559), p=0.118
		Balance (net postural sway - unstable task)	0.148 (-0.200, 0.463), p=0.403
		Cognition (stable task)	-0.088 (-0.414, 0.258), p=0.619
		Cognition (unstable task)	0.151 (-0.197, 0.465), p=0.394
	Motl et al., 2014 [27]	Walking (gait velocity)	0.091 (-0.129, 0.302), p>0.05
		Walking (cadence)	0.012 (-0.206, 0.228), p>0.05
		Walking (step length)	0.109 (-0.111, 0.318), p>0.05
	Prosperini et al., 2015 [28]	Balance (net postural sway)	0.050 (-0.156, 0.252), p=0.638
	Wajda et al., 2014 [33]	Balance (net postural sway)	0.240 (-0.011, 0.462), p>0.05
Balance (n=3)	Ruggieri et al., 2018 [29]	Balance (net postural sway)	0.170 (-0.032, 0.358), p>0.05

	Wajda et al., 2014 (Berg balance scale) [33]	Balance (net postural sway)	-0.080 (-0.276, 0.123), p>0.05
	Wajda et al., 2014 (ABC) [33]	Balance (net postural sway)	-0.160 (-0.349, 0.042), p>0.05
	Wajda et al., 2016 [34]	Walking (gait velocity)	-0.165 (-0.476, 0.184), p>0.05
		Cognition	-0.651 (-0.810, -0.400), p<0.01
Falls risk (n=2)	Wajda et al., 2013 [32]	Walking (gait velocity)	**0.390 (0.05, 0.646), p=0.03**
		Walking (cadence)	-0.305 (-0.587, 0.043), p=0.08
		Walking (stride length)	**0.390 (0.05, 0.646), p=0.03**
	Wajda et al., 2014 [33]	Balance (net postural sway)	0.040 (-0.212, 0.287), p>0.05
Anxiety (n=2)	Butchard-MacDonald et al., 2018 [22]	Balance (net postural sway - stable task)	**0.527 (0.229, 0.734), p<0.001**
		Balance (net postural sway - unstable task)	0.089 (-0.257, 0.415), p = 0.617
		Cognition (stable task)	-0.083 (-0.410, 0.263), p = 0.641
		Cognition (unstable task)	0.174 (-0.175, 0.484), p = 0.326
	Motl et al., 2014 [27]	Walking (gait velocity)	-0.112 (-0.321, 0.108), p>0.05
		Walking (cadence)	-0.117 (-0.326, 0.103), p>0.05
		Walking (step length)	0.073 (-0.146, 0.285), p>0.05
Depression (n=2)	Butchard-MacDonald et al., 2018 [22]	Balance (net postural sway - stable task)	**0.451 (0.133, 0.684), p=0.007**
		Balance (net postural sway - unstable task)	0.342 (0.004, 0.609), p=0.168
		Cognition (stable task)	-0.184 (-0.491, 0.165), p=0.296
		Cognition (unstable task)	0.220 (-0.128, 0.519), p=0.211
	Motl et al., 2014 [27]	Walking (gait velocity)	0.103 (-0.117, 0.313), p>0.05
		Walking (cadence)	0.100 (-0.120, 0.310), p>0.05
		Walking (step length)	0.040 (-0.179, 0.255), p>0.05
Dual-tasking (n=2)	Butchard-MacDonald et al., 2018 [22]	Balance (net postural sway - stable task)	0.106 (-0.241, 0.429), p=0.552
		Balance (net postural sway - unstable task)	0.247 (-0.100, 0.540), p=0.160
		Cognition (stable task)	-0.164 (-0.476, 0.185), p=0.335
		Cognition (unstable task)	0.194 (-0.155, 0.499), p=0.271
	Wajda et al., 2016 [34]	Walking (gait velocity)	0.236 (-0.111, 0.532), p>0.05
Pain (n=1)	Motl et al., 2014 [27]	Walking (gait velocity)	0.100 (-0.120, 0.310), p>0.05
		Walking (cadence)	0.088 (-0.132, 0.299), p>0.05
		Walking (step length)	0.062 (-0.157, 0.275), p>0.05
Spasticity (n=1)	Wajda et al., 2014 [33]	Balance (net postural sway)	-0.130 (-0.368, 0.124), p>0.05

Abbreviations: ABC, Activities-specific Balance Confidence scale; DTC, Dual-task cost; MSNSQ, Multiple Sclerosis Neuropsychological Screening Questionnaire; MSWS, Multiple Sclerosis Walking Scale; SDMT, Symbol Digits Modalities Test; T25FWT, Timed 25ft walk test

Supplementary table 1 Search strategy for the selected electronic databases

Database	Search Strategy
CINAHL (n=182) Medline (n=315) ProQuest (n=116)	"Multiple Sclerosis" AND (("dual task*" or "cognitive motor interference" or "motor cognitive interference") OR (("walking" or "gait" or "gait disorders" or "mobility" or "locomotion" or "balance" or "postur* control" or "postur* stability" or "postural sway" or "posture") AND ("cognition" or "cognitive function" or "executive function" or "mental tracking" or "memory" or "verbal fluency" or "mental function")))
Web of Science (n=176)	"Multiple Sclerosis" AND ("dual task*" OR "cognitive motor interference" OR "motor cognitive interference")