

**Energetics of walking in individuals with cerebral palsy and typical development, across severity and age: A systematic review and meta-analysis**

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## **Abstract**

### **Background**

Individuals with cerebral palsy (CP) report physical fatigue as a main cause of limitation, deterioration and eventually cessation of their walking ability. A consequence of higher level of fatigue in individuals with CP leads to a less efficient and long-distance walking ability.

### **Research question**

This systematic review investigates the difference in 1) walking energy expenditure between individuals with CP and age-matched typically developing (TD) individuals; and 2) energetics of walking across Gross Motor Function Classification System (GMFCS) levels and age.

### **Methods**

Five electronic databases (PubMed, Web of Science, CINAHL, ScienceDirect and Scopus) were searched using search terms related to CP and energetics of walking.

### **Results**

Forty-one studies met inclusion criteria. Thirty-one studies compared energy expenditure between CP and age-matched controls. Twelve studies correlated energy expenditure and oxygen cost across GMFCS levels. Three studies investigated the walking efficiency across different ages or over a time period. A significant increase of energy expenditure and oxygen cost was found in individuals with CP compared to TD age-matched individuals, with a strong relationship across GMFCS levels.

### **Significance**

Despite significant differences between individuals with CP compared to TD peers, variability in methods and testing protocols may play a confounding role. Analysis suggests oxygen cost being the preferred/unbiased physiological parameter to assess walking efficacy in CP. To date, there is a

1 knowledge gap on age-related changes of walking efficiency across GMFCS levels and wider span  
2 of age ranges. Further systematic research looking at longitudinal age-related changes of energetics  
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4 of walking in this population is warranted.  
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9 **Keywords:** Cerebral palsy, walking, energetics, oxygen cost, oxygen consumption  
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## Introduction

Cerebral Palsy (CP) is a non-progressive neurological disorder caused by a perinatal injury occurring in 2.0-3.5 per 1000 live births [1]. It is the most common cause of physical disability in children and primarily affects movement capacity. Individuals with CP have varying degrees of movement limitations depending on the type and level of severity and the affected brain area(s) [2]. Based on the Gross Motor Function Classification System (GMFCS), children with CP can be independently ambulatory (I, II), ambulatory with assistive devices (III), minimally ambulatory (IV) or predominantly use wheelchairs for mobility (V) [3]. Spastic CP is the most common subtype (~80% of cases) [4], characterized by spasticity, muscle weakness and impaired selective motor control, all of which affecting the gait pattern and walking ability [5,6]. Muscles in children with CP also have a significant increase in extracellular matrix (ECM), measured via collagen content [7–9], histologically [10] and transcriptionally [11–13]. Reduced levels of daily physical activity in CP are associated with higher perceived fatigue [5]. Individuals with CP report physical fatigue as one of the main causes of limitation, deterioration and eventually cessation of their walking ability [5,14]. Studies involving functional tasks – such as walking and bimanual movements – showed increased selective muscle fatigue [15,16] and augmented external mechanical work [17]. Importantly, ambulatory children with CP, show reduced daily walking activity levels compared to typically developing (TD) children [18,19].

Walking capacity in individuals with CP often emerges as a multifaceted interplay of impairments at the neuromuscular, cardiorespiratory, and musculoskeletal systems [6,20,21]. Gross motor function in children with CP measured by the Gross Motor Function Measure (GMFM) [22,23] show changes in functional mobility over time, especially for the more severely impaired [24,25]. While GMFCS is normally stable for ambulatory children, those who are dependent on the use of assistive devices show a more pronounced loss of their ambulatory capacity [24,25]. Adults with CP have a reduction in walking capacity, with many studies reporting decline starting in their 20s and 30s [26]. In addition, age-related physiological changes occur earlier in adults with CP, and the

1 prevalence of secondary manifestations (e.g., pain, osteoporosis, and musculoskeletal problems) is  
2 higher in adults with CP compared to age-matched healthy adults [27–29]. Age-related changes in  
3 motor function and in gait proficiency is therefore an important clinical marker to monitor physical  
4 capabilities of the individual with CP over the years from childhood to adulthood. However, a broad  
5 assessment of the relationship between walking efficiency, functional levels, and the natural  
6 progression of ambulatory ability across the lifespan for individuals with CP is still poorly  
7 understood.

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17 Assessment of oxygen uptake ( $\dot{V}O_2$ ) during submaximal exercise is a convenient and  
18 objective measure to determine walking efficiency in CP and evaluate changes after therapeutic  
19 interventions [30–33]. In addition, the measurement of energy expenditure while walking can provide  
20 a quantitative measure to evaluate differences between individuals with CP and age-matched TD  
21 individuals as well as to determine effective therapeutic interventions. Currently, a systematic  
22 approach primarily focused on studies that investigated energy expenditure by measuring  $\dot{V}O_2$  during  
23 walking in population with spastic CP is lacking. Therefore, a comprehensive examination would  
24 further the understanding of the degree of impairment in walking energetics in individuals with  
25 spastic CP compared to age-matched TD individuals. Given the strong relationship between walking  
26 ability and GMFCS levels, it is also clinically relevant to summarize to what extent walking energy  
27 expenditure is related to GMFCS levels, and define the magnitude of change of energy expenditure  
28 across GMFCS levels.

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46 In summary, the aims of this systematic review were to identify, appraise and synthesize the  
47 evidence describing 1) the difference in energy expenditure in walking between individuals with CP  
48 and age-matched TD; 2) the relationship between  $\dot{V}O_2$  and GMFCS levels; and 3) age-related changes  
49 in walking energy expenditure over time in individuals with CP. Findings will provide further insights  
50 into the extent of walking ability and its proficiency in individuals with spastic CP, and outline key  
51 evidence gaps for development of future research.

## Methods

This systematic review was completed following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 statement [34] (S1). The protocol was registered on Prospero (ID: CRD42020146657) [35], where a complete description of the methodology and the complete list of searched terms, the searching process, and data extraction method is available.

### Search strategy

Relevant articles were identified by searching PubMed, Web of Science, CINAHL, ScienceDirect and Scopus databases using search terms related to the target population (*cerebral palsy*) and outcomes related to energetics (*fatigue; energy metabolism; metabolic cost; energy cost;  $\dot{V}O_2$ ; endurance; energy expenditure; aerobic capacity; oxygen consumption*). The full electronic search strategy used for PubMed was as follows: (((((((((((cerebral palsy[MeSH Terms]) OR (cerebral palsy[Title/Abstract])) AND (fatigue[MeSH Terms])) OR (fatigue[Title/Abstract])) OR (energy metabolism[MeSH Terms])) OR (energy metabolism[Title/Abstract])) OR (metabolic cost[Title/Abstract])) OR (energy cost[Title/Abstract])) OR ( $\dot{V}O_2$ [Title/Abstract])) OR (endurance[Title/Abstract])) OR (energy expenditure[Title/Abstract])) OR (aerobic capacity[Title/Abstract])) OR (oxygen consumption[Title/Abstract]). Search strategies for other databases is available in the supplementary material (S2). Two academic librarians were consulted to verify the codes used for the search terms. Studies published between January 1<sup>st</sup>, 1970 and November 30<sup>th</sup>, 2019 were selected. Additional manuscripts were sought through cross referencing.

### Study selection

Three authors (MN, FR, MB) independently searched through the databases and reviewed the titles and abstracts to remove articles that did not meet inclusion criteria. The following inclusion criteria were used: (1) walking tests (either over-ground or on the treadmill), (2) direct measures of physiological energy expenditure or energy cost (no estimation), (3) group comparisons – either CP

1 and TD, CP across GMFCS levels or CP across different age groups. Exclusion criteria were: (1)  
2 animal models, (2) case and technical studies or reports, (3) interventional studies (i.e., drug, surgery,  
3 training and physical therapy) not reporting baseline measures, and (4) articles in other languages  
4 besides English.  
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9 After preliminary screening, if the content from an abstract was unclear, article was included  
10 for a subsequent full manuscript review. The same three authors independently inspected the full  
11 texts, according to the inclusion/exclusion criteria. Any controversial article was discussed among  
12 the authors and resolved by consensus. Furthermore, reference lists of the included articles were  
13 reviewed to identify additional eligible papers that might have been missed during the first round of  
14 search.  
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24 To assess study design, the American Academy of Cerebral Palsy and Developmental  
25 Medicine appraisal for categorization of evidence levels for group designs (Table I) [36] was used.  
26 Quality of study method was evaluated using a modified version of the American Academy of  
27 Cerebral Palsy and Developmental Medicine (AACPDM) guidelines in the protocol proposed by  
28 Morgan et al. [37], with only 12 out of 17 items for group studies (available as supplementary  
29 material: S3). Risk of Bias (RoB) was assessed using the Risk of Bias Assessment Tool for  
30 Nonrandomized Studies (RoBANS) [38]. In all cases, two authors (MN and FR) independently  
31 evaluated the studies, with any disagreements resolved by discussion and consensus. A third reviewer  
32 (MB) was consulted if necessary.  
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#### 48 **Data extraction**

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51 Two authors (MN and FR) extracted the pertinent data from the included articles using a  
52 customized data extraction form (S4). Study population characteristics (i.e., diagnosis, sample size,  
53 age, severity of CP) and details about the protocol used for the evaluation – such as the type of test  
54 (over-ground walking or on a treadmill); testing modality (self-paced, constant speed or incremental  
55 test); protocol phases duration and study findings – were summarized and reported in Table II and  
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1 Table III. The primary outcomes were (1) energy expenditure and (2) energy cost (expressed in  $\dot{V}O_2$ ,  
2  $O_2$ , kcal, MET or Joule), measured through indirect calorimetry or gas dilution methods. Articles  
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4 reporting the same outcome were grouped for a coherent data categorization. Any reported secondary  
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6 outcomes (i.e., HR, walking speed) were also collected. Findings were compared by difference  
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8 between CP versus TD peers; difference between CP severity levels established by the GMFCS [3];  
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10 and differences across age groups or longitudinal changes.  
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14 A meta-analysis to compare the differences between group means in CP and TD, for both  
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16 energy consumption and energy cost, was conducted using a meta-analysis software (Review  
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18 Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane  
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20 Collaboration, 2014). For the studies reporting alternative measure of descriptive statistics (e.g.,  
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22 median, IQ Ranges), Mean and SD or SE were estimated using formulae available in Cochrane's  
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24 Handbook [39]. Due to the heterogeneity in the primary outcomes among studies, and in some cases  
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26 also the relatively small sample size ( $n < 30$ ), a random-effect model was fitted to the data for the  
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28 calculation of the standardized effect size (Hedges'  $d$ ) [40,41] and 95% confidence interval (C.I.)  
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30 [42]. An effect size of 0.2 to 0.49 was interpreted as a small effect, 0.5 to 0.79 a medium effect, and  
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32 over 0.8 a large effect size [43]. Publication bias was assessed by visual inspection of funnel plots,  
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34 then the Egger's test was performed [44]. Heterogeneity was checked by means of the Higgins  
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36 Inconsistency test ( $I^2$ ). Values over 50 % were considered of high heterogeneity [45].  
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44 For each study reporting values of energy consumption and/or energy cost across GMFCS  
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46 levels I to III, linear correlation analysis using Pearson's coefficient was run, with the level of  
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48 impairment as the explanatory variable. Then, using the calculated correlation coefficients ( $r$ ) and  
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50 95% confidence interval (C.I.) of each study, the pooled correlation coefficient ( $r$ ) and 95% C.I. were  
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52 calculated using the Fisher  $r$ -to- $z$  transformed correlation coefficient [46]. The heterogeneity of the  
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54 pooled  $r$  was calculated using the Higgins Inconsistency test ( $I^2$ ) [45]. Values over 50 % were  
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56 considered of high heterogeneity [45]. Publication bias was assessed by visual inspection of funnel  
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plots, then the Egger's test was performed [44]. MedCalc for Windows, version 20.007 (MedCalc® Software Ltd, Ostend, Belgium) was used to perform the statistical analyses.

## Results

### Summary of studies

After removing the duplicates, the initial search resulted in 1016 articles matching inclusion criteria. Eight hundred and nineteen articles were removed after title and abstract screening. The reasons for exclusion were: incorrect population (i.e., physical and mental disability other than CP), lack of metabolic data (e.g., biomechanics estimation or questionnaires score), and incorrect testing protocol (e.g., cycle-ergometer, isometric contractions). After the preliminary screening, 197 articles were kept for full-text review. Of these, 41 articles matched all the inclusion criteria [47–87]; reasons for exclusion of the additional 156 articles are listed in Figure 1.

Regarding the methodological quality, the average score of the methodological quality appraisal was 52.6%. Twenty-three studies ranked medium-high quality (score > 58 %; 7/12 items) [48–52,56–58,63–70,73,74,76,79,82,83,86]. The main areas of methodological weakness found were: sensitivity of the measure to change (item 6), unawareness of outcome assessors during intervention (item 7); reporting the power calculation for the sample size (item 9), and reporting dropout/loss to follow-up (item 11). Individual scores of each article for methodological quality can be found as supplementary material (S3).

All the included studies were screened with the RoBANS [38]. In most of the studies, CP and control groups were selected from comparable population group (80% of the studies). Concerning the confounding variables, these were adequately confirmed and considered during the design phase for 59% of the studies, while it was uncertain whether the confounding variables resulted in a high risk or a low risk of bias for the remaining studies (41%). The experimental protocols were described, and the outcomes used were valid and reliable in all the studies (100%). Low risk of bias for inadequate blinding of outcome assessments and inadequate handling of incomplete outcome data

1 was reported for 98% and 88% of the studies, respectively. Complete summary of results for the ROB  
2 screening can be found in supplementary material (S5).  
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4 A detailed summary of the characteristics and design of each study is provided in Table III,  
5 while details about protocol, energy expenditure outcomes, results and statistical significance for each  
6 study can be found in Table IV.  
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11 Thirty-two articles compared metabolic data in people with CP and TD peers [47–56,58–  
12 62,67–70,73–78,80,82,84–87]. Studies were grouped based on the outcome variable: twenty-one  
13 measured walking  $\dot{V}O_2$  (ml/kg/min – either gross or net measure) [48,49,51,52,55–59,67–69,73–  
14 77,82,84,85,87], one  $\dot{V}O_{2max}$  [61], two  $\dot{V}O_{2peak}$  [56,84], six adopted other measures of energy  
15 expenditure (i.e., kJ/min, kcal/min, J/kg/min) [47,50,54,70,75,80], twelve measured  $O_2$  cost of  
16 walking (ml/kg/m – either gross or net measure) [52,53,55–57,59,60,62,69,73,74,86], six calculated  
17 energy cost (J/kg/m) [49,51,54,58,68,87], and seven adopted other measures of energy cost of  
18 walking (i.e., non-dimensional cost, ml/kg-m) [49,51,54,58,74,77,82]. Seventeen studies reported  
19 more than one outcome and are therefore discussed for both outcomes [49,51,52,54–59,68,69,73–  
20 75,82,84,87].  
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36 Twelve studies described the metabolic data across GMFCS levels [49,51,62–65,71,72,79,81–  
37 83]; grouped based on outcome measures: seven walking  $\dot{V}O_2$  (ml/kg/min – either gross or net  
38 measure) [49,51,63,79,81–83], seven  $O_2$  cost of walking (ml/kg/m – either gross or net measure) [62–  
39 65,71,72,81], two energy cost (J/kg/m) [49,51], and five other measures of energy cost of walking  
40 [49,51,63,81,82]. Of these, five studies reported more than one outcome [49,51,63,81,82].  
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49 Only three studies compared metabolic data in people with CP [66,68,82], either across  
50 different age ranges [68] or longitudinally on the same individuals [66,82]. One of these studies  
51 reported the net  $O_2$  cost of walking (ml/kg/m) [66]; two articles reported multiple outcomes [68,82]:  
52 both measured walking  $\dot{V}O_2$ , one the energy cost (J/kg/m), and one other measures of energy cost of  
53 walking (i.e., non-dimensional cost).  
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Five studies addressed multiple comparisons and thus were included in more than one subgroup: four research papers compared CP to TD and also CP across GMFCS levels [49,51,62,82]; one compared CP to TD and also addressed the effect of age in CP [68]; while one study performed all three comparisons of interest [82]. For this reason, the sum of studies in each subgroup differs from the total of forty-one articles. For a more comprehensive overview and comparison of the study results, and for graphical purposes, we converted – when possible – the originally reported values into  $\dot{V}O_2$  (ml/kg/min) and  $O_2$  cost (ml/kg/m) using equations and formulae available from the literature (see details in [88]). Previously published  $\dot{V}O_2$  and  $O_2$  cost values, and the converted or calculated ones, are shown in Figure 2 and 3, respectively.

## Testing protocols

Protocol details and testing modalities were heterogeneous across studies (Table V). Few studies administered multiple tests with different outcomes, and are hereby included only for findings on energy expenditure and energy cost of walking. The most common testing modality was overground walking. Twenty-five studies tested subjects while walking on different tracks/paths of variable length and shape [49–54,57–60,62–66,69,70,73,74,79–83,86]; whereas twelve studies adopted a treadmill protocol [47,48,61,67,68,75–78,85,87]. One study used both testing modalities [56], while protocol description was unavailable for three studies [55,71,72]. Five studies administered an incremental walking test [61,68,76–78], thirty-two selected a constant speed walking protocol [47–52,54,57–60,62–67,69,70,73–75,79–87]. One study administered both an incremental and a constant-speed test [56]. In twenty-eight studies, subjects were asked to walk at comfortable, self-paced speed [47,49,51–54,56–60,62–66,69,70,73,74,79–83,86,87]. In nine studies, subjects were asked to walk at pre-determined speed and groups were compared at matched speed [47,48,56,67,68,75,83–85]. In three studies details were not provided [55,71,72]. Six-minute walking at self-paced speed [89] was the most common protocol, adopted by seven studies [49,51,56,69,70,80,83] with varying path/track length.

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2 In patients with CP, the higher the level of mobility impairment (i.e., GMFCS level above II)  
3 the greater is the necessity of using assistive devices or orthoses for daily-life ambulation [3]. Nine  
4 studies did not report whether subjects were allowed to use their walking aids during test  
5 [59,68,71,72,75–78,83]. In twenty-two studies, subjects used their habitual walking aids and/or could  
6 hold on the handrail when the testing was on treadmill [47,49,51–56,60,62–67,69,70,74,79–82]. In  
7 ten studies, participants were not allowed to use or did not need walking aids for the test  
8 [48,50,57,58,61,73,84–87]. In nineteen studies subjects wore their habitual orthoses for the test  
9 [47,49,51–55,58,60,62–66,69,70,74,81,82], whereas in 4 studies subjects did not [57,61,73,87].  
10 Eighteen studies did not provide information about the use of orthoses [48,50,56,59,67,68,71,72,75–  
11 80,83–86].  
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### 26 **Comparison of people with CP and typically developing peers**

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29 Thirty-one out of 41 studies compared people with CP and TD. There were discrepancies  
30 across studies on group matching modality: some controlled for age, sex and body sizes, others only  
31 for age. In several studies the sample size was relatively small ( $n < 30$ ) [90], while in others the enrolled  
32 controls were fewer than the experimental CP group.  
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### 41 ***Walking oxygen consumption ( $\dot{V}O_2$ )***

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44 Oxygen consumption during walking (walking  $\dot{V}O_2$ ) was the outcome for energy expenditure  
45 estimation in 19 studies [48,52,55–59,75,76,78,84,85,87]. Testing protocols used in these studies  
46 varied widely in terms of duration of resting (2 to 10 min) and walking time (3 to 10 min), setting  
47 (e.g., laboratory corridor, indoor and outdoor tracks) as well as testing modality (treadmill vs.  
48 overground walking) and walking speed (constant vs. incremental).  
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56 One study measured  $\dot{V}O_2$  (ml/kg/min) but then reported it in terms of energy units  
57 (Joule/kg/min) [54]; these values were re-converted for further comparison by the authors in the  
58 present review. Three studies [49,51,82] presented data for subgroups based on GMFCS levels and  
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did not report an overall mean for CP, thus a weighted average was calculated using mean, standard deviation (SD) and sample size of the subgroups. Figure 2 shows the values reported in each of these studies. *Original values* (mean [Range]) TD: 14.28 [6.3–25.1] ml/kg/min; CP: 18.50 [9.72–26.86] ml/kg/min; *recalculated values*: TD: 17.94 [16.1–20] ml/kg/min; CP: 20.35 [17.06–22.46] ml/kg/min. Most of the studies reported a higher  $\dot{V}O_2$  during walking for people with CP [48,49,51,54,55,58,59,69,74,75,78,82,84,87], however some studies described an opposite trend [57,73,76], and others revealed no appreciable difference between groups [47,56,87].

### ***Walking oxygen cost (O<sub>2</sub> cost)***

Fifteen studies measured values of walking O<sub>2</sub> cost [52–60,62,69,73,74,86,87]. Four of these studies [54,58,86,87] reported it in J/kg/m; thus, these values were re-converted into ml/kg/min. We estimated O<sub>2</sub> cost based on group means for 8 additional studies [48,49,51,61,75,76,82,84]. Three studies presented data for subgroups based on GMFCS levels [49,51,82] and 2 studies based on topographical distribution [53,59], without reporting an overall mean for CP. For this reason, a weighted average was calculated using mean, SD, and sample size of the subgroups. Figure 3 provides an overview of these 23 studies. Each study reported a higher O<sub>2</sub> cost of walking for people with CP: *Original values* (mean [Range]) TD: 0.21 [0.05–0.28] ml/kg/m; CP: 0.49 [0.27–0.86] ml/kg/m; *recalculated values*: TD: 0.21 [0.12–0.36] ml/kg/m; CP: 0.34 [0.18–0.43] ml/kg/m, with a large heterogeneity in the magnitude of difference.

### **Differences across CP severity levels (GMFCS)**

Twelve articles addressed comparison based on the level of severity (i.e., GMFCS levels) [49,51,62–65,71,72,79,81–83]. Two studies reported data for both  $\dot{V}O_2$  and O<sub>2</sub> cost [63,81].

### ***Walking oxygen consumption across severity levels***

Walking  $\dot{V}O_2$  across severity was measured in seven studies [49,51,63,79,81–83]. One of these studies measured  $\dot{V}O_2$  (ml/kg/min) but reported energy expenditure in METs [83]; thus, values were reconverted for analyses in the present review. Only three of these articles reported data for TD group [49,51,81]. Five out of seven studies reported a slight increment in  $\dot{V}O_2$  increasing with GMFCS level with on average 15.1% (Range 3.8 – 44.0) increment between GMFCS I and II, and 5.1% (Range -6.0 – 14.2) between GMFCS II and III. Values of walking  $\dot{V}O_2$  across GMFCS levels are displayed in supplementary material (S6), with data of TD as a reference.

Surprisingly, data in Thomas et al. [81] and Slaman et al. [79] showed an opposite trend for the GMFCS II - III comparison:  $\dot{V}O_2$  in GMFCS III is lower than in GMFCS II, -2.4% and -6.0%, respectively. Results in Slaman et al. [79] also showed a steep  $\dot{V}O_2$  increment between GMFCS I and II: +44.0%.

### ***Walking oxygen cost across severity levels***

Seven articles reported directly measured values  $O_2$  cost across the different severity stages [62–65,71,72,81]. We estimated values of  $O_2$  cost for the other five articles [49,51,79,82,83] using group mean data for  $\dot{V}O_2$  walking speed or time, and distance travelled during evaluation test. Values of  $O_2$  cost across GMFCS levels are reported in Figure, with data of TD as a reference. In each study,  $O_2$  cost increased as a function of GMFCS level with a positive trend: on average 21.9% (Range 2.2 – 55.6) increment between TD and GMFCS I, 37.8 % (Range 13.3 – 59.1) increment between GMFCS I and II, and 56.0% (Range 9.5 – 87.1) between GMFCS II and III. Only three studies [62,64,65] reported values of  $O_2$  cost for GMFCS IV and therefore are not shown in Figure 4; nevertheless, they confirmed the positive trend between  $O_2$  cost and severity level. Values are very heterogeneous across these studies: increase between GMFCS III and IV ranging from 16.1% [65] to 244.4% [62].

## Age-related differences

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2 Only three studies considered age as potential confounder of  $\dot{V}O_2$  and/or  $O_2$  cost during  
3 walking [66,68,82]. Two longitudinal studies [66,82] assessed changes in the energy expenditure  
4 parameters over time in the same group of individuals with CP. The authors tested them at baseline  
5 and after 1 year [82] or 2 years and 7 months [66], respectively. Net  $O_2$  cost of walking was calculated  
6 by Kerr et al. [66], whereas walking  $\dot{V}O_2$  was considered in the study by Thomas et al. [82]. The third  
7 study considering age was a cross-sectional design project testing subjects with CP at different speed  
8 on the treadmill while measuring  $\dot{V}O_2$  and energy cost (EC; J/kg/m) [68]. Marconi et al. grouped  
9 subjects based on age ranges and clinical subtype (hemiplegia vs diplegia). Findings of these studies  
10 are contrasting. In the study by Kerr et al. [66]  $O_2$  cost deteriorated over time in individuals with CP,  
11 following a quadratic relationship with age ( $r=0.079$ ;  $p=0.035$ ). Thomas et al. [82] reported a  
12 significant decrease in walking  $\dot{V}O_2$  over time only for TD peers, while there was no significant  
13 change in individuals across GMFCS levels of CP [82]. In the work of Marconi et al. [68] it was  
14 found that walking  $\dot{V}O_2$  of individuals with diplegic CP was significantly higher than TD at each age,  
15 whereas in individuals with hemiplegic CP it was significantly higher only for the first age group (4-  
16 7 years); however, they did not run statistical analysis to determine differences across age groups of  
17 the same CP subtype [68].

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19 All three studies only evaluated young age ranges (years:months): 4:7–17:6 [66], 5:7–18 [82],  
20 and 4–14 [68], thus their results should be cautiously considered when generalizing the effect of age  
21 for older individuals. Because of the heterogeneity across studies in design, protocol, and outcome  
22 measures, it was not possible to gather data together or to perform additional statistical analysis (e.g.,  
23 regression).

## Meta-analysis

### TD vs CP

Comparison between TD and CP was feasible for both our main outcomes. Nineteen studies were included for the energy consumption analysis [48,49,51,52,54–58,69,73–76,78,82,84,85,87], while seventeen studies were included for the energy cost analysis [49,51–58,60,62,69,73,74,80,86,87]. Effect size and C.I. were calculated for CP over TD group based on the random-effects model. Meta-analysis revealed a significant moderate to large effect of CP on both walking energy expenditure (Hedges'  $g = 0.67$  (95% CI: 0.34-0.99;  $Z = 4.03$ ,  $p < 0.001$ ; Heterogeneity:  $I^2 = 76\%$ ; Figure 5) and energy cost of walking (Hedges'  $g = 1.34$  (95% CI: 1.21-1.47;  $Z = 20.44$   $p < 0.001$ ; Heterogeneity:  $I^2 = 0\%$ ; Figure 6), respectively. Concerning the heterogeneity in the walking energy expenditure comparison, three studies presented a negative estimate for Hedges'  $g$  [57,73,76], with a higher walking  $\dot{V}O_2$  for TD subjects compared to subjects with CP. Reasons for the contrasting results may be explained by the characteristics of the testing protocols. In the study by Piccinini et al. [73] and Cimolin et al. [57], participants walked for a short distance (250m), while in the study by Rose et al. [76], an incremental testing protocol was used and values at final step of the test are reported for both groups. Participants in TD group reached a higher maximal walking speed and  $\dot{V}O_2$  at maximum speed ( $\dot{V}O_{2peak}$ ) was higher than CP, in accordance with similar studies on cycle-ergometer [117,118] and treadmill [56,61,84]. It is worth to note that the results are consistent among studies when  $O_2$  cost, which takes into account walking speed, is considered (Figure 3 and Figure 6). The study by Rigby et al. [75] stands out for the considerable estimate of Hedges'  $g$  ( $>3$ ). The sample size of the study was relatively small (8 TD, 8 CP) and the CP group was characterized by a medium-to-high severity involvement (4 spastic quadriplegia, 2 spastic diplegia) [75] which may have exacerbated the between-group differences. Visual inspection of both funnel plots did not reveal asymmetry. There was no evidence of publication bias for the walking energy expenditure and the energy cost of walking comparisons ( $p = 0.446$  and  $p = 0.628$ , respectively).



## Across GMFCS

Seven studies were included in the analysis for the  $\dot{V}O_2$  [49,51,63,79,81–83]. The pooled  $r$  resulting from all the studies, based on the random-effects model was 0.965 (95% CI: 0.875-0.991;  $p < 0.001$ ) and exhibited a notable heterogeneity ( $I^2 = 98.07\%$ ). In particular, two studies [79,81] presented estimates much lower than the main bulk of results. In both studies, participants classified as GMFCS III had a lower  $\dot{V}O_2$  during walking than participants classified as GMFCS II. This result could be explained by the reduced number of participants in the most impaired group ( $n=6$ ) and the characteristics of the protocol (i.e., self-paced walking for 3 minutes) in the study by Slaman et al. [79]. In the study by Thomas et al. [81] the lower  $\dot{V}O_2$  in GMFCS III could be ascribed to the functional limitations, and thus the much lower velocity reached by this group (difference between GMFCS II and III is appreciable when  $O_2$  cost is considered) [81]. Conversely, the study by Bolster et al. [51] resulted in an extremely high correlation coefficient. Nevertheless, sample size and participants distribution across groups appears appropriate and no obvious reason for considering it an outlier was apparent to the present authors. Twelve studies were included in the analysis for the  $O_2$  cost [49,51,62–65,71,72,79,81–83]. The pooled  $r$  resulting from all the studies, based on the random-effects model was 0.979 (95% CI: 0.966, 0.986;  $p < 0.001$ ) and exhibited a notable heterogeneity ( $I^2 = 94.19\%$ ). In particular, among the included studies, the one by Kerr et al. [65] stands out for the lowest correlation. As already mentioned, we only considered values of GMFCS I to III for the correlation analysis, while the study by Kerr et al. tested participants even with the level IV. Moreover, the difference in  $O_2$  cost between GMFCS I and II was minimal [65], lowering the correlation coefficient when considering only level I to III. In a similar, yet opposite manner, the extremely high correlation coefficient for the study by Johnston et al. [82] results from the exclusion of values for GMFCS IV – showing a marked increase in  $O_2$  cost and its variability – from our analysis. The study by Bolster et al. [51] also resulted in a high correlation. Nevertheless, sample size and participants distribution across groups appears appropriate and no obvious reason for considering

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it an outlier was apparent to the present authors. Forest plots for both analyses are displayed as supplementary material (S7). Visual inspection of the funnel plot did not reveal asymmetry for the studies included for the  $\dot{V}O_2$  correlation analysis. however, the number of studies included in the meta-analysis was too low to use tests for funnel plot asymmetry, as suggested in the Cochrane's Handbook (<10 studies) [39]. Visual inspection of the funnel plot did not reveal asymmetry for the studies included for the  $O_2$  cost correlation analysis. Egger's test indicated that there was no obvious publication bias ( $p = 0.268$ ).

## Discussion

In the present systematic review, we aimed to 1) appraise and synthesize the difference in energy expenditure in individuals with CP compared to their age-matched peers; 2) identify the rate of  $\dot{V}O_2$  across different severity levels, based on GMFCS; and 3) define the age-related changes of walking energy expenditure in individuals with CP. Forty-one studies met the inclusion criteria. Specifically, 31 studies compared  $\dot{V}O_2$  during walking between individuals with CP and age-matched healthy subjects, 13 studies reported the changes of metabolic data across GMFCS and only 3 studies were found to investigate the variation of walking energy expenditure related to different ages. It is worth noting that several studies were considered for more than one aim of the current review.

Overall, individuals with CP spend more energy (32% higher  $\dot{V}O_2$  on average) than healthy controls while walking (average effect size equal to 0.67) [48,49,51,52,54–58,69,73–76,78,82,84,85,87]. However, there were some conflicting results. For example, among the 20 considered, 3 studies did not show any noticeable difference between CP and control group [47,56,87] and 3 studies found the opposite trend with healthy controls having higher walking  $\dot{V}O_2$  [57,73,76]. The contrasting results may be related to the testing protocols. In the study by Piccinini et al. [73] and Cimolin et al. [57], participants walked for a short distance (~250m), equal to less than 4 minutes for TD and 5 minutes for CP group on average, respectively. In the study by Cardona García et al. [56], subjects walked for 6 minutes over a 5-meter path presenting several turns with corresponding

1 acceleration/deceleration phases in the walking cycle, which might represent a possible confounding  
2 effect and therefore a difference in the results obtained. Rose et al. [76] used an incremental testing  
3 protocol: values at final step of the test are reported for both groups. Participants in TD group reached  
4 a higher maximal walking speed and  $\dot{V}O_2$  at maximum speed ( $\dot{V}O_{2peak}$ ) was higher than CP, in  
5 accordance with similar studies on cycle-ergometer [117,118] and treadmill [56,61,84]. Finally,  
6 values of  $\dot{V}O_2$  in Aviram et al. [47] were reported in kcal/min; this measure does not take into account  
7 for differences in body mass between groups, possibly masking the difference in walking energetics  
8 between groups.  
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19 Conversely, when  $O_2$  cost –  $\dot{V}O_2$  normalized by walking speed – was considered as the  
20 metabolic measure to evaluate walking efficiency, a remarkable difference was found between  
21 individuals with CP and healthy controls (average effect size equal to 1.34) [49,51–  
22 58,60,62,69,73,74,80,86,87]. All studies reported significant higher values of  $O_2$  cost in CP during  
23 walking, as well as for those with estimated values by the authors. Thus, the distinguishable difference  
24 of  $O_2$  cost between groups was consistent with the testing type and protocol. On average, the  $O_2$  cost  
25 in individuals with CP was twofold than the age-matched controls with a range difference from 0.04  
26 to 0.62 ml/kg/m, which resulted with an increased  $O_2$  cost ranged from 1.3 to 3.5 times than controls.  
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39 The remarkable greater cost of walking in CP respect to TD peers confirms the perceived  
40 effort and fatigue reported by children and adults with CP [5,91]. The  $O_2$  cost is considered a  
41 physiological marker describing the degree of locomotion impairment in pathological conditions such  
42 as multiple sclerosis [92], stroke [93], and Parkinson disease [94], and reflecting either an increase in  
43 the rate of  $\dot{V}O_2$  during normal walking speed or an abnormal rate of  $\dot{V}O_2$  respect to a reduced walking  
44 speed. It is worthwhile to consider that there is a U-shaped relationship between  $O_2$  cost and gait  
45 speeds, which indicates that there is a particular gait speed minimizing the  $O_2$  cost in each individual  
46 [95,96]. For this reason, when comparing CP to TD, the selection of walking speed needs to be  
47 carefully considered. A similar U-shaped relationship has been hypothesized in individuals with CP,  
48 however, to date it has not been confirmed by experimental results [68]. Recently, Schwartz et al.  
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1 [97,98] suggested an interesting way to compare data by means of a non-dimensional measure of  
2 energy expenditure, however the use of a non-dimensional outcome may not translate to clinical  
3 practice. Therefore, based on our results, we suggest O<sub>2</sub> cost as the parameter to physiologically  
4 characterize the walking efficiency in people with CP.  
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9 The ability to sustain a walking task for long period of time, maintaining an adequate force  
10 production with the lower possible O<sub>2</sub> cost, is dependent on the integration of the neuromuscular and  
11 cardiorespiratory systems. Several factors play a role on one or more of these physiological systems  
12 that can lead to insurgence of fatigue and increase the energy cost of a functional task like ambulation.  
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14 Among these factors specific have been recognized as the main ones affecting the duration of walking  
15 in CP. Neural-driven weakness, defined as a loss of excitatory motor signals descending in the  
16 cortico-spinal tract resulting in reduced muscle activation and reduced muscle size [99–101], seems  
17 to be a major limiting factor in this population. Rose and McGill [102] demonstrated an equivalent  
18 ratio between recruitment and firing rate modulation at submaximal contractions between subject  
19 with CP and controls. However, they showed that submaximal contractions required more voluntary  
20 effort for subjects with CP, such that the neuromuscular activation level corresponded about 50% of  
21 the maximum voluntary contraction (MVC) in individuals with CP compared to control whose  
22 neuromuscular activation level was related to about 20% of the MVC [102]. This means that a person  
23 with CP might require full voluntary effort compared to a submaximal effort for the healthy control.  
24 This reduced force-generating capacity of the muscle in individuals with CP might result with high  
25 relative demand of lower limb skeletal muscles during walking, making these individuals more prone  
26 to fatigue. These results are consistent with findings showing lower muscle endurance in quadriceps  
27 muscles of CP undergoing a submaximal repetition-to-fatigue protocol compared to control subjects  
28 [103]. In addition, it has been recently shown that the decrease of EMG median frequency and  
29 increase of EMG amplitude in lower leg muscles were larger in children with CP compared to  
30 typically developing peers during overground walking at self-selected speed [15].  
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1 Greater energy cost during walking in CP has been associated with higher external mechanical  
2 work [86,87], which has been associated with greater potential, vertical and later kinetic mechanical  
3 work [17]. The higher mechanical work was proposed to be related to the equinus gait pattern  
4 commonly seen in children with CP due to a less effective exchange between potential and kinetic  
5 energy by the legs to lift and redirect the center of mass [17,104–106]. Furthermore, it has been  
6 recently shown that reduced knee and hip joint extension are associated with gait inefficiency in  
7 children and adolescents with CP [107]. However, these results are in contrast with the work of Steele  
8 et al. [80] who found the crouch gait severity correlated poorly with elevated  $\dot{V}O_2$  in children with  
9 CP. Furthermore, it has also been recently reported that long-term reduction of spasticity by selective  
10 dorsal rhizotomy does not lead to reduced oxygen consumption [108].

11 Abnormal muscle activation patterns of agonist-antagonist, higher levels of co-contraction  
12 and impaired selective motor control are typical clinical signs of damaged corticospinal projections  
13 in CP [2,109,110], which have been shown to additionally contribute to gait abnormalities in this  
14 population [6]. It has been suggested that these impaired neural mechanisms of muscle activation  
15 might further contribute to the early manifestation of fatigue in CP [111]. Unnithan et al. [84] found  
16 that co-contraction of the quadriceps and hamstrings explained 51% of the variance in gross  $\dot{V}O_2$   
17 among children with CP walking on a treadmill [84]. However, Damiano et al. [112] found the  
18 opposite relationship, with greater co-contraction between the quadriceps and hamstrings related to a  
19 lower energy expenditure index [112], and Steele et al. [80] showed that co-contraction of the rectus  
20 femoris and biceps femoris only explained 2–3% of the variance in  $\dot{V}O_2$  during gait in children with  
21 bilateral CP. Moreover, despite the fact that the impaired selective motor control has showed a strong  
22 correlation with severity scales and gait abnormalities in CP [113–116], it is still uncertain whether  
23 decreased selective motor control is correlated with higher oxygen consumption during gait.

24 Studies have reported lower maximal aerobic power in CP compared to controls without  
25 disabilities on treadmill and cycle ergometer tests [61,117]. Unnithan et al. [84] have shown that  
26 children with CP work at higher percentage of their maximal  $\dot{V}O_2$  compared to healthy controls during  
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1 gait (53.5 % and 22.5 % respectively), which might explain an additional early onset of fatigue in  
2 individuals with CP since they work harder than the typically developing peers given speed.  
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4 Interestingly, the respiratory exchange ratio has been found equivalent between individuals with CP  
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6 and healthy controls, demonstrating similar cardiorespiratory responses in both group during  
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8 submaximal exercise [76,117]. Though, it has been speculated that spastic muscles could cause local  
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10 obstruction of venous return and, therefore, result in inhibition of muscle lactate clearance leading to  
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12 increased acidity and local muscular fatigue [61,118]. However, no evidence has been provided to  
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14 support this hypothesis, as well as it has yet been investigated the mechanism underlying skeletal  
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16 muscle oxidative capacity in CP and its contribution to exercise intolerance and fatigue.  
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22 Muscle metabolic factors might also reflect the increased O<sub>2</sub> cost of movement in children  
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24 with CP. Force generation is highly energetic and requires the constant replenishment of adenosine  
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26 triphosphate (ATP) for the cross-bridge cycle, which is created aerobically within mitochondria by  
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28 utilizing food substrates and oxygen consumption by the electron transport chain. Recent work shows  
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30 that hamstring muscle mitochondria in even independently ambulatory children (GMFCS I and II)  
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32 have a 50-80% lower capacity for energy production [119]. The metabolic machinery within the  
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34 muscle also depends on the appropriate delivery of O<sub>2</sub> to the mitochondria through appropriate  
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36 development of the capillary network. In young adults with CP, reduced capillary density has been  
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38 reported in wrist flexor contractures compared to control subjects [120], suggesting that it may have  
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40 a role to play in reduced metabolic capacity. Exercise studies have shown that young adults with CP  
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42 do get exhausted at lower exercise intensities, but they are able to dynamically increase muscle  
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44 vascularization in response to exercise [121]. In general, more information is needed on how muscle  
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46 metabolism is linked to the increased walking cost.  
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53 We identified twelve studies that addressed the comparison between energy expenditure and  
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55 GMFCS levels [49,51,62–65,71,72,79,81–83]. Overall, the results showed that the increased gross  
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57 motor function severity was associated with an increased  $\dot{V}O_2$  during walking. Yet, the considered  
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59 studies revealed a higher reliability of the O<sub>2</sub> cost to discriminate the differences between GMFCS  
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1 level and the O<sub>2</sub> expenditure compared to  $\dot{V}O_2$ . The increase of O<sub>2</sub> cost was more accentuated between  
2 GMFCS II vs III (+56 %) compared to GMFCS I vs II (+38 %). Only three studies reported the O<sub>2</sub>  
3 cost for GMFCS IV, therefore they were not considered in the regression analysis with the other  
4 GMFCS levels. However, the results for these studies reported a trend of remarkable increased of O<sub>2</sub>  
5 cost in comparison of GMFCS III. Moreover, it is worth noting that the least difference (+22%) on  
6 cost was found between GMFCS I and TD age-matched controls considering both the originally  
7 measured and estimated values. This is not surprising since according to GMFCS individuals  
8 classified as level I can walk and run without any particular limitations that could impact their  
9 participation to daily activities [3].  
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21 As far as the age-related changes of walking energy expenditure in CP, we identified three  
22 studies that satisfied the search inclusion criteria [66,68,82]. However, only two studies analyzed and  
23 compared the cost of walking at different ages or over time [66,82]. Both studies reported an average  
24 increase of cost of walking in children with CP over a time period of 12 [82] or 31 months [66]. In  
25 comparison of the healthy control peers, Thomas et al. [82] found that all the GMFCS levels (I, II and  
26 III) had an increase in O<sub>2</sub> cost over one year. Nevertheless, a lack of statistical difference was found  
27 in the magnitude of O<sub>2</sub> cost increment by the GMFCS levels, which could had been influenced, as  
28 stated by the authors, by the short time period considered and the small sample size recruited for  
29 GMFCS levels I and II. The study by Kerr et al. [66] evaluated a large number of subjects with an  
30 age range (years:months) from 4:7 to 17:6. The relationship between the net O<sub>2</sub> cost and age was  
31 found to have a turning point with the highest walking inefficiency at 12 years of age [66]. The authors  
32 argued that the energy inefficiency during walking at that age could be explained by the onset of the  
33 puberty and the changes of child's education demands. The distinction across GMFCS levels was not  
34 accounted for in their analysis. It has been reported that gross motor function remains stable with age  
35 for children and adolescents classified as GMFCS level I [23]. Individuals that are more severely  
36 impaired (levels III and IV) see a decline in gait function with age [24,25]. Nonetheless, it remains  
37 still unclear whether the rate of decline in walking efficiency with age is also reflected by GMFCS  
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1 levels. There is still a knowledge gap on the changes of O<sub>2</sub> expenditure during walking in individuals  
2 at the early and late middle age with CP compared to age-matched unimpaired population. Further  
3 cross-sectional and longitudinal studies with larger sample size are needed to assess the trend of  
4 energy expenditure of walking with a broader range of ages classified at different GMFCS levels.  
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6 Additionally, the wide range in energy expenditure and cost of walking values, and sometime  
7 inconsistent results, points out the need for more standardized protocols in clinical and experimental  
8 settings, as well as encouraging for large multicenter studies. This would provide a more  
9 comprehensive understanding of the progress of walking efficiency in individuals with CP at different  
10 severity levels from childhood to the adulthood.  
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## 24 **Conclusion**

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27 The results of this review demonstrate a meaningful higher energy expenditure and energy  
28 cost during walking in individuals with CP despite a variability in the experimental protocols and  
29 testing type. A strong association between walking inefficiency and gross motor function was found  
30 across studies with a noticeable increase of cost of walking for GMFCS levels II and III. The analysis  
31 of the studies suggests a preference for using the O<sub>2</sub> cost as a physiological parameter to assess  
32 walking efficiency in CP. Due to a limited number of studies, partially with small sample sizes, the  
33 impact of age-related changes on walking efficiency with different functional severity remains still  
34 undetermined, as well as the trend of these longitudinal changes across the lifespan for individuals  
35 with CP.  
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## 51 **Contributions**

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54 MB, SD and AA conceived and designed the study. MN, FR and MB screened, selected and  
55 extracted data from appropriate studies. MN and FR assessed methodological quality. MN and FR  
56 drafted the manuscript with input from MB, SD, AA and LOD. All authors have read and approved  
57 the final manuscript.  
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## **Conflict of interest statement**

The authors have no conflict of interest.

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## **Supporting information**

The following additional material may be found online:

Appendix S1: PRISMA checklist.

Appendix S2: Search strategies.

Appendix S3: Scores and questions used for methodological quality appraisal of included studies.

Appendix S4: Data extraction form template.

Appendix S5: Summary of results for risk of bias.

Appendix S6: Box plot showing values of  $\dot{V}O_2$  in TD and in CP across severity levels.

Appendix S7: Forest plots showing the pooled correlation values of  $\dot{V}O_2$  and  $O_2$  cost across GMFCS levels.

Appendix S8: Funnel plots and Egger's test results for publication BIAS.

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## Figure Captions

**Figure 1:** Article selection flowchart

**Figure 2:** Values of walking  $\dot{V}O_2$  in studies comparing data of CP to TD. Horizontal bars represent the mean for each group and error bars denote SD. Studies are listed in chronological order. Originally reported values are placed on the upper part, while the values estimated by the authors of the review are placed below.

**Figure 3:** Values of walking  $O_2$  cost in studies comparing data of TD to CP. Horizontal bars represent the mean for each group and error bars denote SD. Studies are listed in chronological order. Originally reported values are placed on the upper part, while the values estimated by the authors of the review are placed below.

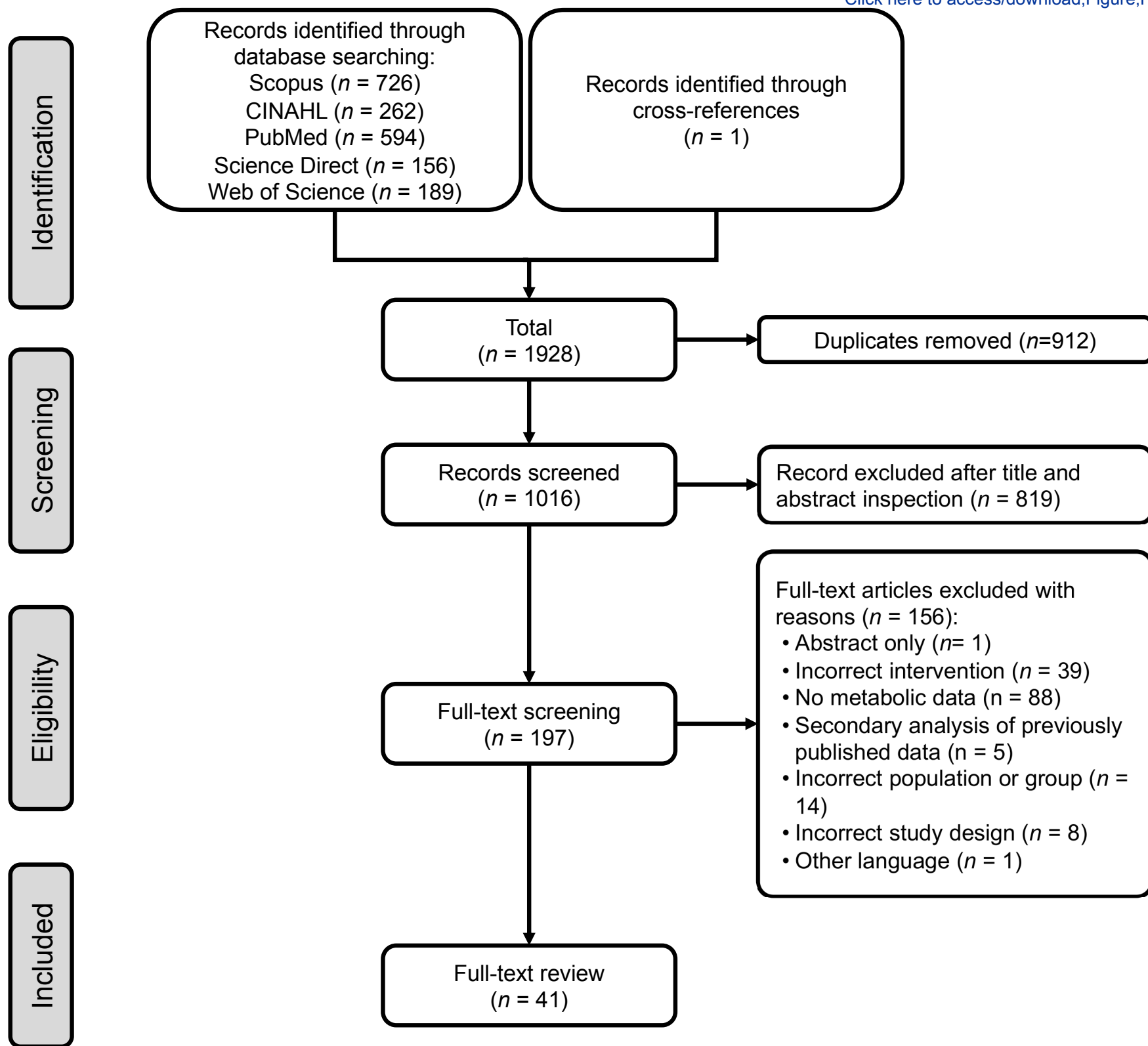
**Figure 4:** Box plot showing values of  $O_2$  cost in TD and in CP across severity levels (GMFCS I to III). Triangles represent studies where values were converted or estimated by the authors of the review; dots indicate study originally measured data. Box plots depict the median and the 25<sup>th</sup> and 75<sup>th</sup> quartiles and the whiskers showing the minimum and maximum values. Note, the highest point for TD (triangles) corresponds to the data in the study by Rose et al.,1989 [76], where they measured  $\dot{V}O_2$  with participants walking at maximum speed.

**Figure 5:** Forest plot with standardized effect sizes (Hedges'  $g$ ) and C.I. for walking energy consumption in the comparison TD-CP. Positive values correspond to an effect of CP on the walking energy consumption. #Studies in which measures of data dispersion other than SD or SE were reported (e.g., IQR).

**Figure 6:** Forest plot with standardized effect sizes (Hedges'  $g$ ) and C.I. for walking energy cost in the comparison TD-CP. Positive values correspond to an effect of CP on the energy cost. #Studies in which measures of data dispersion other than SD or SE were reported (e.g., IQR).

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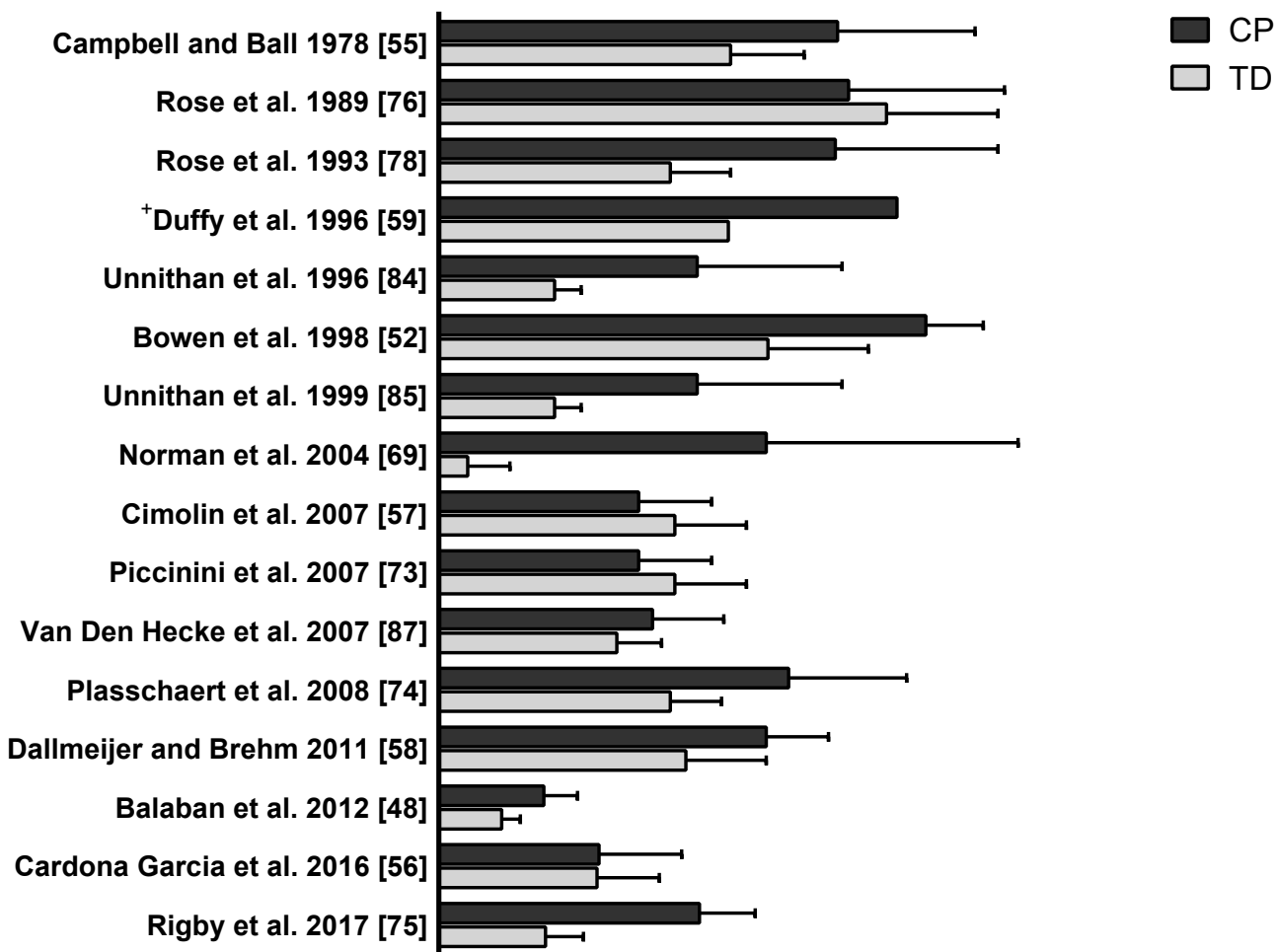
Figure 1



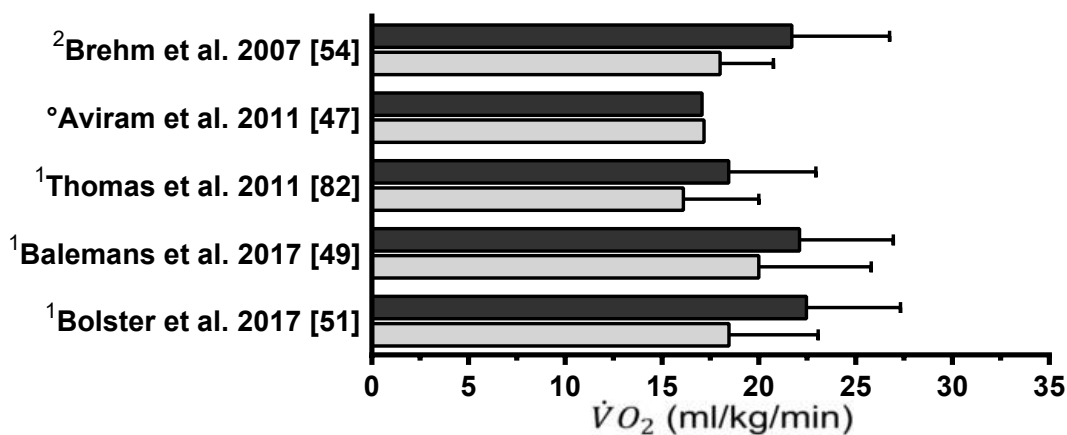


## Walking energy consumption

### Measured values



### Recalculated values



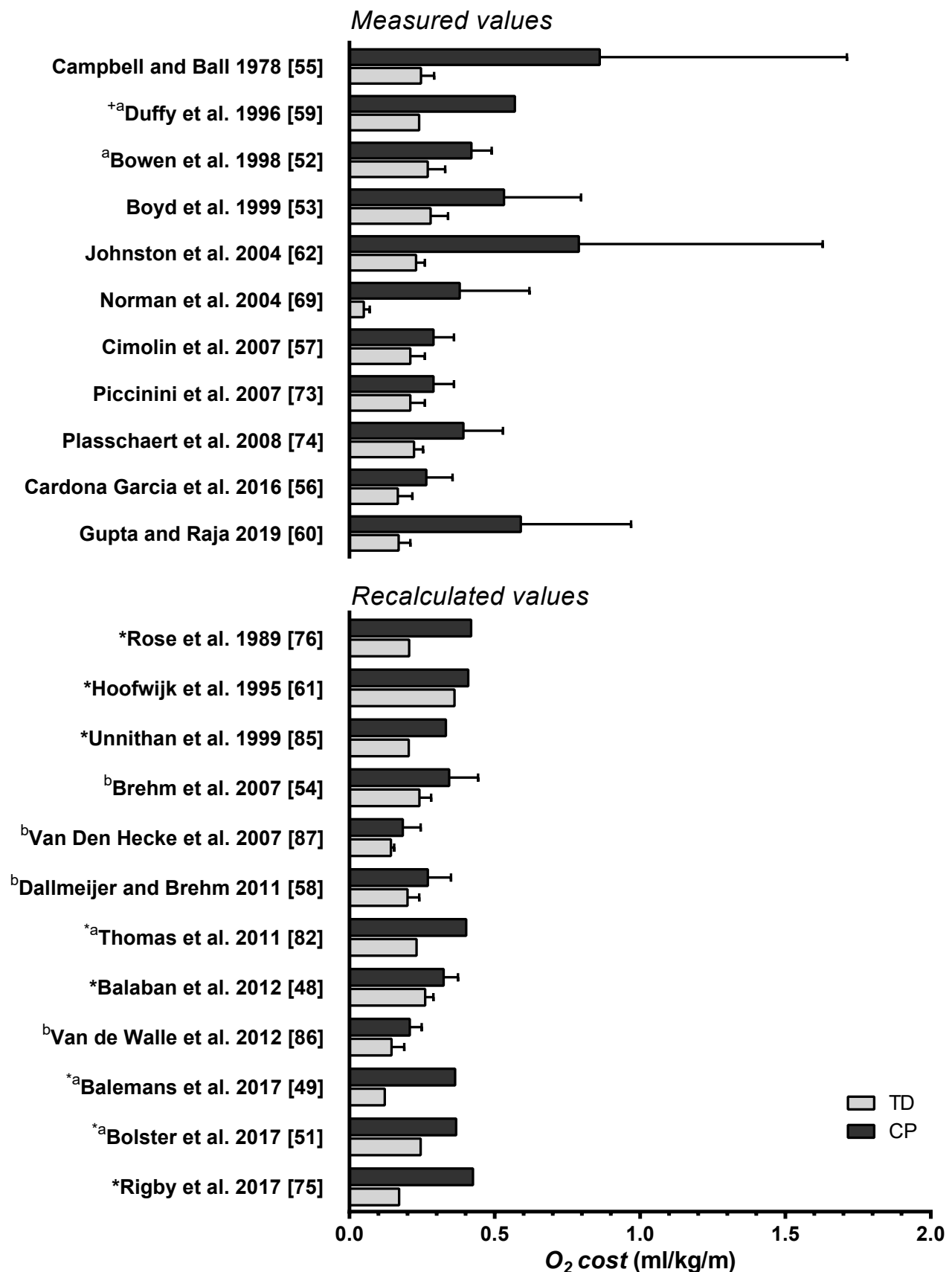
<sup>+</sup>SD is not reported in the original paper;

<sup>°</sup>Originally reported in kcal/min (converted and normalized by group mean body mass);

<sup>1</sup>CP(total) mean is calculated (weighted average of subgroups of CP);

<sup>2</sup>Originally reported in j/kg/min.

# Energy cost of walking

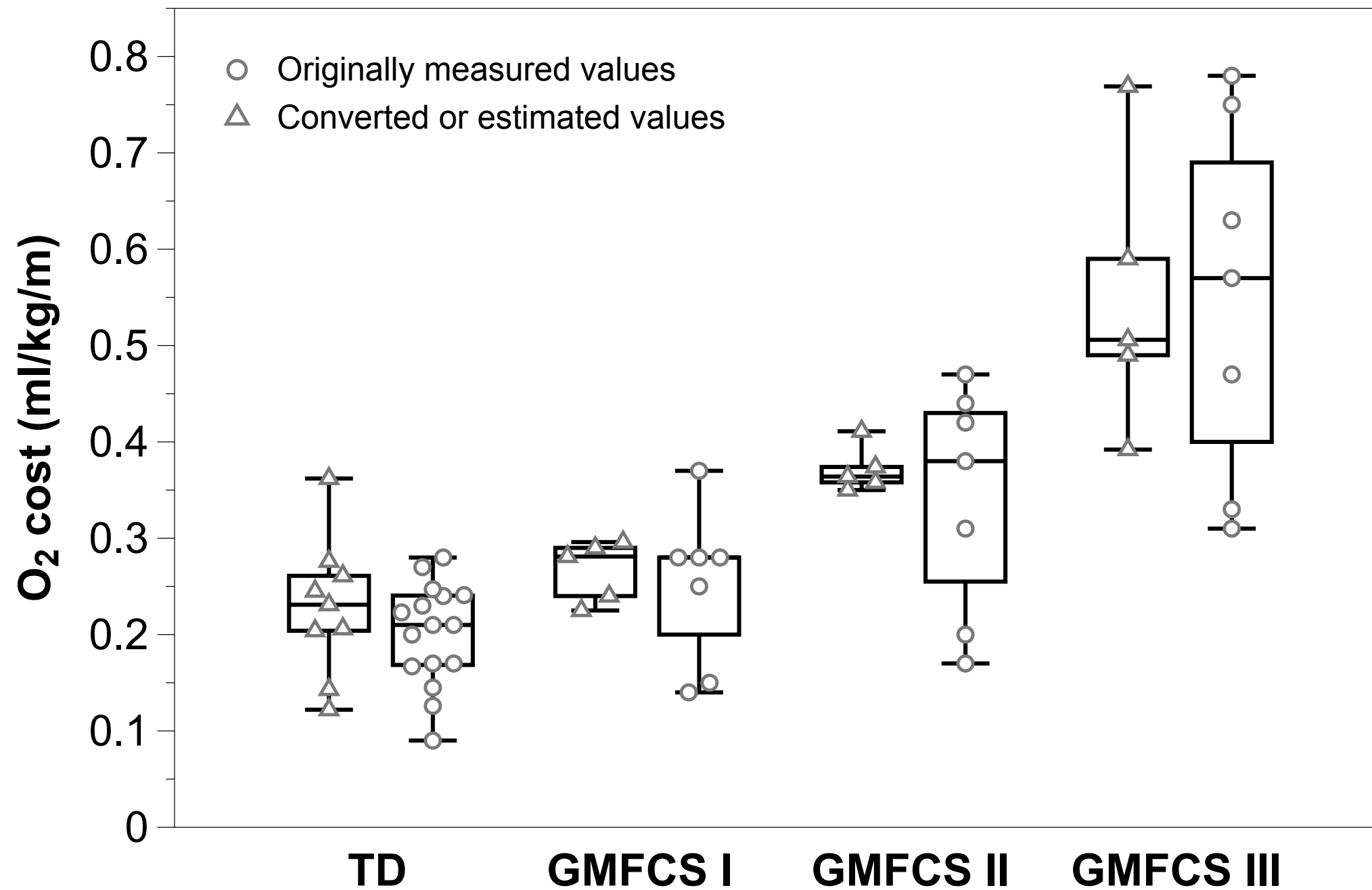


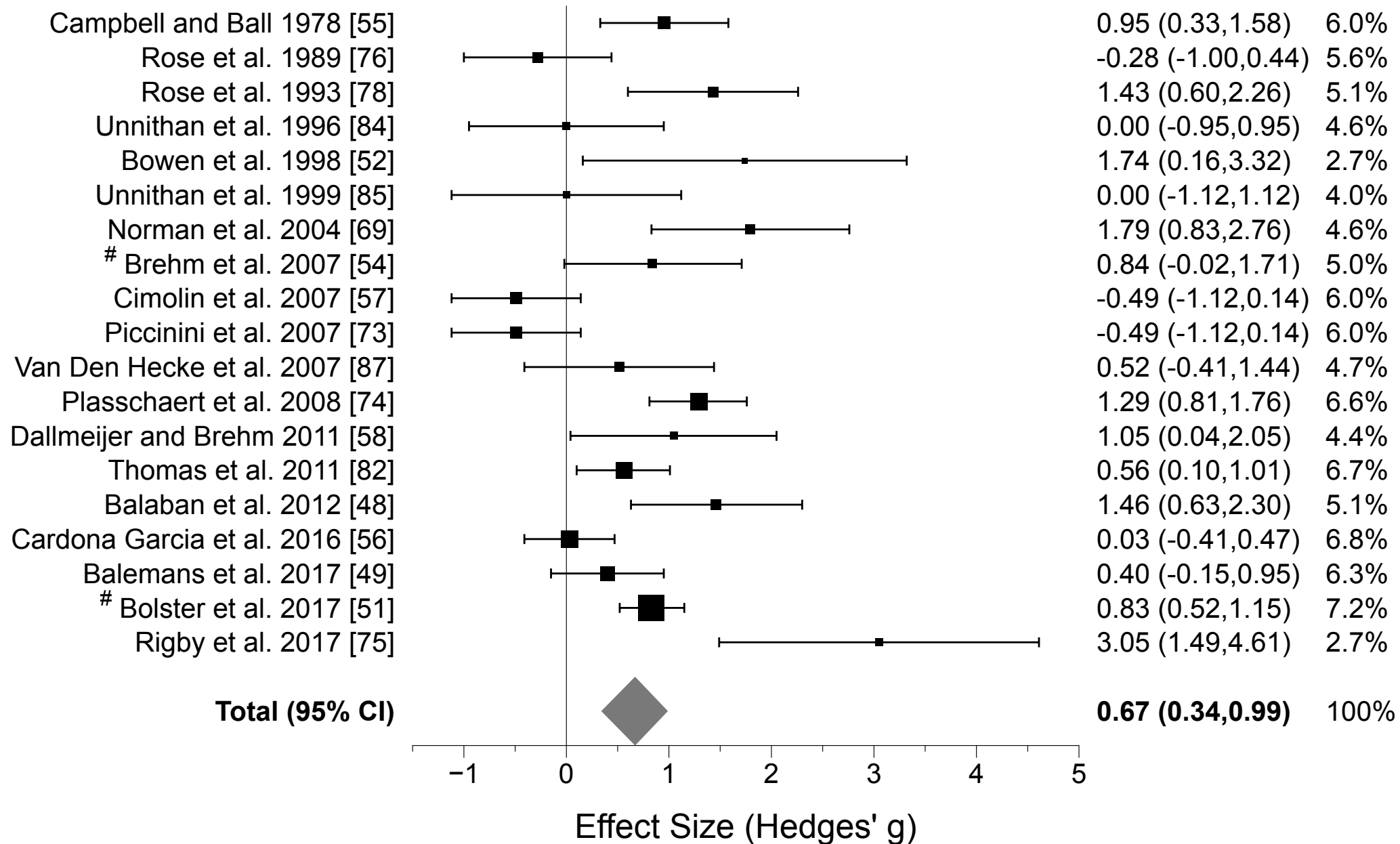
<sup>\*</sup> O<sub>2</sub>cost is estimated (avg VO<sub>2</sub>/avg speed);

<sup>+</sup>SD is not reported in the original paper;

<sup>a</sup>CP(total) mean is estimated (weighted average of subgroups of CP);

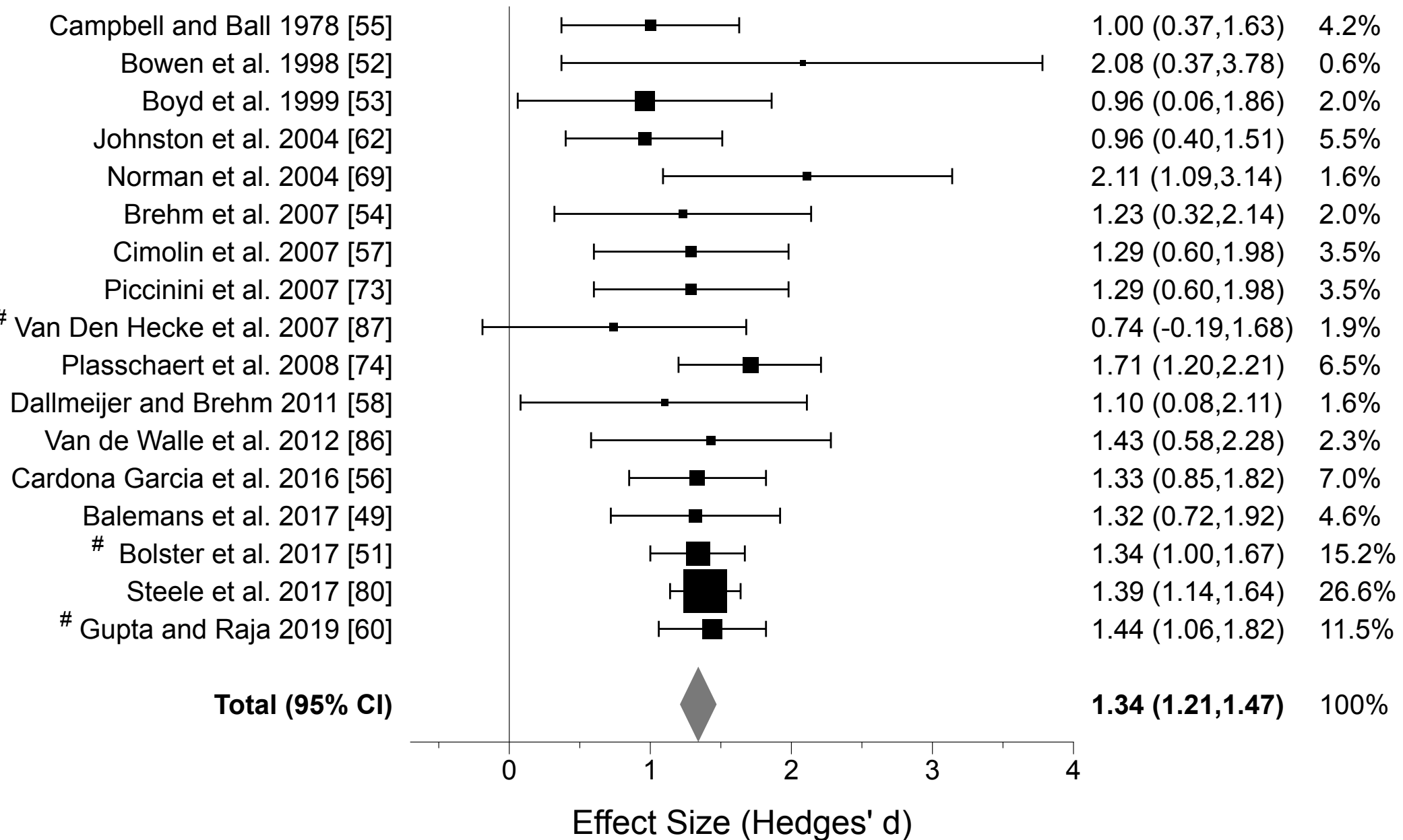
<sup>b</sup>conversion from other measures (i.e. ml/kg/m from J/kg/m).





Heterogeneity:  $I^2 = 76\%$

Test for overall effect:  $Z = 4.03$  ( $p < 0.001$ )



Heterogeneity:  $I^2 = 0\%$

Test for overall effect:  $Z = 20.44$  ( $p < 0.001$ )

**Table I.** American Academy of Cerebral Palsy and Developmental Medicine appraisal for categorization of evidence levels for group designs. Level V studies (Expert opinion, Case studies/reports, Bench research) were excluded according to exclusion criteria.

<b>Level</b>	<b>Intervention group studies</b>
I	Systematic review of randomized controlled trials (RCTs) Large RCT (with narrow confidence intervals) (n >100)
II	Smaller RCT's (with wider confidence intervals) (n <100) Systematic reviews of cohort studies "Outcomes research" (very large ecologic studies)
III	Cohort studies (must have concurrent control group) Systematic reviews of case control studies
IV	Case series Cohort study without concurrent control group (e.g., with historical control group) Case-control Study
V	Expert Opinion Case study or report Bench research Expert opinion based on theory or physiologic research Common sense/anecdotes

**Table II.** Summary of characteristics of the included studies.

Study	Research design - level of evidence	GMFCS level (I-V)	Population and sample size (subgroups)	Age (years:months; mean + SD)	Testing type
Aviram et al., 2011 [47]	Cross sectional study - III	I-III	28 children (7 TD, 21 CP: 8 GMFCS I, 6 GMFCS II, 7 GMFCS III)	TD = 7:3 ± 1:0 CP = 6:5 ± 1:11	treadmill walking
Balaban et al., 2012 [48]	Interventional study - II/III	N/A	29 children (13 TD, 16 spastic CP)	TD = 11:5 ± 2:10 CP = 11:1 ± 1:8	treadmill test (submaximal)
Balemans et al., 2017 [49]	Cross sectional study - II/III	I-III	57 children and adolescents (20 TD, 37 spastic CP: 13 GMFCS I, 17 GMFCS II, 7 GMFCS III)	TD = 11:10 ± 3:6 GMFCS I = 11:5 ± 3:1 GMFCS II = 13:1 ± 3:8 GMFCS III = 16:5 ± 4:1	self-paced walking
Bell and Davies 2010 [50]	Cross sectional study - III	I-II	32 children (16 TD, 16 spastic CP: 8 GMFCS I, 8 GMFCS II)	TD = 8:7 ± 2:7 CP = 8:11 ± 2:2	self-paced walking
Bolster et al., 2017 [51]	Cross sectional study - II	I-III	191* Children and young adults (63 TD, 128 CP: 48 GMFCS I, 56 GMFCS II, 24 GMFCS III) *value at <b>rest</b> for <b>180</b> (net and NN EC)	TD = 12:5 ± 4:11 GMFCS I = 10:8 ± 3:9 GMFCS II = 12:8 ± 4:3 GMFCS III = 11:6 ± 4:3	self-paced walking
Bowen et al., 1998 [52]	Cross sectional study - III	N/A	10 children (5 TD, 5 CP)	TD = 9:6 ± 3:1 CP = 10:0 ± 4:5	self-paced walking
Boyd et al., 1999 [53]	Cross sectional study - II/III	N/A	182 children with <b>motor disabilities</b> (5 TD, <b>133 CP</b> [4 Hemiplegia, 10 Quadriplegia, <b>119 Diplegia</b> ], 26 Spina bifida, 18 Femoral shaft fractures)	N/A	self-paced walking
Brehm et al., 2007 [54]	(preliminary) Repeated measure - III	I-III	23 children (10 TD, 13 spastic CP) *6 TD, 9 CP (resting and net values)	TD = 8:11 ± 3:3 CP = 8:7 ± 3:4	self-paced walking
Campbell and Ball 1978 [55]	Cross sectional study - III	N/A <sup>a</sup>	TD children ( <i>n</i> not reported) and 22 spastic diplegic CP	TD = 10:0 ± 2:1 CP = 10:6 ± 2:9	N/A
Cardona Garcia et al., 2016 [56]	Cross sectional study - II	I-II	80 children (40 TD, 40 CP)	TD: 11 ± 3:7 CP: 11 ± 3:4	1) self-paced walking 2) Incremental treadmill walking test
Cimolin et al., 2007 [57]	Cross sectional study - II	N/A	40 children (20 TD, 20 spastic hemi/diplegic CP)	TD = 7:9 ± 2:1 CP = 8:8 ± 2:7	self-paced barefoot walking
Dallmeijer and Brehm 2011 [58]	Cross sectional study - III	I-II	18 children (10 TD, 8 mild spastic CP)	TD = 9:10 ± 2:11 CP = 9:11 ± 3:0	self-paced walking
Duffy et al., 1996 [59]	Cross sectional study - III	N/A <sup>a</sup>	56 children (16 TD; <b>CP: 13 Diplegia, 6 Hemiplegia</b> ; Spina bifida: 11 L3/4, 10 L5/S1)	TD = 9 (5-12) Diplegia = 8:6 (4-12) Hemiplegia = 5:6 (5-7) (Range)	self-paced walking
Gupta and Raja 2019 [60]	Longitudinal study - III	I-III	138 children (58 TD, 80 spastic diplegic CP: 6 GMFCS I, 11 GMFCS II, 63 GMFCS III)	Overall range: 6-18 (mean and SD not reported)	self-paced (outdoor) walking
Hoofwijk et al., 1995 [61]	Cross-sectional study - III	N/A <sup>a</sup>	18 children (9 TD; 9 CP)	TD = 14:0 ± 2:5 CP = 13:6 ± 2:8	maximal incremental treadmill walking test
Johnston et al., 2004 [62]	Cross sectional study - III	I-IV	57 children (30 TD, 27 CP: 5 GMFCS I, 10 GMFCS II, 9 GMFCS III, 6 GMFCS IV)	TD = 10:0 ± 1:6 CP = 9:6 ± 2:4	self-paced walking
Kamp et al., 2014 [63]	(retrospective) Cross-sectional study - II	I-III	276 children with spastic CP (79 GMFCS I, 123 GMFCS II, 74 GMFCS III)	GMFCS I: 12:10 (4:11) GMFCS II: 12:6 (4:11) GMFCS III: 11:3 (4:8) *Median (Interquartile range)	self-paced walking

Study	Research design - level of evidence	GMFCS level (I-V)	Population and sample size (subgroups)	Age (years:months; mean + SD)	Testing type
Kerr et al., 2007 [64]	Cross sectional study - II	I-IV	47 children with bilateral spastic CP (6 GMFCS I, 27 GMFCS II, 10 GMFCS III, 3 GMFCS IV)	CP (overall): 11:8 ± 3:6 GMFCS I: 11:11 ± 3:3 GMFCS II: 10:9 ± 3:6 GMFCS III: 13:5 ± 3:5 GMFCS IV: 13:5 ± 2:1	self-paced walking
Kerr et al., 2008 [65]	Cross-sectional study - II	I-IV	<b>115/184</b> ambulant children with CP ( <b>64/94</b> unilateral-, <b>47/84</b> bilateral-spastic, <b>4/6</b> non-spastic) ( <b>44/57</b> GMFCS I, <b>55/91</b> GMFCS II, <b>11/22</b> GMFCS III, <b>5/14</b> GMFCS IV) <b>*O<sub>2</sub> cost</b> assessment	CP (overall): 10:9 ± 3:7 GMFCS I: 12:1 ± 0:5 GMFCS II: 9:11 ± 0:4 GMFCS III: 10:11 ± 0:11 GMFCS IV: 11.9 ± 0:11	self-paced walking
Kerr et al., 2011 [66]	Longitudinal study - II	I-IV	ambulant children with CP <b>baseline:</b> 184* (57 GMFCS I, 91 GMFCS II, 22 GMFCS III, 14 GMFCS IV) <b>2<sup>nd</sup> visit:</b> 157* (55 GMFCS I, 70 GMFCS II, 16 GMFCS III, 10 GMFCS IV, 6 Missing) <b>*85</b> matched net O <sub>2</sub> cost data	CP (visit 1) = 10:10 ± 3:7 CP (visit 2) = 13:4 ± 3:6	self-paced walking
Maltais et al., 2004 [67]	Cross sectional study - III	I-II	20 children and adolescents (10 TD, 10 mild spastic hemi/diplegic CP)	TD = 13:0 (10:7-16:7) CP = 13:0 (10:4-16:4) (Range)	submaximal treadmill walking in the heat
Marconi et al., 2012 [68]	Cross sectional study - II/III	N/A	63 children (20 TD, 43 CP: 11 Hemiplegia, 32 Diplegia)	TD = 9:4 ± 2:6 CP (Hemiplegia) = 8:6 ± 4 CP (Diplegia) = 7:6 ± 7:6	incremental treadmill walking test
Norman et al., 2004 [69]	Cross sectional study - III	N/A	25 children (15 TD, 10 spastic diplegic CP)	TD = 11:8 ± 2:8 CP = 12:10 ± 2:11	self-paced walking
Norman et al., 2006 [70]	Cross sectional study - III	N/A	15 children (10 TD, 5 spastic diplegic CP)	TD = 12:7 ± 2:10 CP = 13:8 ± 3:7	self-paced walking
Oeffinger et al., 2004 [71]	(retrospective) Cross sectional study - II	I-III	1047 <b>[419]</b> ambulatory children with CP (GMFCS I: 457 <b>[179]</b> ; GMFCS II: 286 <b>[134]</b> ; GMFCS III: 304 <b>[106]</b> ) <b>*in brackets [ ]:</b> subjects with O <sub>2</sub> cost assessment	CP (overall) = 11:2 ± 4 GMFCS I = 10:9 ± 4 GMFCS II = 11:2 ± 4:3 GMFCS III = 10:7 ± 4:2 <b>*all participants (not everyone with O<sub>2</sub> cost)</b>	walking test
Oeffinger et al., 2007 [72]	Cross sectional study - II	I-III	562 children with hemi/diplegic CP ( <b>180/240</b> GMFCS I, <b>140/196</b> GMFCS II, <b>65/126</b> GMFCS III) <b>*O<sub>2</sub> cost</b> assessment	CP (overall) = 11:1 ± 3:8 GMFCS I = 11:4 ± 3:8 GMFCS II = 11:0 ± 3:8 GMFCS III = 12:7 ± 3:4	N/A
Piccinini et al., 2007 [73]	Cross sectional study - II	N/A	40 children (20 TD, 20 spastic hemi/diplegic CP)	TD = 7:9 ± 2:1 CP = 8:8 ± 2:7	self-paced barefoot walking test
Plasschaert et al., 2008 [74]	Cross sectional study (repeated measures) - II	N/A	84 children (42 TD, 42 CP)	TD = 11:5 ± 2:1 CP = 12:0 ± 2:7	self-paced walking tests (2 conditions: normal, +10% BW)
Rigby et al., 2017 [75]	Interventional study - II/III	N/A	16 children (8 TD, 8 spastic CP)	TD = 10:7 ± 2:1 CP = 10:4 ± 4:5	treadmill test (submaximal)
Rose et al., 1989 [76]	Cross sectional study - III	N/A <sup>a</sup>	31 children (18 TD, 13 spastic CP: 4 Hemiplegia, 9 Diplegia)	TD = 12:6 (7-17) CP = 11:2 (7-16) (Range)	incremental treadmill walking test
Rose et al., 1990 [77]	Cross sectional study - III	N/A <sup>a</sup>	31 children (18 TD, 13 spastic CP: 3 Hemiplegia, 10 Diplegia)	TD = 12:6 (7-17) CP = 11:2 (7-16) (Range)	incremental treadmill walking test
Rose et al., 1993 [78]	Cross sectional study - III	N/A <sup>a</sup>	31 children (18 TD, 12 spastic CP: 3 Hemiplegia, 9 Diplegia)	TD = 12:7 ± 3:8 CP = 11:6 ± 2:5	incremental treadmill walking test



Study	Research design - level of evidence	GMFCS level (I-V)	Population and sample size (subgroups)	Age (years:months; mean + SD)	Testing type
Slaman et al., 2013 [79]	Cross-sectional study - III	I-III	36 adults with spastic bilateral CP (9 GMFCS I, 21 GMFCS II, 6 GMFCS III)	CP (overall) = 36 ± 6 *not reported for subgroups	self-paced walking
Steele et al., 2017 [80]	(retrospective) Cross-sectional study - II	N/A	650 children (77 TD*, 573 bilateral CP) *data from a TD database	TD = 10:8 ± 4:2 CP = 10:4 ± 3:11	self-paced walking
Thomas et al., 2009 [81]	Cross sectional study - III	I-III	23 children with spastic diplegic CP (10 GMFCS I, 8 GMFCS II, 5 GMFCS III)	CP (overall) = 11:2 ± 0:2 GMFCS I = 11:6 ± 0:2 GMFCS II = 11:0 ± 0:4 GMFCS III = 11:0 ± 0:5	self-paced walking
Thomas et al., 2011 [82]	Longitudinal cohort study - III	I-III	79 children (45 TD; 34 spastic diplegic CP: 16 GMFCS I, 13 GMFCS II, 5 GMFCS III)	TD = 11:1 ± 3:5 GMFCS I = 12:8 ± 3:0 GMFCS II = 12:4 ± 3:6 GMFCS III = 11:0 ± 4:9	self-paced walking
Trost et al., 2016 [83]	Cross sectional study - II/III	I-III	51 youth with CP (27 GMFCS I, 12 GMFCS II, 12 GMFCS III)	GMFCS I = 12:5 ± 3:4 GMFCS II = 12:4 ± 3:5 GMFCS III = 12:8 ± 3:1	3 walking trials: comfortable-, brisk- and fast-speed
Unnithan et al., 1996 [84]	Cross sectional study - III	N/A*	18 children (8 TD*; 9 spastic CP: 7 diplegic, 1 hemiplegic, 1 quadriplegic) *8/9 TD considered	TD = 13:7 ± 2:1 CP = 12:8 ± 2:10	maximal and submaximal treadmill walking test
Unnithan et al., 1999 [85]	Cross sectional study - III	N/A	13 children (5 TD, 8 spastic CP: 6 diplegic, 1 hemiplegic, 1 quadriplegic)	TD = 13:5 ± 2:10 CP = 12:2 ± 2:8	submaximal treadmill walking test
Van de Walle et al., 2012 [86]	Cross-sectional study - III	I-II	48 children (18 TD children, 11 TD adults, 19* children with spastic diplegic CP) *11 O <sub>2</sub> cost measures available	TD children = 9:4 [7:8–10:7]* TD adults = 24:8 [23:6–28:6]* CP children = 10:1 [9:10 -10:10]* *Median and inter quartile ranges [IQ1–IQ3]	self-paced walking
Van Den Hecke et al., 2007 [87]	Cross sectional study - II/III	N/A	26 children (6 TD, 20 spastic hemiplegic CP)	TD = 9:11 ± 0:7 CP = 8:1 ± 1:7	treadmill walking (at comfortable overground speed)
CP, cerebral palsy; TD typically developing; GMFCS, Gross Motor Function Classification System (level); CWS, comfortable walking speed; FWS, fastest walking speed; N/A, not available; avg, average; *article published before 1997 (year of GMFCS development); s-s, at steady-state. Age is reported in years:months for all the included studies (converted when originally reported in years only).					

**Table III.** Summary of protocol, outcome measures, main results and statistics for the included studies.

Study	Protocol	Energy expenditure outcome (s)	Main results	SS
Aviram et al., 2011 [47]	1) self-paced walking (4 min); 2) treadmill walking at CWS +20-30%	<b>EE rate</b> (Kcal/min) <b>CWS:</b> TD: 2.10 ± 0.28 CP: 1.71 ± 0.79 <b>CWS +20-30%:</b> TD: 2.07 ± 0.36 CP: 2.43 ± 1.14	N/A	N/A
Balaban et al., 2012 [48]	5 min treadmill constant speed (0.5 m/s) walking.	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 7.83 ± 0.83 CP (baseline): 9.72 ± 1.51	Higher $\dot{V}O_2$ in CP group at baseline.	P=0.001
Balemans et al., 2017 [49]	6 min walking on an oval track.	<b>(gross) Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 20.0 ± 5.8 GMFCS I: 21.2 ± 4.0 GMFCS II: 22.0 ± 5.6 GMFCS III: 24.0 ± 4.4 <b>EC</b> (J/kg/min): TD: 4.9 ± 1.1 GMFCS I: 6.0 ± 1.2 GMFCS II: 7.2 ± 1.5 GMFCS III: 10.6 ± 2.9	Higher EC in CP, increasing with severity.	P<0.001 (each comparison)
Bell and Davies 2010 [50]	5 min rest (sitting); 10 min walking (oval 20m track); 5 min rest (sitting).	<b>Walking EE</b> (kJ/min): TD: 10.3 ± 2.3 CP: 13.8 ± 4.9 * adjusted for body size (power function models)	Higher walking EE in CP	P<0.05
Bolster et al., 2017 [51]	5 min rest; 6 min walking on an indoor oval track (40 m).	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 18.46 (0.58) GMFCS I: 20.81 (0.67) GMFCS II: 22.75 (0.62) GMFCS III: 25.09 (0.95) <b>Gross [net] EC</b> (J/kg/m): TD: 4.93 (0.19) [3.11 (0.16)] GMFCS I: 5.90 (0.22) [4.00 (0.20)] GMFCS II: 7.69 (0.20) [5.45 (0.17)] GMFCS III: 10.89 (0.31) [7.68 (0.27)] <b>*Mean (SE)</b>	Higher walking $\dot{V}O_2$ , gross EC, net EC in CP subgroups. All EC measures differ significantly between GMFCS levels, walking $\dot{V}O_2$ only between level I and III.	P<0.001
Bowen et al., 1998 [52]	2 min rest (supported sitting); walking on an indoor oval track for a recorded distance (219-598 m); 2 min rest (supported sitting). *5 measurements within 65 days	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 19.78 ± 4.51 CP: 26.86 ± 2.58 <b>O<sub>2</sub> cost*</b> (ml/kg/m) <b>*<math>\dot{V}O_2</math>/distance</b> walked: TD: 0.27 ± 0.06 CP: 0.42 ± 0.07	Higher O <sub>2</sub> cost and $\dot{V}O_2$ in CP group.	P<0.001

Study	Protocol	Energy expenditure outcome (s)	Main results	SS
Boyd et al., 1999 [53]	5 min rest; 10 min walking (10m oval track).	<b>(gross) O<sub>2</sub> cost</b> (ml/kg/m): TD group: 0.28 ± 0.06 Hemiplegic CP: 0.36 ± 0.17 Quadriplegic CP: 0.51 ± 0.23 Diplegic CP (total): 0.54 ± 0.27	Higher O <sub>2</sub> cost in the most impaired (hemiplegia<quadriplegia and diplegia).	N/A
Brehm et al., 2007 [54]	10 min rest (sitting, watching a video); 5 min walking (50-m indoor oval track). *Repeated 4 times in 4 weeks	<b>Gross (net) ECS</b> (J/kg/min) TD: 359 (224) ± 55 (35) CP: 433 (275) ± 101 (67) <b>Gross (net) EC</b> (J/kg/m): TD: 4.80 (2.90) ± 0.8 (0.3) CP: 6.84 (4.40) ± 2.0 (1.5) *missing values at rest for 8 subjects (4 CP, 4 TD)	Higher gross- and net energy consumption (ECS), energy cost (EC) in CP; higher ECS at rest in CP.	P<0.001, P<0.013 (ECS at rest)
Campbell and Ball 1978 [55]	N/A	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 18.1 ± 3.30 CP: 22.9 ± 6.17 <b>O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.247 ± 0.045 CP: 0.862 ± 0.851	Higher $\dot{V}O_2$ and O <sub>2</sub> cost in CP group	P<0.0005
Cardona Garcia et al., 2016 [56]	1) Walking test: 6-min walk (over 5 m) 2) Incremental treadmill walking*: Initial speed: 2.0 km/h + 0.1 km/hr and 0.5% grade every 15 sec until exhaustion *not clear if allowed to run	<b><math>\dot{V}O_2</math> walk</b> (ml/kg/min): CP: 12.2 ± 3.7 TD: 12.1 ± 2.8 <b>O<sub>2</sub> cost</b> (ml/kg/m): CP: 0.265 ± 0.09 TD: 0.167 ± 0.05	Higher O <sub>2</sub> cost in CP	P<0.001
Cimolin et al., 2007 [57]	2 min rest (sitting); 7 laps (250m in total) of walking; 2 min recovery (sitting)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 15.6 ± 3.21 CP: 13.97 ± 3.28 <b>O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.21 ± 0.05 CP: 0.29 ± 0.07	Higher O <sub>2</sub> cost in CP group.	P<0.05
Dallmeijer and Brehm 2011 [58]	<b>Resting energy expenditure:</b> 10 min (sitting while watching a video); <b>5-min walk test:</b> 5 min walking (circular 50-m indoor track)	<b>Gross (net) <math>\dot{V}O_2</math> walk</b> (ml/kg/min): CP: 19.7 (13.7) ± 2.8 (2.2) TD: 16.1 (11.1) ± 3.6 (3.3) <b>EC</b> (J/kg/m) CP: 5.47 ± 1.45 TD: 3.96 ± 0.73 <b>(gross) O<sub>2</sub> cost</b> (ml/kg/m): CP: 0.27 ± 0.08 TD: 0.20 ± 0.04	Higher gross walking $\dot{V}O_2$ , O <sub>2</sub> cost and EC in CP	P<0.05
Duffy et al., 1996 [59]	2-3 min rest; 3-4 min walking (10-m laboratory laps)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 18.0 Diplegic CP: 28.0 Hemiplegic CP: 20.3 <b>O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.24 Diplegic CP: 0.64 Hemiplegic CP: 0.42	Higher $\dot{V}O_2$ in diplegic CP compared to TD; higher O <sub>2</sub> cost in both CP groups	P<0.05

Study	Protocol	Energy expenditure outcome (s)	Main results	SS
Gupta and Raja 2019 [60]	3 min rest (sitting); 5 min outdoor walking (uneven surface - 100m figure-8 pathway)	<b>Net O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.17 (0.13-0.19) CP: 0.59 (0.37-0.88) *Data as <b>MEAN (C.I.)</b>	Higher net O <sub>2</sub> cost in CP	P<0.05
Hoofwijk et al., 1995 [61]	CWS: avg of 3x20m corridor walks Incremental test: <b>Start:</b> CWS + increments* (2 min) until FWS, then increments (2 min): 0.2-0.5 km/hr +2.4-5% gradient until exhaustion *not specified	<b><math>\dot{V}O_2</math>max</b> (ml/kg/min): TD: 45.2 ± 8.4 CP: 32.7 ± 4.8 <b><math>\dot{V}O_2</math>max</b> (L/min): TD: 2.29 ± 0.80 CP: 1.58 ± 0.68	Lower $\dot{V}O_2$ max in CP	P=0.001
Johnston et al., 2004 [62]	5 min rest (sitting); 2 min walking warm up; 5 min (at least) s-s walking (24-m oval track); 3 min rest (sitting)	<b>O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.23 ± 0.03 CP: 0.79 ± 0.84 GMFCS I: 0.28* GMFCS II: 0.44* GMFCS III: 0.63* GMFCS IV: 2.17* *as reported in graph	Higher O <sub>2</sub> cost in CP. Increasing O <sub>2</sub> cost as a function of GMFCS levels - correlation (0.87)	P<0.0001 (between-groups), P<0.01 (correlation)
Kamp et al., 2014 [63]	5 min rest (sitting); 6 to 8 min walking; 5 min rest (sitting)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): GMFCS I: 15.51 (5.78) GMFCS II: 16.57 (6.64) GMFCS III: 18.92 (5.86) <b>gross O<sub>2</sub> cost</b> (ml/kg/m): GMFCS I: 0.25 (0.89) GMFCS II: 0.31 (0.14) GMFCS III: 0.47 (0.27) <b>EC</b> (J/kg/m) GMFCS I: 5.20 (1.81) GMFCS II: 6.38 (2.68) GMFCS III: 9.80 (5.44) *Data as <b>MEAN (IQ range)</b>	EC increases with severity: inverse relationship between EC and GMFCS level (R <sup>2</sup> =0.42)	P<0.0001 (EC across GMFCS levels)
Kerr et al., 2007 [64]	5 min rest (sitting); 5 min walking (20-m oval track); 5 min recovery (sitting)	<b>Net O<sub>2</sub> cost</b> (ml/kg/m): GMFCS I: 0.14 GMFCS II: 0.20 GMFCS III: 0.33 GMFCS IV: 0.54 *reported in figure only	Higher net O <sub>2</sub> cost in GMFCS level II compared to III and III compared to IV	P<0.001 (GMFCS II vs III and III vs IV)
Kerr et al., 2008 [65]	5-min rest (sitting); 5-min walking (20-m oval track); 5-min recovery (sitting)	<b>Net O<sub>2</sub> cost</b> (ml/kg/m): CP (total): 0.18 ± 0.10 GMFCS I: 0.15 ± 0.04 GMFCS II: 0.17 ± 0.07 GMFCS III: 0.31 ± 0.12 GMFCS IV: 0.36 ± 0.27	Net O <sub>2</sub> cost increases with severity (GMFCS level)	P<0.001 (except for GMFCS I vs II and III vs IV)
Kerr et al., 2011 [66]	5-min rest (sitting); 5-min walking (20-m oval track); 5-min recovery (sitting) *re-assessment 2 years 7 months after baseline	<b>Net O<sub>2</sub> cost</b> (ml/kg/m): CP (baseline): 0.188 ± 0.105 CP (2 <sup>nd</sup> visit – 2 years, 8): 0.204 ± 0.110	O <sub>2</sub> cost decreased from 1st visit; weak relationship for age and O <sub>2</sub> cost.	P=0.04 (between visits)

Study	Protocol	Energy expenditure outcome (s)	Main results	SS
Maltais et al., 2004 [67]	10 min rest; 10-min treadmill walking (3 bouts) speed and slope set to yield the <b>selected HR*</b> (140-150 b/min) in the <b>heat</b> (35 ± 1°C, 45-50% RH) *CP group (matched TD at same speed)	$\dot{V}O_2$ (L/min) - bout 1, 2, 3 CP: 0.84 ± 0.08, 0.88 ± 0.11, 0.86 ± 0.12; TD: 0.57 ± 0.05, 0.62 ± 0.07, 0.62 ± 0.07	Higher $\dot{V}O_2$ in CP group at each walking bout	P<0.001
Marconi et al., 2012 [68]	3 min rest (standing); Incremental treadmill test (1km/h every 3/4 min – range: 1-6 km/h)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min) – multiple subgroups at different walking speeds <b>Net EC</b> (J/kg/m) in figure only	walking $\dot{V}O_2$ interaction between “group” and “age”: Higher $\dot{V}O_2$ and EC in diplegic CP for each age group; Higher $\dot{V}O_2$ and EC in hemiplegic CP only for younger group.	P<0.001
Norman et al., 2004 [69]	7 min rest; 6 min walking (50-m oval path)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 6.3 ± 1.9 CP: 19.7 ± 11.3 <b>OCl - net O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.05 ± 0.02 CP: 0.38 ± 0.24 <b>O<sub>2</sub> cost*</b> (ml/kg/m): TD: 0.09 ± 0.02 CP: 0.55 ± 0.38 <b>*<math>\dot{V}O_2</math>/distance</b> walked	Higher $\dot{V}O_2$ at rest and during walking in CP; Higher O <sub>2</sub> cost* and net O <sub>2</sub> cost (OCl) in CP	P<0.05 ( $\dot{V}O_2$ at rest, P<0.001
Norman et al., 2006 [70]	7 min [last 2 min] rest; 6 min [4 <sup>th</sup> and 5 <sup>th</sup> ] walking (50-m oval path) [considered for the analysis]	<b>Walking Energy Expenditure</b> (kcal): TD: 5.6 ± 1.1 CP: 14.6 ± 5.1	Net relative walking $\dot{V}O_2$ higher in CP ( <u>values not reported</u> )	P<0.03
Oeffinger et al., 2004 [71]	N/A	<b>O<sub>2</sub> cost</b> (ml/kg/m): GMFCS I: 0.37 (0.11-1.4) GMFCS II: 0.47 (0.06-1.1) GMFCS III: 0.78 (0.28-2.5) <b>*Data as MEAN (range)</b>	Higher O <sub>2</sub> cost with increasing severity - positive relationship between GMFCS level and O <sub>2</sub> cost (r= 0.61)	P<0.05 (O <sub>2</sub> cost across GMFCS), P<0.0001 (relationship)
Oeffinger et al., 2007 [72]	N/A	<b>O<sub>2</sub> cost</b> (ml/kg/m): GMFCS I: 0.28 ± 0.1 GMFCS II: 0.38 ± 0.2 GMFCS III: 0.57 ± 0.3	O <sub>2</sub> cost increases with severity (GMFCS levels)	P<0.05 (between each level)
Piccinini et al., 2007 [73]	2 min rest (sitting); 7 laps (250m in total) of walking; 2 min recovery (sitting)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 15.6 ± 3.21 CP: 13.97 ± 3.28 <b>O<sub>2</sub> cost</b> (ml/kg/m) TD: 0.21 ± 0.05 CP: 0.29 ± 0.07	Higher O <sub>2</sub> cost in CP	P<0.05
Plasschaert et al., 2008 [74]	5 min rest (sitting); 8 min walking (34-m figure 8 track); 5 min recovery (sitting) *2 tests in random order: 1) <b>standard condition</b> , 2) addition of a 10% BW waist-belt	<b>(gross) Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 15.4 ± 2.3 CP: 20.7 ± 5.3 <b>gross O<sub>2</sub> cost</b> (ml/kg/m): TD: 0.223 ± 0.031 CP: 0.393 ± 0.136 (Values for standard condition only)	Higher $\dot{V}O_2$ , gross O <sub>2</sub> cost, in CP for both conditions	P<0.001
Rigby et al., 2017 [75]	5 min rest; 5-10 min treadmill walking (1.60934 km/h, 0% grade)* with 3-5 min s-s *speed originally reported in mph	<b>(gross) Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 9.80 ± 1.70 CP: 16.70 ± 2.50 <b>EE</b> (Kcal/min) TD: 2.20 ± 0.50 CP: 2.80 ± 1.30	Higher gross walking $\dot{V}O_2$ in CP (Effect size= 0.71)	P<0.001

Study	Protocol	Energy expenditure outcome (s)	Main results	SS
Rose et al., 1989 [76]	<b>starting speed:</b> 21.5 m/min <b>Steps</b> (2 min): 29.5, 35.9, 51, 64.4, 77.8, 91.2, 104.6, 118, 131.4 m/min <b>End:</b> running, unsteady gait or exhaustion	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 25.1 ± 5 CP: 23.4 ± 7	No between-group differences in $\dot{V}O_2$ , walking speed is lower in CP however	NS
Rose et al., 1990 [77]	<b>starting speed:</b> 21.5 m/min <b>Steps</b> (2 min): 29.5, 35.9, 51, 64.4, 77.8, 91.2, 104.6, 118, 131.4 m/min <b>End:</b> running, unsteady gait or exhaustion	<b>Economical EEI(O<sub>2</sub>)</b> (ml/kg-m): TD: 0.17 ± 0.02 CP: 0.48 ± 0.22 Hemiplegic: 0.21 ± 0.01 Diplegic: 0.56 ± 0.18	Higher Economical EEI(O <sub>2</sub> ) in CP; higher in diplegic compared to hemiplegic group.	P<0.0003 (CP-TD); P<0.004 (diplegia-hemiplegia)
Rose et al., 1993 [78]	<b>starting speed:</b> 21.5 m/min <b>Steps</b> (2 min): 29.5, 35.9, 51, 64.4, 77.8, 91.2, 104.6, 118, 131.4 m/min <b>End:</b> running, unsteady gait or exhaustion	<b><math>\dot{V}O_2</math></b> (ml/min/kg): <i>Slow speed</i> (21.5 m/min) TD: 8.63 ± 1.27 CP: 14.25 ± 3.67 <i>Faster speed</i> (37.6 m/min) TD: 10.55 ± 1.24 CP: 19.08 ± 7.20 <i>Economical speed</i> TD: 15.4 ± 2.7 CP: 22.8 ± 7.3	At slow (21.5 m/min) and faster speed (37.6 m/min), higher $\dot{V}O_2$ in CP, higher in diplegic compared to hemiplegic group. At <i>economical speed</i> , higher $\dot{V}O_2$ for CP compared to TD and for diplegic compared to hemiplegic group.	<i>Slow speed:</i> P=0.0001 (CP-TD); P=0.008 (Diplegic-Hemiplegic) <i>Faster speed:</i> P=0.0001 (CP-TD) P=0.0006 (Diplegic-Hemiplegic) <i>Economical walking speed:</i> P<0.05
Slaman et al., 2013 [79]	3 min walking (12-m trajectory with smooth turns)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): CP (all): 15.0 ± 4.4 GMFCS I: 11.6 ± 3.2 GMFCS II: 16.7 ± 3.9 GMFCS III: 15.7 ± 4.9	N/A	N/A
Steele et al., 2017 [80]	3-10 min rest 6-min walking test	<b>net nondimensional oxygen consumption (nn O<sub>2</sub>):</b> TD: 0.10 ± 0.03 CP: 0.18 ± 0.06	At similar walking speed, average nn O <sub>2</sub> for children with CP was 2.9 times that of speed-matched controls. Crouch severity was modestly related to nn O <sub>2</sub>	N/A
Thomas et al., 2009 [81]	10-min rest; 10 min walking (33m track); (3 tests within 1 month)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): CP(all): 19.77 ± 4.51 GMFCS I: 18.66 ± 3.16 GMFCS II: 20.81 ± 6.35 GMFCS III: 20.32 ± 3.64 <b>gross O<sub>2</sub> cost</b> (ml/kg/min): CP(all): 0.43 ± 0.24 GMFCS I: 0.28 ± 0.05 GMFCS II: 0.42 ± 0.13 GMFCS III: 0.75 ± 0.23	Significant day-to-day differences between all GMFCS levels for gross O <sub>2</sub> cost; GMFCS level accounts for 58% of variance in gross O <sub>2</sub> cost	P<0.01
Thomas et al., 2011 [82]	10-min rest; 10 min walking (33m track); *re-assessment after 1 year (no intervention)	<b>Walking <math>\dot{V}O_2</math></b> (ml/kg/min): <b>BASELINE</b> <b>1yr</b> TD: 16.1 ± 3.9; 13.7 ± 2.8 GMFCS I: 17.0 ± 4; 16.9 ± 4.6 GMFCS II: 19.5 ± 5; 19.4 ± 3.8 GMFCS III: 20.3 ± 4; 16.9 ± 3.8	<b>Baseline:</b> Higher $\dot{V}O_2$ in GMFCS II compared to TD; <b>1-year changes:</b> reduction in resting and walking $\dot{V}O_2$ (TD), significant increase in walking $\dot{V}O_2$ for GMFCS I and II compared to TD	P<0.001 P<0.01 (1-year change GMFCS I – TD)
Trost et al., 2016 [83]	3 walking trials ( <b>comfortable</b> -, brisk- and fast-speed); 6 min rest (sitting) between tests	<b>(net) EE</b> (METs): <b>Comfortable speed</b> GMFCS I: 2.8 (2.6-3.1) GMFCS II: 3.3 (2.9-3.7) GMFCS III: 3.5 (3.0-4.0) *Data as <b>MEAN (95% CI)</b>	N/A	N/A

Study	Protocol	Energy expenditure outcome (s)	Main results	SS
Unnithan et al., 1996 [84]	1)Maximal test: speed increments (every 2 min) until FWS (no running), then gradient increments (every 2 min) 2) Submaximal test (2 stages): 4 min rest; 4 min walking (3 km/h); 8 min rest; 4 min walking (90% of individual FWS)	<b>Gross (net) walking <math>\dot{V}O_2</math></b> (ml/kg/min) <b>3km/h:</b> TD: 10.2 (5.8) $\pm$ 1.2 (0.84) CP: 16.6 (12.0) $\pm$ 6.5 (5.9) <b>90% FWS:</b> TD: 20.6 (16.2) $\pm$ 2.7 (1.9) CP: 20.5 (16.1) $\pm$ 4.9 (4.5)	At low speed (3 km/h) higher $\dot{V}O_2$ in CP.	P<0.01 (net $\dot{V}O_2$ at 3 km/h) P<0.05 (gross walking $\dot{V}O_2$ at 3 km/h)
Unnithan et al., 1999 [85]	4 min rest (sitting); 4 min treadmill walking (3 km/h, 0% grade)	<b>(net) Walking <math>\dot{V}O_2</math></b> (ml/kg/min) TD: 10.2 $\pm$ 1.2 CP: 16.6 $\pm$ 6.5	Higher walking $\dot{V}O_2$ in CP	P<0.05
Van de Walle et al., 2012 [86]	5 min rest (sitting); 3 min rest (standing); 8 min walking (figure-eight track, 34 m)	<b>Net O<sub>2</sub> cost</b> (J/kg/m): TD adults: 1.8 [1.7 - 2.0] TD children: 2.7 [2.4 - 3.6] CP children: 4.2 [3.6 - 4.7] Median [IQ Range; IQ1 - IQ3]	Net O <sub>2</sub> cost increases progressively from TD adults, TD children and children with CP	P=0.036 (CP-TD children), P<0.001 (CP-TD adults, TD adults-TD children)
Van Den Hecke et al., 2007 [87]	2 min rest (standing, s-s); 2 min treadmill walking (s-s)	<b>Net walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 6.80 $\pm$ 2.00 CP: 8.00 $\pm$ 2.60 <b>gross walking <math>\dot{V}O_2</math></b> (ml/kg/min): TD: 13.00 $\pm$ 2.00 CP: 14.60 $\pm$ 3.20 <b>Net energy cost - C</b> (J/kg/m) TD: 2.85 $\pm$ 0.22 CP: 3.68 $\pm$ 1.21	Mean C value 1.3 time greater in CP. Gross and net $\dot{V}O_2$ 1.2 times	N/A

CP, cerebral palsy; TD, typically developing;  $\dot{V}O_2$ , oxygen consumption; GMFCS, Gross Motor Function Classification System (level); CWS, comfortable walking speed; FWS, fastest walking speed; N/A, not available; s-s, at steady-state; SS, statistically significant; NS, not (statistically) significant; ECS, Energy Consumption; EC, Energy cost; NN, non-dimensional (normalized by leg length); ND NOC, net non-dimensional O<sub>2</sub> cost (normalized by body mass and gravity); NOCh, net O<sub>2</sub> cost with speed normalized to height.







## PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Yes
<b>BACKGROUND</b>			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
<b>METHODS</b>			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
<b>RESULTS</b>			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
<b>DISCUSSION</b>			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
<b>OTHER</b>			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>



# PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Page 1-2,6
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	See above
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6-7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6; S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7-10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7-10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 10-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 11-14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8-9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6-8



# PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9-11; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Page 9-15
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9-10; S5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 12-16; Figure 2 and 3;
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 8-12; Table III Table IV
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 16; Figure 5 and 6; S7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 17-22
	23b	Discuss any limitations of the evidence included in the review.	Page 17-22
	23c	Discuss any limitations of the review processes used.	Page 22-23
	23d	Discuss implications of the results for practice, policy, and future research.	Page 22-23
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1, 3, 23
Competing interests	26	Declare any competing interests of review authors.	Page 23
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	S4; Table III, Table IV

**Search strategy in PubMed:**

(((((cerebral palsy[MeSH Terms]) OR (cerebral palsy[Title/Abstract])) AND (fatigue[MeSH Terms])) OR (fatigue[Title/Abstract])) OR (energy metabolism[MeSH Terms]) OR (energy metabolism[Title/Abstract])) OR (metabolic cost[Title/Abstract]) OR (energy cost[Title/Abstract]) OR (VO2[Title/Abstract]) OR (endurance[Title/Abstract]) OR (energy expenditure[Title/Abstract]) OR (aerobic capacity[Title/Abstract]) OR (oxygen consumption[Title/Abstract]))

**Search strategy in CINAHL:**

#1	(MH "cerebral palsy")
#2	(MH "fatigue") OR (MH "energy metabolism") OR (MH "metabolic cost") OR (MH "energy cost") OR (MH "VO2") OR (MH "endurance") OR (MH "aerobic capacity") OR (MH "oxygen consumption")
#3	#1 AND #2

**Search strategy in Scopus:**

((cerebral palsy) AND (fatigue OR "energy metabolism" OR "metabolic cost" OR "energy cost" OR VO2 OR endurance OR "energy expenditure" OR "aerobic capacity" OR "oxygen consumption"))

**Search strategy in Web of Science:**

((cerebral palsy) AND (fatigue OR "energy metabolism" OR "metabolic cost" OR "energy cost" OR VO2 OR endurance OR "energy expenditure" OR "aerobic capacity" OR "oxygen consumption"))

**Search strategy in ScienceDirect:**

((cerebral palsy) AND (fatigue OR "energy metabolism" OR "metabolic cost" OR "energy cost" OR VO2 OR endurance OR "energy expenditure" OR "aerobic capacity" OR "oxygen consumption"))

**S3: Scores for methodological quality assessment for included studies (questions reported below).**

Study	Research design - Level of evidence	Total Score (%)	Items											
			1	2	3	4	5	6	7	8	9	10	11	12
Aviram et al., 2011	Case-control study - IV	5/12 (41.7)	0	0	0	1	1	0	0	1	0	1	0	1
Balaban et al., 2012	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Balemans et al., 2017	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Bell and Davies, 2010	Case-control study - IV	8/12 (66.7)	1	1	1	1	1	0	0	1	0	1	0	1
Bolster et al., 2017	Case-control study - IV	8/12 (66.7)	1	1	0	1	1	1	0	1	0	1	0	1
Bowen et al., 1998	Case-control study - IV	7/12 (58.3)	0	0	1	1	1	1	0	1	0	1	0	1
Boyd et al., 1999	Case-control study - IV	6/12 (50.0)	0	0	0	1	1	1	0	1	0	1	0	1
Brehm et al., 2007	Case-control study - IV	5/12 (41.7)	0	0	0	1	1	0	0	1	0	1	0	1
Campbell and Ball, 1978	Case-control study - IV	3/12 (25.0)	0	0	0	0	0	0	0	0	0	1	0	1
Cardona Garcia et al., 2016	Case-control study - IV	8/12 (66.7)	1	1	1	1	1	0	0	1	0	1	0	1
Cimolin et al., 2007	Case-control study - IV	7/12 (58.3)	1	0	1	1	1	0	0	1	0	1	0	1
Dallmeijer and Brehm, 2011	Case-control study - IV	8/12 (66.7)	1	1	1	1	1	0	0	1	0	1	0	1
Duffy et al., 1996	Case-control study - IV	5/12 (41.7)	0	1	0	1	1	0	0	0	0	1	0	1
Gupta and Raja, 2019	Case-control study - IV	4/12 (33.3)	0	0	0	1	1	0	0	0	0	1	0	1
Hoofwijk et al., 1995	Case-control study - IV	6/12 (50.0)	0	0	1	1	1	0	0	0	0	1	1	1
Johnston et al., 2004	Case-control study - IV	4/12 (33.3)	0	0	0	1	1	0	0	0	0	1	0	1
Kamp et al., 2014	Cohort study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Kerr et al., 2007	Cohort study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Kerr et al., 2008	Cohort study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Kerr et al., 2011	Cohort study - IV	8/12 (66.7)	1	1	0	1	1	0	0	1	0	1	1	1
Maltais et al., 2004	Case-control study - IV	7/12 (58.3)	0	0	1	1	1	0	0	1	0	1	1	1
Marconi et al., 2012	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Norman et al., 2004	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Norman et al., 2006	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Oeffinger et al., 2004	Cohort study - IV	3/12 (25.0)	0	0	0	0	0	0	0	1	0	1	0	1
Oeffinger et al., 2007	Cohort study - IV	6/12 (50.0)	1	1	0	0	0	0	0	1	1	1	0	1
Piccinini et al., 2007	Case-control study - IV	7/12 (58.3)	1	0	1	1	1	0	0	1	0	1	0	1
Plasschaert et al., 2008	Case-control study - IV	7/12 (58.3)	0	0	1	1	1	0	0	1	1	1	0	1
Rigby et al., 2017	Case-control study - IV	6/12 (50.0)	1	1	0	1	0	0	0	1	0	1	0	1
Rose et al., 1989	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Rose et al., 1990	Case-control study - IV	6/12 (50.0)	1	1	0	1	1	0	0	0	0	1	0	1
Rose et al., 1993	Case-control study - IV	6/12 (50.0)	1	1	0	1	1	0	0	0	0	1	0	1
Slaman et al., 2013	Cohort study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Steele et al., 2017	Cohort study - IV	6/12 (50.0)	1	1	0	1	1	0	0	1	0	1	0	0
Thomas et al., 2009	Cohort study - IV	6/12 (50.0)	1	0	0	1	1	0	0	1	0	1	0	1
Thomas et al., 2011	Case-control study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1
Trost et al., 2016	Cohort study - IV	7/12 (58.3)	1	1	0	1	1	0	0	1	0	1	0	1

Unnithan et al., 1996	Case-control study - IV	6/12 (50.0)	0	0	1	1	1	0	0	1	0	1	0	1
Unnithan et al., 1999	Case-control study - IV	5/12 (41.7)	0	0	0	1	1	0	0	1	0	1	0	1
Van de Walle et al., 2012	Case-control study - IV	7/12 (58.3)	1	1	1	1	1	0	0	1	0	0	0	1
Van den Heke et al., 2007	Case-control study - IV	5/12 (41.7)	1	1	0	0	1	0	0	0	0	1	0	1

Quality appraisal questions for methodological quality evaluation of articles (group research design studies). Adapted from the American Academy of Cerebral Palsy and Developmental Medicine (AACPD) guidelines in the protocol by *Morgan & J. McGinley (2014) Gait function and decline in adults with cerebral palsy: a systematic review, Disability and Rehabilitation, 36:1, 1-9, DOI: 10.3109/09638288.2013.775359*

1. Were inclusion and exclusion criteria of the study population well described and followed?
2. Is the sampling procedure (recruitment strategy) likely to minimize bias?
3. The groups were similar at baseline regarding the most important prognostic indicators?
4. Was the intervention well described and was there adherence to the intervention assignment? (For 2-group designs, was the control exposure also well described?) Both parts of the question need to be met to score 'yes'.
5. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest?
6. Were the measures sensitive to change for this population? Statement about the sensitivity of the measure to change.
7. Was the outcome assessor(s) unaware of the intervention status of the participants (i.e., were the assessors masked)?
8. Did the authors conduct and report appropriate statistical evaluation including measures of central tendency and variation?
9. Did the authors report the power calculations for the sample size?
10. Was a comparison made between groups with preservation of original group assignments?
11. Were dropout/loss to follow-up reported for all subjects and less than 20%? For 2-group or more designs, was dropout balanced?
12. The results of between-group statistical comparisons are reported for at least one key outcome?

**S4: Template of the data extraction form**

**Data extraction form**

Paper title \_\_\_\_\_

**Level of evidence**

Study design: \_\_\_\_\_

Level of evidence: \_\_\_\_\_

Study meets inclusion criteria: \_\_\_\_\_

CP vs TD

GMFCS

AGE

Notes:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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**Information about the study**

Participants (and controls): \_\_\_\_\_

Diagnosis: \_\_\_\_\_



Age (range): \_\_\_\_

Number of subjects: \_\_\_\_ /Number of control subjects: \_\_\_\_

Intervention: \_\_\_\_\_

Type: \_\_\_\_\_

Duration: \_\_\_\_\_

Results and comments:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

CP		TD	
GMFCS			
I	II	III	IV

AGE

## S5: Summary of results for risk of bias

	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Aviram et al., 2011	+	+	+	+	+	+
Balaban et al., 2012	+	+	+	?	+	+
Balemans et al., 2017	+	+	+	+	+	+
Bell and Davies, 2010	+	+	+	+	+	+
Bolster et al., 2017	-	+	+	+	+	+
Bowen et al., 1998	+	+	+	+	+	+
Boyd et al., 1999	+	?	+	+	+	+
Brehm et al., 2007	+	?	+	+	+	+
Campbell and Ball, 1978	-	+	+	+	+	+
Cardona Garcia et al., 2016	+	+	+	+	+	+
Cimolin et al., 2007	+	?	+	+	+	+
Dallmeijer and Brehm, 2011	+	+	+	+	+	+
Duffy et al., 1996	+	?	+	+	+	+
Gupta and Raja, 2019	+	+	+	+	?	+
Hoofwijk et al., 1995	+	?	+	+	?	+
Johnston et al., 2004	+	?	+	+	+	+
Kamp et al., 2014	-	+	+	+	+	+
Kerr et al., 2007	+	?	+	+	+	+
Kerr et al., 2008	+	?	+	+	+	+
Kerr et al., 2011	+	+	+	+	+	+
Maltais et al., 2004	+	+	+	+	+	+
Marconi et al., 2012	+	+	+	+	+	+
Norman et al., 2004	+	+	+	+	+	+
Norman et al., 2006	+	+	+	+	+	+
Oeffinger et al., 2004	-	?	+	+	+	+
Oeffinger et al., 2007	-	+	+	+	+	+
Piccinini et al., 2007	+	?	+	+	+	+
Plasschaert et al., 2008	+	?	+	+	+	+
Rigby et al., 2017	+	+	+	+	+	+
Rose et al., 1989	+	?	+	+	+	+
Rose et al., 1990	+	?	+	+	+	+
Rose et al., 1993	+	?	+	+	+	+
Slaman et al., 2013	-	?	+	+	?	+
Steele et al., 2017	-	+	+	+	+	+
Thomas et al., 2009	+	+	+	+	+	+
Thomas et al., 2011	+	+	+	+	+	+
Trost et al., 2016	+	?	+	+	?	+
Unnithan et al., 1996	+	+	+	+	+	+
Unnithan et al., 1999	+	+	+	+	+	+
Van de Walle et al., 2012	-	+	+	+	+	+
Van den Heke et al., 2007	+	?	+	+	?	+

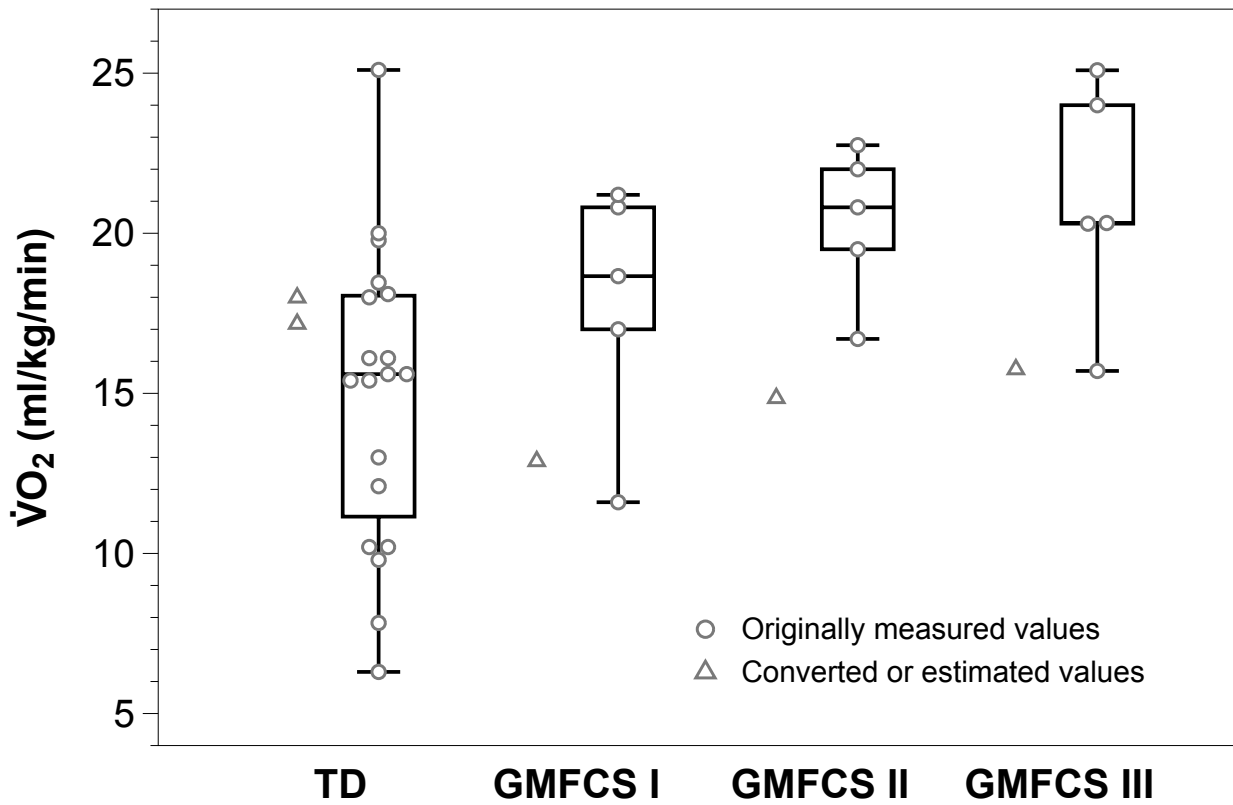
⊕ Low risk of bias

⊛ Unclear risk of bias

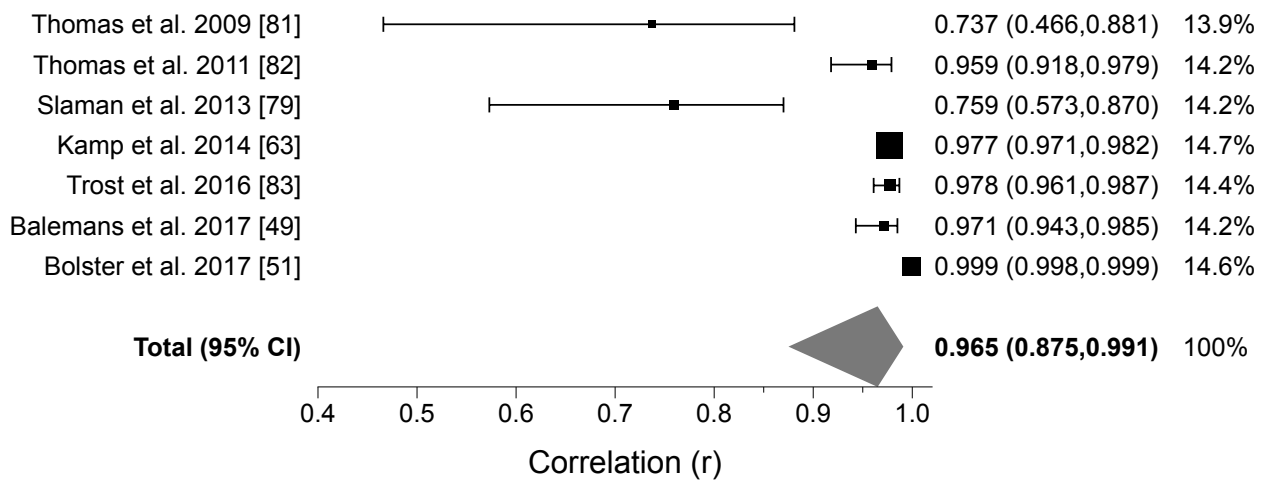
⊖ High risk of bias

**S6:** Box plot showing values of  $\dot{V}O_2$  in TD and in CP across severity levels (GMFCS I to III).

Triangles represent studies where values were converted or estimated by the authors of the review; dots indicate study originally measured data. Box plots depict the median and the 25<sup>th</sup> and 75<sup>th</sup> quartiles and the whiskers showing the minimum and maximum values.



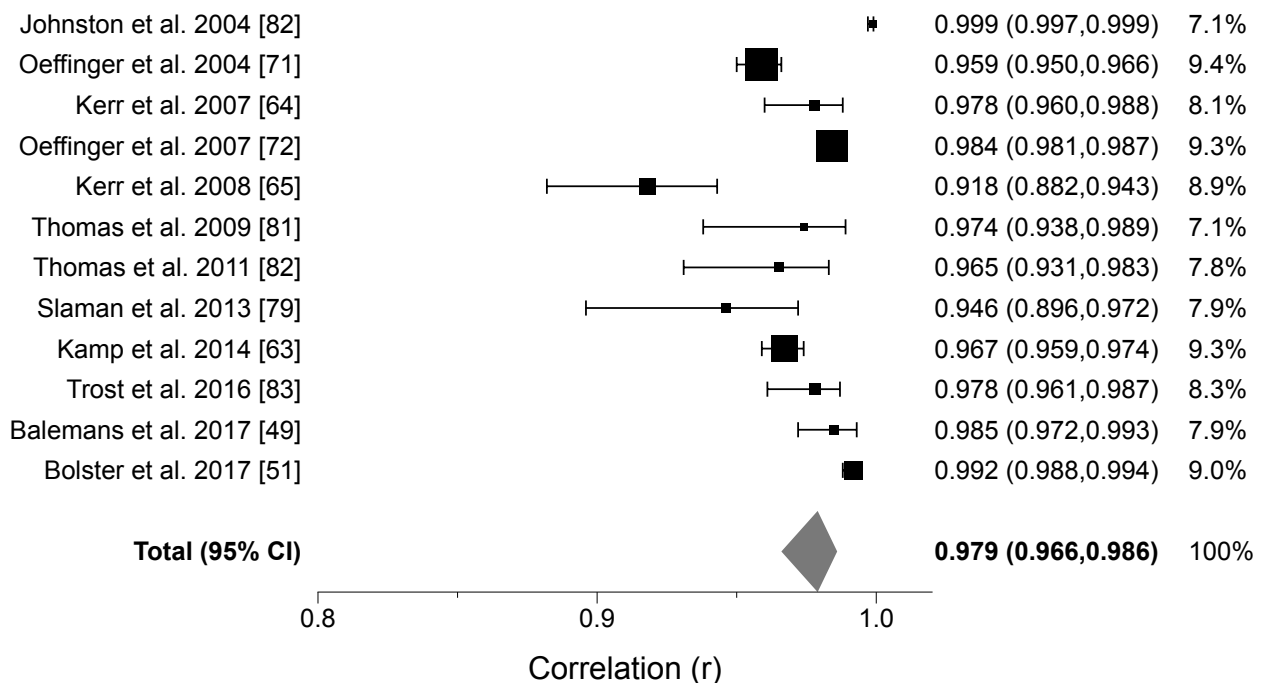
**S7a:** Forest plot with pooled correlation coefficients (r) and C.I. for walking energy consumption across GMFCS levels.



Heterogeneity:  $I^2 = 98.07\%$

Test for overall effect:  $Z = 5.97$  ( $p < 0.001$ )

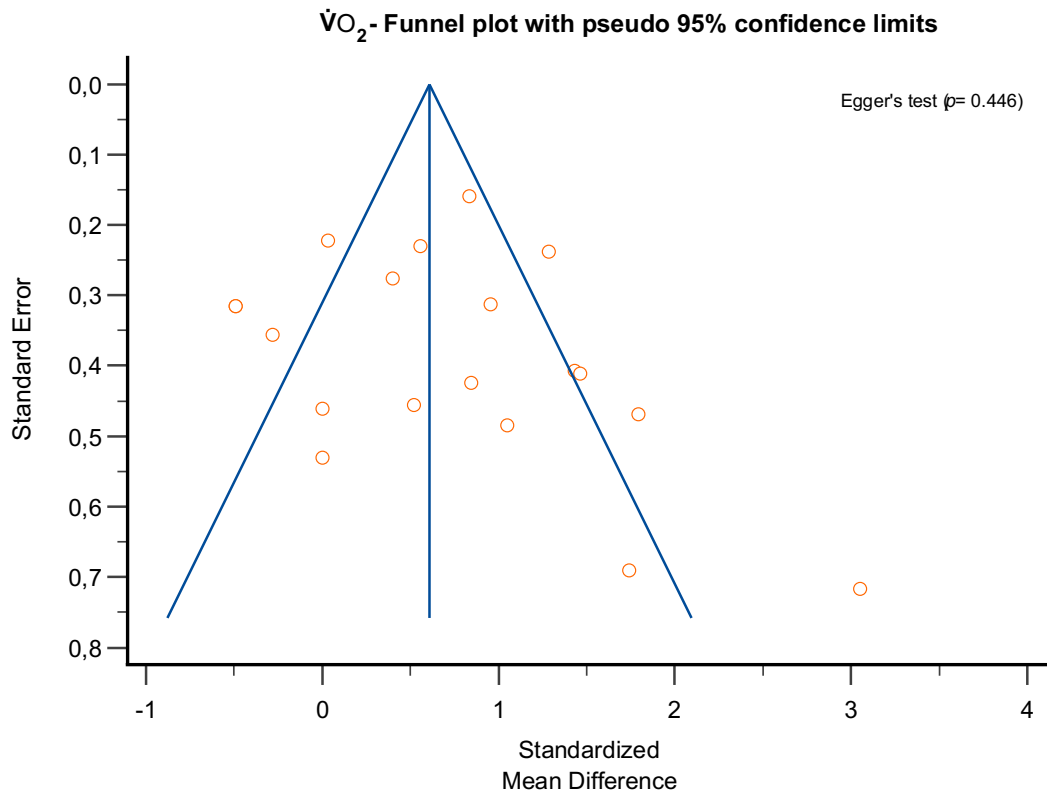
**S7b:** Forest plot with pooled correlation coefficients (r) and C.I. for walking energy cost across GMFCS levels.



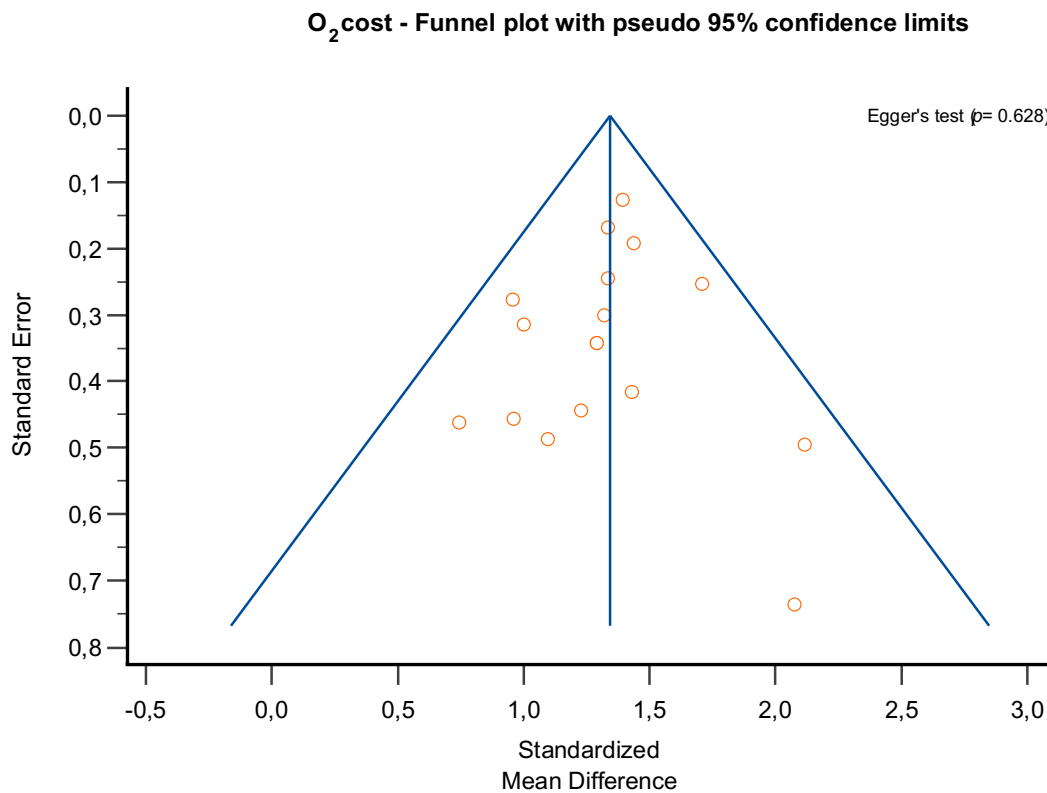
Heterogeneity:  $I^2 = 94.19\%$

Test for overall effect:  $Z = 19.46$  ( $p < 0.001$ )

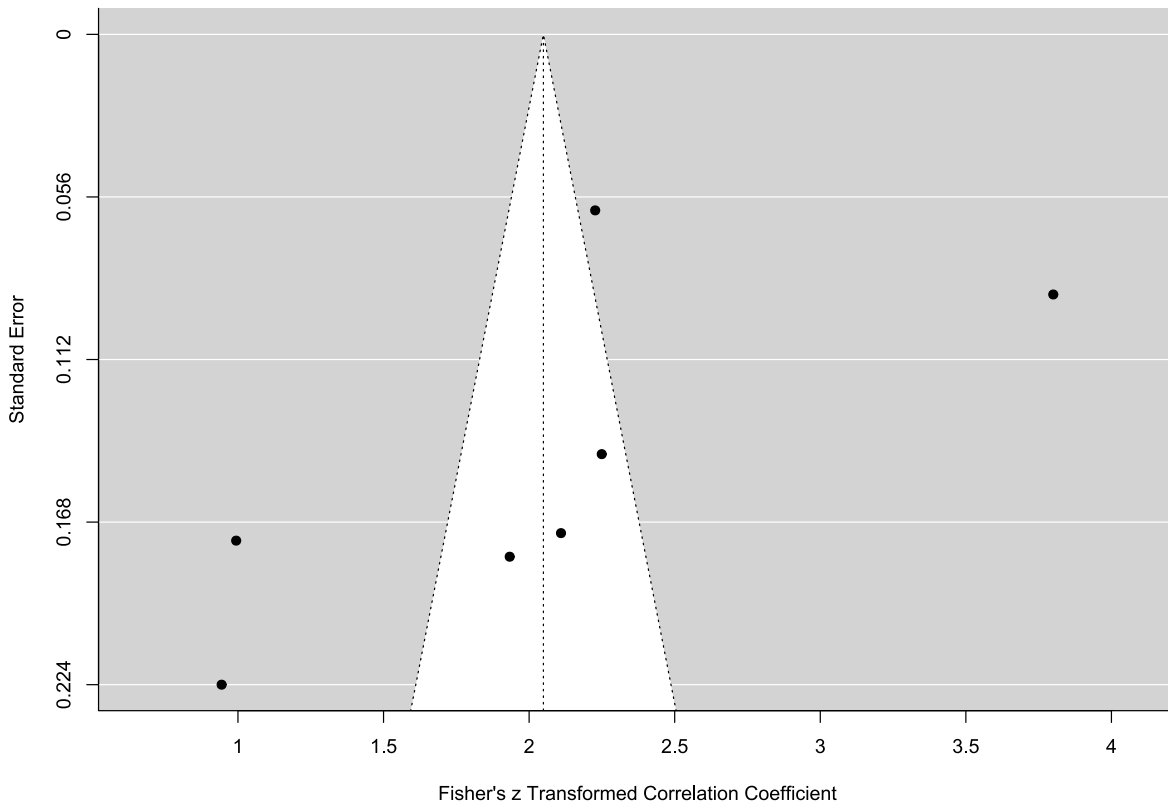
**S8:** Funnel plots and Egger's test results for publication BIAS.



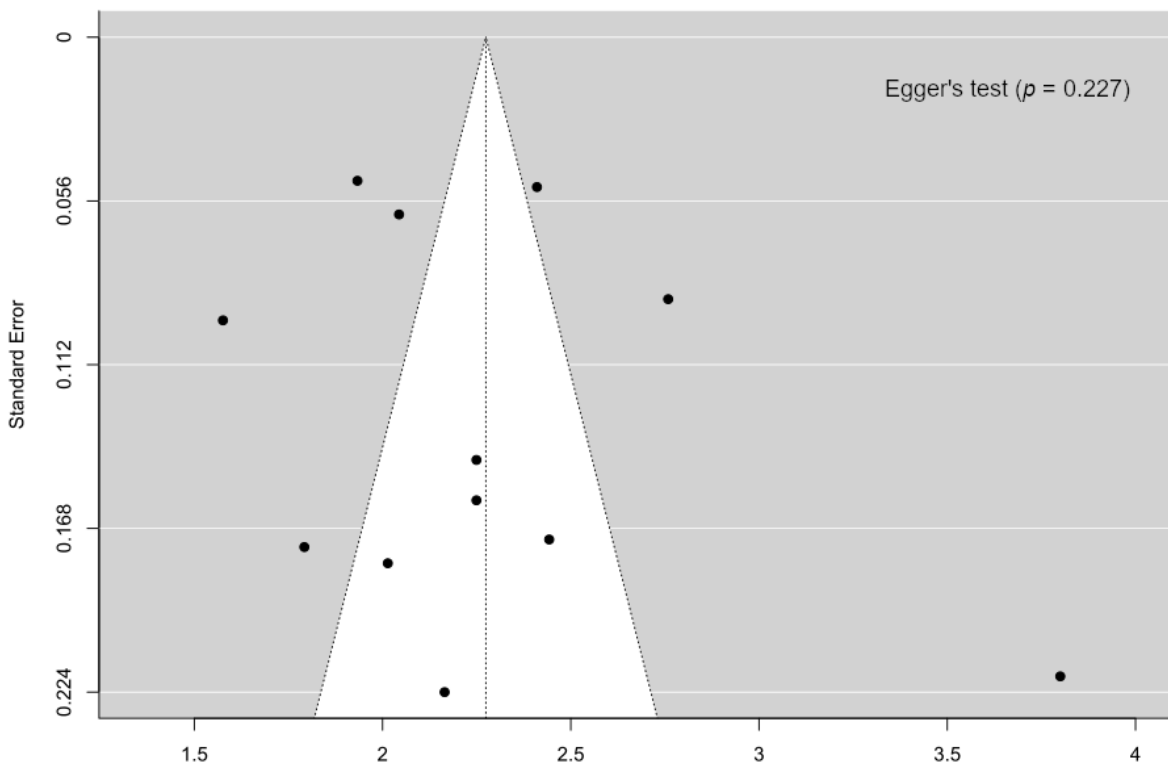
Funnel plot 1: estimated publication bias for studies included in the  $\dot{V}O_2$  analysis (TD-CP comparison). Egger's test not significant ( $p = 0.446$ ).



Funnel plot 2: estimated publication bias for studies included in the  $O_2$  cost analysis (TD-CP comparison). Egger's test not significant ( $p = 0.628$ ).



Funnel plot 3: estimated publication bias for studies included for the  $\dot{V}O_2$  correlation analysis (across GMFCS levels). Egger's test was not performed (study  $n < 10$ ).



Funnel plot 4: estimated publication bias for studies included for the  $O_2$  cost correlation analysis (across GMFCS levels). Egger's test not significant ( $p = 0.227$ ).