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Review

Pain in adults with cerebral palsy: A systematic review and meta-analysis of individual participant data

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ABSTRACT

Background: There is little focus on adults with cerebral palsy (CP) in research and health care and insufficient knowledge on how to identify and manage pain in this population.
Objectives: This systematic review and meta-analysis aimed to determine whether pain prevalence in adults with CP is high and to explore variations in pain prevalence of subgroups, pain locations, pain severity and pain interference.
Methods: Potential datasets were identified by experts in the field and literature searches in Embase, MEDLINE, and Cochrane, from January 2000 to October 2016. Included studies had a representative sample of ≥ 25 adults with CP and ≥ 1 pain outcomes. Methodological quality assessment, pain prevalence estimates and logistic regression models for subgroup effects on pain prevalence were conducted.
Results: In total, 17 eligible studies were identified from 4584 publications. A meta-analysis was performed with individual participant data from 15 studies totalling 1243 participants (mean [SD] age 34.3 [12.6] years). Overall mean pain prevalence was 70% (95% CI 62–78). Women were more likely to have pain than men ($P < 0.001$). The odds of pain was increased in adults with gross motor function level II (odds ratio [OR] 1.92, 95% CI 1.22–3.12) and IV (OR 1.77, 95% CI 1.03–4.29). Participants with pain reported pain predominantly in the legs (76%, 95% CI 66–84), and mean pain severity was 3.7/10 (95% CI 2.7–4.7) and pain interference 3.5/10 (95% CI 2.5–4.5).

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Conclusions: This meta-analysis provides the first reliable pain prevalence estimate in a large international sample of adults with CP. The high prevalence of pain, 70%, suggests that adults with CP should be routinely screened for pain and treated accordingly. The range of measurement instruments used by the included studies emphasizes using common outcome measures specific to pain internationally.

1. Introduction

Cerebral palsy (CP) describes a group of permanent disorders of movement and posture causing activity limitation, attributed to non-progressive disturbances in the developing brain [1]. CP is the most common physical disability in childhood, occurring in 2 to 2.5 per 1000 live births [2]. Presently, most people with CP are adults [3].

Clinical experiences indicate that many adults with CP report pain due to various risk factors in this complex and heterogeneous condition. The early brain injury in CP and subsequent alterations in sensory and autonomic functioning may predispose to pain [4]. Furthermore, pain may be provoked by the abnormal neuromotor functioning itself such as muscle spasticity as well as clinical procedures and therapy (passive limb mobilization, surgery) [5,6]. Also, as people with CP age, they may develop painful secondary conditions, such as joint dislocations or contractures, osteoarthritis, and neuropathy [7–9]. These secondary conditions may result in chronic pain syndromes [6,9,10]. In addition to physical and sensory origins, there is growing evidence that psychosocial factors, such as depression, may play a role in developing or perpetuating this multimodal pain in people with chronic disabilities [11,12]. Of concern, pain may escalate functional decline and adversely affects quality of life in adults with CP [13–15].

Despite these known issues, there is little focus on adults with CP in research and health care and insufficient knowledge on how to identify and manage pain in this population [16]. In published studies of adults with CP, pain prevalence ranged from 36% to 82% [17,18]. Generalizability of these results is hampered by small sample sizes and differing age ranges and clinical subgroups. Evidence of whether pain is disproportionately prevalent among adults with CP is necessary to inform healthcare providers, researchers and policy makers regarding specific services required and enhance the development of effective treatments. A reliable prevalence estimate of pain in the adult CP population is lacking. Investigating whether prevalence varies according to clinical and sociodemographic characteristics, as well as other aspects of pain (i.e., pain location, intensity and interference) may offer insight into subgroups of adults with CP at increased risk, pain etiology and possible targets for management.

To address these knowledge gaps, we conducted a systematic review and meta-analysis with individual participant data (IPD) from internationally representative samples. The primary aim was to estimate the overall prevalence of pain in adults with CP. Secondary aims were variations in pain prevalence estimates by age, sex, subtype of CP and level of gross motor functioning. In addition, we synthesized data from individuals with pain regarding pain location, pain severity and interference of pain with daily life.

2. Methods

The meta-analysis was performed according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD Statement) and Meta-analysis of Observational Studies In Epidemiology guidelines (MOOSE) [19,20]. Methods were pre-specified in a protocol and approved by the Medical Ethics Committee of Erasmus Medical Center, Rotterdam, The Netherlands (MEC-2015-742).

2.1. Search strategy

Potential datasets were identified by experts working in the field of adult CP who initially met through conferences and telephone meetings. Additional, study authors were contacted, and hand searches of abstracts and conference proceedings of the American, European and Australasian Academies for Developmental Disabilities and cross-checking of references were performed. A comprehensive literature search of health outcomes in adults with CP was conducted to identify other suitable datasets. Searches were undertaken in 3 electronic databases (Embase, Medline, and Cochrane) with medical subject heading (MeSH) terms and text words (or synonyms) for "cerebral palsy, adult, treatment outcome, outcome assessment, and health survey, and prevalence". "Pain" was not included in the search strategy because pain is often a secondary or tertiary outcome. The final search included studies in any language published from January 2000 to October 2016.

2.2. Study selection

After removing duplicates, title/abstract screening was performed by one reviewer (JB) to exclude clearly ineligible studies. Subsequently, 2 reviewers (JB, MR) independently performed full-text screening of the remaining potentially eligible studies. Corresponding authors were contacted if eligibility for inclusion was unclear from the publication. Any discrepancies regarding inclusion were resolved by consensus. A third reviewer (WS) arbitrated any unresolved issues.

2.3. Eligibility criteria

Inclusion criteria for full-text publications were 1) observational study or trial (baseline data); 2) medical ethical approval and informed consent of the study participants; 3) data collection in 2000 or later; 4) including $\geq$ 25 adults with CP aged $\geq$ 18 years; 5) a representative sample (no specific subsamples, such as recruited to follow-up effects of specific surgery); and 6) assessing pain and clinical sample characteristics (subtype of CP or level of gross motor functioning). In addition to 5), for the first aim of the meta-analysis (pain prevalence), recruitment of a sample was regardless of the presence of pain.

2.4. Procedure after study selection

The primary investigators of eligible datasets were asked to collaborate and agree on data-sharing. Anonymized datasets were provided, consisting of eligible IPD and pre-specified variables: assessment year, age, sex, subtype of CP, level of gross motor functioning, intellectual disability, pain prevalence, location, severity and interference. Data were checked thoroughly with

clarification by primary investigators in the case of uncertainty. If IPD were not available from investigator(s), applicable aggregate data were extracted from the full-text publication. All available IPD, regardless of methodological quality score, were included. In case outcomes or factors were not assessed or were missing for a particular study, these IPD were not included in that part of the analysis. Sample inclusion was performed up to 2017.

2.5. Methodological quality assessment

Methodological quality of included samples was graded by 11 selected applicable items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Appendix I) [21]. Two pairs of independent reviewers (JB/MR or JB/SH) rated whether items were well reported: no (0), partially (0.5) or yes (1) [22,23]. A sum score of ≥ 8 was considered good methodological quality. If reporting was unclear, other publications of the same study sample were reviewed, IPD were checked, and/or the primary investigator of the study was contacted for clarification. Disagreements were resolved by discussion.

2.6. Outcome measures

The primary outcome was pain prevalence defined as having any pain 1) currently, 2) in the past 4 weeks/month, or 3) up to 3 months or longer. Pain was dichotomized as 0, no pain (scores no pain, none, no hurt) or 1, pain (all other scores) (see Appendix II).

Secondary outcomes were pain location, pain severity and pain interference and only studied in participants reporting pain. Pain location was allocated to 3 areas: neck/back, arms and legs, and dichotomized as no (0, no pain) or yes (1, pain). Pain interference was defined as how much pain interfered with daily activities, household activities and work. Because the scaling of pain severity and pain interference differed across datasets, if applicable, original scales were converted to a common scale: an 11-point numeric rating scale (0, no pain; 10, extreme pain). A complete list of individual study procedures, measurement instruments and scale conversion are in Appendix II.

Subgroups of adults with CP were distinguished by age, sex, CP subtype and gross motor functioning to estimate the effect of each of these factors on pain prevalence and pain location. On the basis of the MeSH thesaurus, age was classified in 4 categories: 19–24, 25–44, 45–64, and 65–84 years. CP subtype was classified according to the Surveillance of Cerebral Palsy in Europe (SCPE) [2]: neurological symptoms (spastic, ataxic, dyskinetic) and limb distribution (unilateral or bilateral). Three subtypes of CP were distinguished: spastic unilateral CP (SUCP), spastic bilateral CP (SBCP) and a mixed group of ataxic, dyskinetic and mixed CP (AtDysMix). Gross motor functioning was classified according to the Gross Motor Function Classification System (GMFCS), a 5-level classification system grading severity of gross motor limitations by activity level, ranging from level I, "walks without restrictions" to level V, "self-mobility is severely limited even with use of assistive technology" [24].

2.7. Data analysis

For primary and secondary outcomes, an overall prevalence of pain with corresponding 95% confidence interval (CI) was estimated by a 2-stage meta-analysis model. First, proportions of pain prevalence and corresponding standard errors, within each sample, were estimated from the IPD. Aggregate data from one study not providing IPD were included in an additional analysis [25]. Second, overall mean prevalence was estimated with a random-effects meta-analysis model using the DerSimonian and Laird estimator [26] and the Freeman–Tukey double arcsine-transformation [27,28]. The random-effects model accounts for the heterogeneity of different samples by adding more weight to larger samples when calculating the overall mean prevalence. The statistical heterogeneity between samples was quantified by the I^2 measure, which describes the percentage of variation that can be attributed to heterogeneity rather than sampling error across samples [29]. The overall means and 95% CIs for pain severity and interference were obtained from the corresponding one-stage univariate mixed-effects linear regression models rather than the 2-stage approach because of violations in the normality assumption when estimating the study specific means.

Variation in the odds of pain prevalence and pain location was explored by adjusting for age, sex, CP subtype and GMFCS level. Odds ratios (ORs) and 95% CIs were estimated. The effect of these factors was estimated by univariate mixed-effects logistic regression models adjusted for all the aforementioned factors, taking into account the correlations of the data within each sample, and the between-sample variability [30]. A random effect per study was included to account for heterogeneity between them. Univariate Wald-type tests and likelihood ratio tests were used with no correction for multiple testing to assess the factors' effect [30]. *P*-value ≤ 0.05 was considered significant.

An additional analysis, including only participants without intellectual disability, explored whether results were biased by this characteristic. Furthermore, sensitivity analyses were conducted to assess the impact of excluding specific samples on the overall estimates. The excluded samples were selected on the basis of whether their sample-specific estimates deviated substantially compared to other samples or by study-specific differences regarding the assessed outcome.

3. Results

Twelve samples were identified by experts in the field. Handsearching of abstracts and conference proceedings revealed no additional studies. The subsequent literature search returned 4583 articles. After removing duplicates, 4584 articles were screened for eligibility (Fig. 1). Ninety-five articles underwent full-text review, including one French and one Turkish language article, with disagreement on 8 articles, which was resolved by consensus. Overall, 78 articles were excluded (Appendix III) and IPD were sought for 17 studies. The IPD were obtained for 15 studies (1243 participants) and aggregate data for one study (48 participants) [25]. Included studies were performed in Europe, West Asia, Australia and North America during 2000–2016. The mean (SD) age of all participants was 34.3 (12.6) years; other study characteristics are presented in Table 1.

The primary outcome, pain prevalence, was estimated in 1192 participants from 14 samples, excluding missing data ($N = 25$) and the Vogtle sample ($N = 26$) [31]. Secondary outcomes were assessed in participants reporting pain from 12 different samples per outcome (Table 1). Regarding subgroups, CP subtype was not assessed in the French sample [17]. For additional analyses of adults without intellectual disability, IPD for 652 participants from 10 samples were available.

The methodological quality of the included studies is summarized in Appendix IV. All studies had good methodological quality (rated ≥ 8; including 8 studies rated ≥ 10), except for one study rated as 6.5 [18].

The overall mean prevalence of pain in adults with CP was estimated at 70% (95% CI 62–78) (Fig. 2). Pain prevalence within individual samples ranged from 38% (95% CI 22–56) [18] to 89% (95% CI 82–94) [32]. In individuals with pain, pain was located in the legs in 76% (95% CI 66–84), the neck/back in 66% (95% CI 58–74), and the arms in 38% (95% CI 30–45) (Fig. 3). The level of

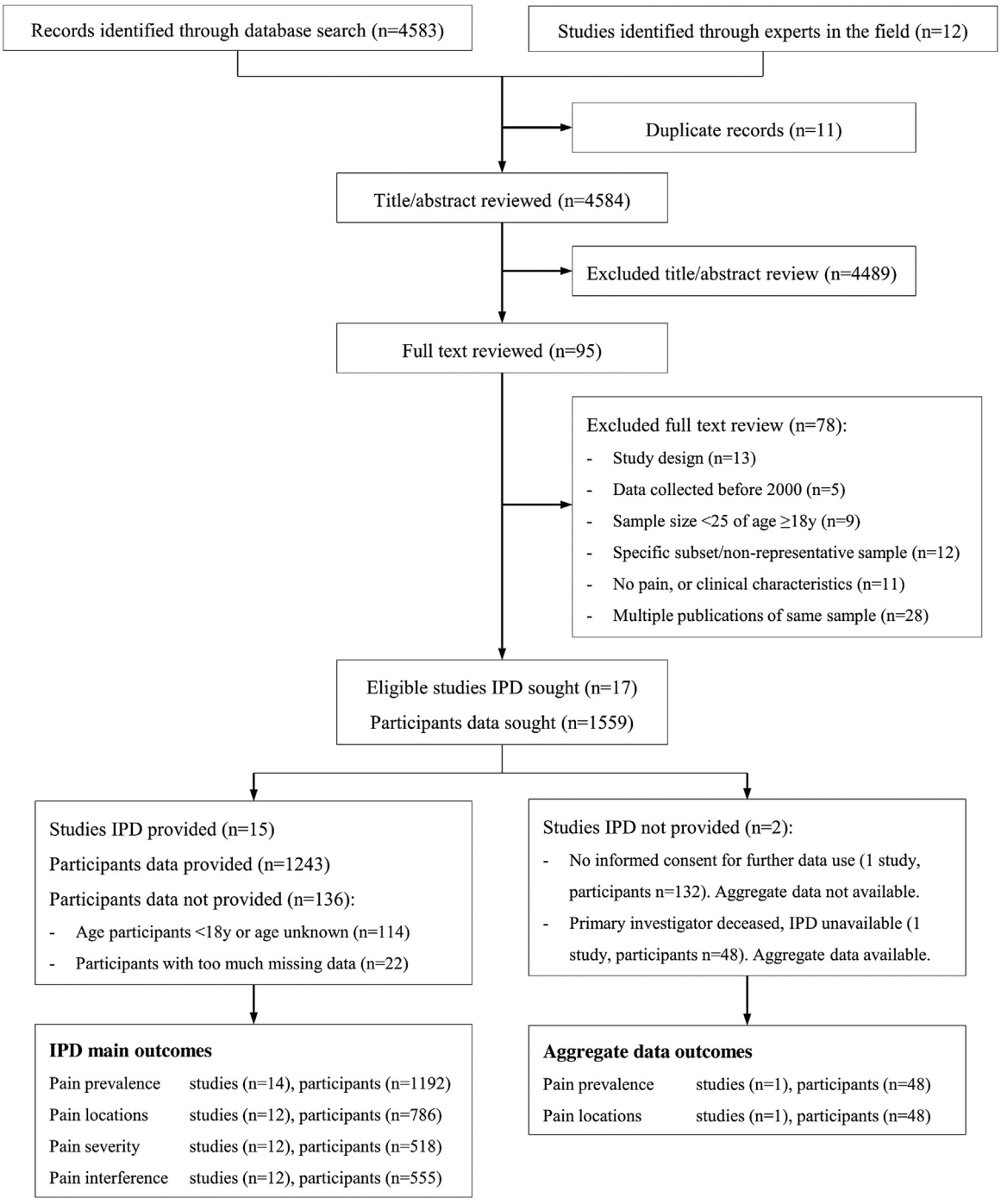

Fig. 1. Flow chart of the study selection. IPD, individual participant data.

heterogeneity was high for overall mean pain prevalence (I^2 = 89%) and pain location (I^2 = 73–86%), which reflects substantial variation in results between studies (Figs. 2 and 3).

Women were significantly more likely to have pain than men ($P < 0.001$; OR 1.96, 95% CI 1.08–2.59), and pain prevalence differed by GMFCS level ($P = 0.025$) (Table 2). Results were similar when adjusting for CP subtype, with significantly greatly risk of pain for adults with GMFCS level II (OR 1.92, 95% CI 1.22–3.12) and IV (OR 1.77, 95% CI 1.03–4.29) (Table 3). In participants with GMFCS level III versus level I, pain was more prevalent in the legs (OR 2.09, 95% CI 1.41–5.04). Older individuals (age ranges 45–64 and 65–84 years), were more likely to have pain in the arms: OR 1.73 (95% CI 1.39–2.87) and OR 2.21 (95% CI 1.15–5.99), respectively (Table 4). Age ($P = 0.53$) and CP subtype ($P = 0.99$) did not affect overall pain prevalence. The mean pain severity was 3.7/10 (95% CI 2.7–4.7) and the mean pain interference with daily activities and household/work was 3.5/10 (95% CI 2.5–4.5).

Additional analyses were performed to assess the robustness of results. When incorporating the study with aggregate data [25] in the meta-analysis, the results changed minimally: overall mean pain prevalence was 70% (95% CI 62–78), with heterogeneity I^2 = 88% (Appendix V). When excluding the 2 samples with the most deviating pain prevalence estimates [18,32], the mean pain prevalence remained close: 71% (95% CI 62–78), I^2 = 85% (Fig. 4). Results were similar without the 2 samples that assessed pain duration up to 3 months or longer: mean pain prevalence 71% (95%

Table 1
Characteristics and outcome numbers of the included samples and synthesis.

Study	Design	Assessment	Sample characteristics					Pain outcomes (*N*)			
		Year	*N*	Age (range)	Sex (M/F)	CP type (%)	GMFCS level (%)	Prevalence	Location	Severity	Interference
Pooled data			1243	34.3 (12.6) (18-84)	612/630	SU 33, SB 54, ATDYSMIX 13	I 29, II 28, III 14, IV 16, V 13	1192			
Pooled data subset "with pain"			889	35.2 (12.7) (18-84)	395/494	SU 32, SB 55, ATDYSMIX 13	I 26, II 31, III 14, IV 17, V 12		786	518	555
Van der Slot et al., Netherlands [12]	Cross-sectional	2005–2006	56	36.4 (5.8) (25–47)	35/21	SB 100	I 23, II 50, III 20, IV 7	56	43	43	43
Hilberink et al., Netherlands [16]	Cross-sectional	2000	54	30.0 (3.4) (25–36)	26/28	SU 35, SB 46, ATDYSMIX 19	I 28, II 34, III 7, IV 24, V 7	54	cmd	cmd	cmd
Van den Berg–Emons et al., Netherlands [54]	RCT (baseline)	2009–2011	45	21.0 (2.2) (18–27)	23/22	SU 50, SB 50	I 59, II 32, III 7, IV 2	45	cmd	21	21
Opheim et al., Norway [15]	Cross-sectional	2006	149	40.4 (10.7) (24–76)	76/73	SU 54, SB 46	I 46, II 24, III 15, IV 13, V 2	146	86	86	85
Maanum et al., Norway [32]	RCT (baseline)	2006–2008	126	38.7 (12.4) (18–65)	53/73	SU 47, SB 53	I 9, II 75, III 16	126	112	112	112
Rodby–Bousquet et al., Sweden [41]	Cross-sectional	2009–2011	102	20.7 (1.1) (19–23)	63/39	SU 25, SB 44, ATDYSMIX 31	I 37, II 20, III 13, IV 10, V 20	102	63	58	55
Gallien et al., France [17]	Cross-sectional	2007	327	37.0 (13.3) (18–84)	160/167	cmd	I 27, II 14, III 7, IV 24, V 28	319	270	cmd	cmd
Riquelme et al., Spain [34]	Cross-sectional	2008	34	23.2 (3.5) (19–30)	22/12	SU 6, SB 56, ATDYSMIX 38	I 20, II 9, III 9, IV 12, V 50	26	18	19	cmd
Tarsuslu Şimşek et al., Turkey [18]	Cross-sectional	2005–2008	34	25.8 (7.2) (18–43)	16/18	SU 41, SB 44, ATDYSMIX 15	I 59, II 18, III 17, IV 6	34	13	13	13
Morgan et al., Australia [42]	Cross-sectional	2011	25	40.6 (9.3) (30–65)	9/16	SU 52, SB 36, ATDYSMIX 12	I 16, II 64, III 20	25	21	21	21
Morgan et al., Australia [14]	Cross-sectional	2014	30	44.6 (9.1) (26–67)	11/19	SU 31, SB 42, ATDYSMIX 27	I 10, II 47, III 43	30	cmd	26	26
Brunton et al., Canada [55]	Cross-sectional	2012	52	22.3 (4.1) (18–31)	20/31	SU 29, SB 71	I 15, II 38, III 25, IV 14, V 8	52	42	41	41
Engel et al., USA [33]	Cross-sectional	2002–2007	83	40.3 (13.6) (18–74)	37/46	SU 12, SB 38, ATDYSMIX 50	I 22, II 7, III 20, IV 35, V 16	83	29	52	50
Thorpe et al., USA [53]	Cohort study (baseline)	2007–2010	100	32.7 (11.6) (21–65)	51/49	SU 30, SB 70	I 32, II 25, III 19, IV 20, V 4	94	63	cmd	63
Vogtle, USA [31]	Cohort study (baseline)	2006–2007	26	42.3 (11.3) (23–63)	10/16	SU 11, SB 58, ATDYSMIX 31	I 15, II 4, III 23, IV 46, V 12	–	26	26	25
Sandström et al., Sweden [25]	Cross-sectional (aggregate data)	2000	48	32.9 (8.2) ([a])	23/25	SU 27, SB 58, ATDYSMIX 15	I 14, II 31, III 17, IV 19, V 19	48	33	cmd	cmd

M: male; F: female; RCT: randomised controlled trial; SU: spastic unilateral CP; SB: spastic bilateral CP; AtDysMix: ataxic: dyskinetic or mixed CP; GMFCS: gross motor function classification system; cmd: complete missing data.
[a] Age range is missing.

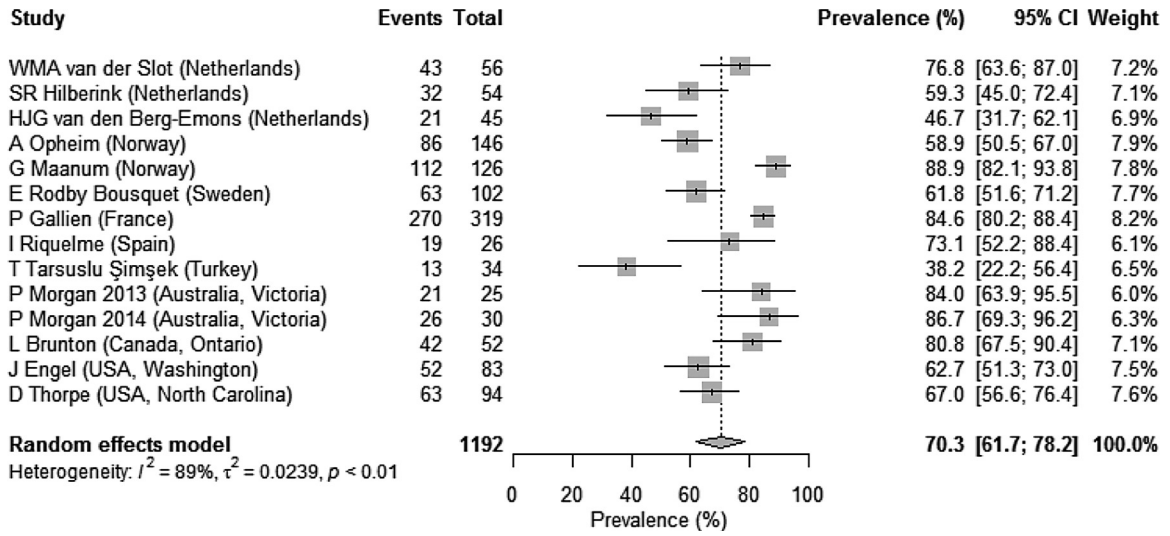

Fig. 2. Forest plot of random-effects meta-analysis of mean prevalence of pain in adults with cerebral palsy (CP) (N = 1192).

CI 61–79), I^2 = 90% (Fig. 5) [33,34]. For the subgroup of individuals without intellectual disability, the overall mean pain prevalence was also similar: 69% (95% CI 58–79), I^2 = 87% (Fig. 6 and Appendix VI).

4. Discussion

This meta-analysis including 15 studies and 1243 participants from Europe, West Asia, Australia and North America demonstrated a high prevalence of pain, 70%, in adults with CP. This is a more precise and reliable estimate than the wide variation of pain prevalence in the original studies, reflected in a high variance from 38% to 89% between individual samples, and affirms clinical observations that many adults with CP experience pain.

Pain prevalence is much higher in adults with CP than in the general population (globally around 20%) [35–37]. It is also higher than in adults with acquired brain injury (e.g., stroke: up to 49%) [38]. However, it is similar to younger individuals with CP (e.g., adolescents with CP in Europe, 74%), which indicates that pain starts early in this population, as underlined by the relative young mean (SD) age (34.3 [12.6] years) in the current study [6,39]. Similar to the general population, painful conditions in CP may increase with age and even more because of worsening of the neuromusculoskeletal pathology in CP [6,8]. The present results indicate that pain in the arms increased with age; overuse related to reduced walking ability and using walking aids or a wheelchair may explain this. We found no other effects of age on pain prevalence. However, no longitudinal tracking of individuals with CP was performed, and in the current study, the proportion of individuals 65 to 84 years old was relatively small, which may have affected findings.

Pain was more prevalent in women than men with CP, which is in contrast to the gender non-specific effects of the complex neuromotor and biomechanical disorder of CP. Hence, the gender effect of pain in adults with CP may be similar to that in the general population [39,40].

When adjusting for CP subtype, pain was more prevalent with GMFCS levels II and IV versus level I. Furthermore, we found a high prevalence of leg pain in adults with GMFCS level III. The increased level of pain in adults with GMFCS level II might be related to the often asymmetric involvement and walking disability with increased biomechanical strain. This relatively mobile group may also be at risk of overexertion, thereby resulting in abnormal loading of the musculoskeletal system [8,12,15,41]. The high prevalence of pain in the legs in individuals with GMFCS level III might be due to the more severe motor deficits and bony deformities in this subgroup, with even more abnormal biomechanics and joint loading while walking, often resulting in a progressive flexion pattern. These mechanisms may coincide with knee pain [7], early degenerative joint disease and/or tendinitis. Individuals with GMFCS level IV have "whole body involvement," with poor posture, musculoskeletal problems such as scoliosis, joint contractures and/or hip subluxation, prolonged sitting with an inability to change position and physical inactivity, which might explain the increased pain prevalence in this group [8,41]. However, this finding seemed not apparent in individuals with GMFCS level V who face similar problems [41]. People with GMFCS level V may be provided greater help by caregivers and assistive devices, thus minimizing pain. Another likely explanation may be inaccurate reporting of pain due to communication problems.

Regarding the high pain prevalence in adults with CP, pain in other origins should also be taken into account. Six studies assessed other pain locations (e.g. head, abdomen [see Appendix II]), which were reported by one of 5 individuals with pain [15,31,33,34,41,42]. Reported pain severity and pain interference with daily activities and work were mild, on average. Pain might not have affected adults with CP as much as could be assumed in able-bodied persons, because adults with CP may be "used to it" as part of a lifelong disorder and have adapted their activities to manage their pain [7,43]. Furthermore, pain was assessed in a subset with a variety of measurement instruments.

Strengths of the systematic review are a sensitive literature search strategy, without language criteria. The meta-analysis enabled inclusion of 1243 adults with CP, facilitating adequate power to calculate precise and reliable estimates of pain prevalence and to identify subgroups at risk. This feature meets the disadvantage of single studies, in which specific subgroups of adults with CP are often under-represented. The pooled data showed a representative distribution of CP subtypes over all 3 categories, similar to the distribution reported in the European SCPE registry (Chi^2 P = 0.068) [44]. We assume that the data pool is representative for the population of adults with CP because 12 studies recruited broadly in society (e.g., a population-based registry; using historical registers of pediatric rehabilitation; via patient organizations, community-based services, insurance companies; by advertisements in newspapers, on Facebook and websites), and the other 2 were small studies and used various recruitment methods as well. Thus, selection of only individuals under treatment or known to adult medical clinics was avoided.

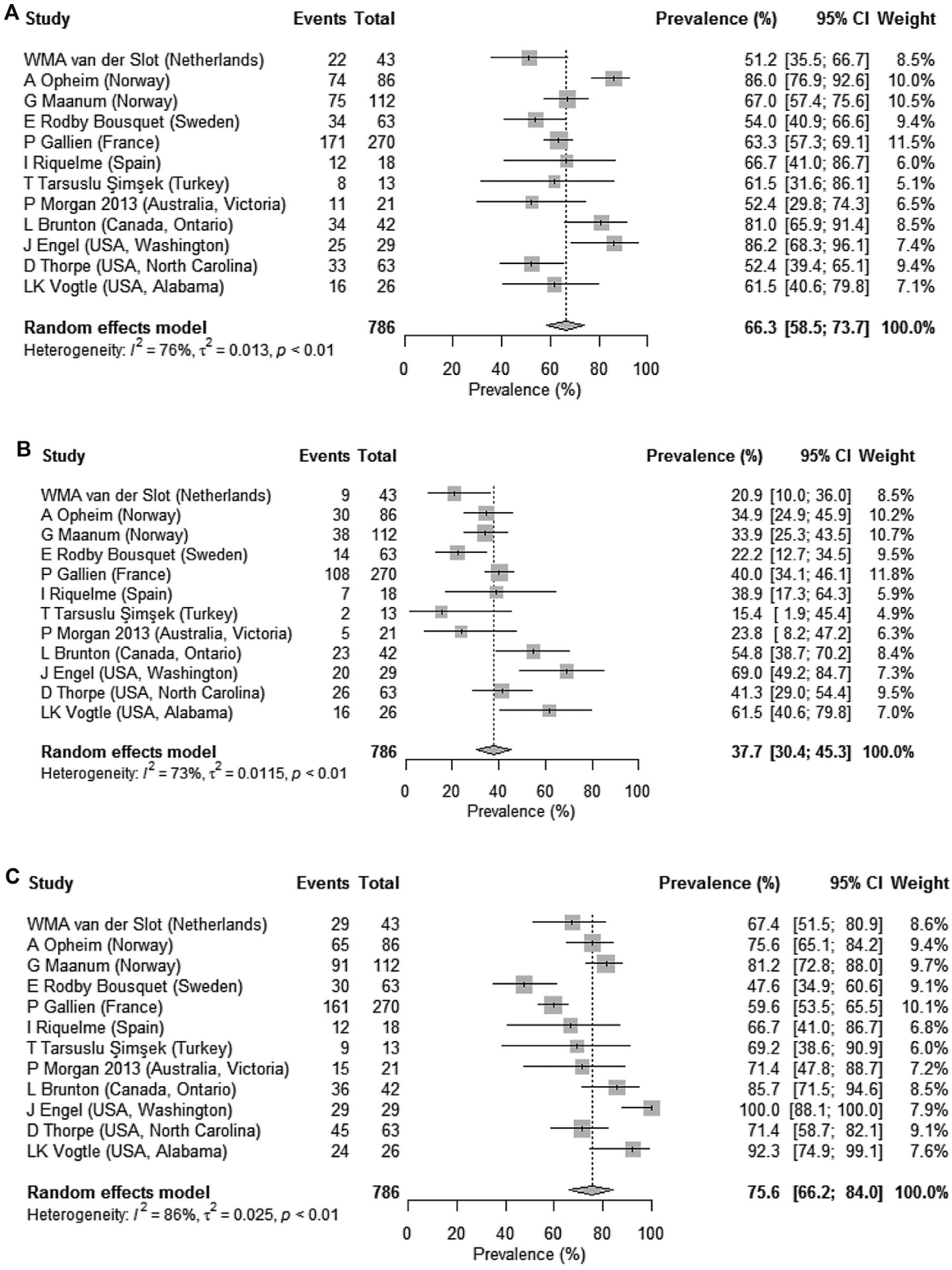

Fig. 3. Forest plots of random-effects meta-analysis of mean prevalence of pain locations in adults with CP (N = 786). Pain in the: A) neck/back; B) arms; C) legs.

The study has some limitations. First, selection bias may be present owing to exclusion of older or more recent studies. We excluded studies before 2000 for various reasons. The first is that representative studies of adults with CP at that time were scarce. Before 2000, the umbrella term CP was not yet used worldwide, nor were samples specified by GMFCS level or standardized subtypes of CP [2]. Twenty years ago, different treatment approaches may have been used, which limits the generalizability of findings to current times. Also, owing to restrictions for data storage for a period longer than 15 years, we expected that the use of IPD was not feasible with studies before 2000. For the period after 2016, we checked the present results with another systematic search recently performed by our research group that also included the literature published from 2017 to January 2019 but used a

Table 2
Effect of age, sex and GMFCS level on pain prevalence ($N = 1192$).

Factor	N	Prevalence (95% CI)	OR (95% CI)
Intercept			1.21 (0.98–2.73)
Age (years)			
18–24	342	66 (60–71)	Reference
25–44	591	74 (70–77)	1.25 (0.85–1.80)
45–64	238	77 (72–83)	1.29 (0.85–1.87)
65–84	21	81 (58–95)	1.92 (0.84–5.72)
Sex			
Male	591	65 (61–69)	Reference
Female	600	80 (76–83)	1.96 (1.08–2.59)
GMFCS			
Level I	350	64 (59–69)	Reference
Level II	342	80 (75–84)	1.61 (0.90–2.24)
Level III	168	71 (64–78)	1.10 (0.65–1.45)
Level IV	181	77 (71–83)	1.42 (0.74–2.17)
Level V	148	70 (63–78)	0.85 (0.49–1.09)

OR: odds-ratio; 95% CI: 95% confidence interval (obtained from univariate mixed-effects logistic regression models); GMFCS: Gross Motor Function Classification Scale. Missing data: sex (1), and GMFCS level (3). Number of samples = 14.

Table 3
Effect of age, sex, GMFCS level and CP subtype on pain prevalence in adults with CP ($N = 873$).

Factor	N	Prevalence (95% CI)	OR (95% CI)
Intercept			0.98 (0.70–2.11)
Age (years)			
18–24	279	63 (57–68)	Reference
25–44	427	69 (65–74)	1.19 (0.54–1.69)
45–64	155	73 (65–80)	1.21 (0.53–1.87)
65–84	12	75 (43–95)	1.68 (0.33–11.56)
Sex			
Male	433	58 (53–63)	Reference
Female	439	78 (74–82)	2.29 (1.62–3.76)
GMFCS			
Level I	262	56 (50–62)	Reference
Level II	296	78 (73–83)	1.92 (1.22–3.12)
Level III	147	69 (61–77)	1.21 (0.72–2.01)
Level IV	104	72 (63–81)	1.77 (1.03–4.29)
Level V	61	59 (46–72)	1.01 (0.39–1.87)
CP subtype			
Spastic unilateral	295	65 (60–71)	Reference
Spastic bilateral	462	70 (66–74)	0.98 (0.57–1.43)
AtDysMix	105	67 (57–76)	1.00 (0.41–2.26)

OR: odds ratio; 95% CI: 95% confidence interval (obtained from univariate mixed-effects logistic regression models); GMFCS: gross motor function classification scale; AtDysMix: ataxic, dyskinetic, mixed CP. Missing data: sex (1), CP-subtype (11) and GMFCS level (3). Effect of age, sex and GMFCS level on pain prevalence, additionally adjusted for CP subtype. Number of samples = 13.

Table 4
Effect of age, sex and GMFCS level on pain location in adults with CP ($N = 784$).

Factor	N	Neck/back ($N = 760$)	Arms ($N = 760$)	Legs ($N = 760$)
Intercept		1.65 (1.29–4.34)	0.41 (0.27–0.70)	1.60 (1.05–3.02)
Age (years)				
18–24	202	Reference	Reference	Reference
25–44	381	1.42 (0.92–1.80)	1.02 (0.82–1.58)	1.02 (0.63–1.31)
45–64	161	1.54 (1.00–2.15)	1.73 (1.39–2.87)	0.99 (0.69–1.47)
65–84	16	1.36 (0.54–3.12)	2.21 (1.15–5.99)	1.44 (0.61–4.26)
Sex				
Male	344	Reference	Reference	Reference
Female	416	1.13 (0.68–1.20)	1.21 (0.94–1.58)	1.60 (1.15–1.97)
GMFCS				
Level I	196	Reference	Reference	Reference
Level II	241	0.76 (0.38–1.13)	0.96 (0.64–1.29)	1.40 (0.96–1.95)
Level III	98	0.83 (0.43–1.24)	1.37 (0.66–1.86)	2.09 (1.41–5.04)
Level IV	124	0.90 (0.57–1.17)	1.32 (0.52–1.45)	1.17 (0.72–1.41)
Level V	101	0.92 (0.56–1.22)	1.20 (0.73–1.67)	0.98 (0.73–1.48)

GMFCS: gross motor function classification scale. Missing data: predictors ($N = 0$); cases where the outcome is missing ($N = 24$). Number of samples = 11. Data are OR (95% CI) (obtained from univariate mixed-effects logistic regression models. The sample of Gallien (France) [17] was included, but CP subtype was not.

broad scope on functioning, impairments and disabilities in adults with CP, so not specifically tailored to pain. This check revealed only 4 recent samples of adults with CP (Dautner 2017, de Albuquerque Botura 2017, Sienko 2018, Lundh 2018) [45–48], reporting on proportions of pain varying from 58% to 85%. Because these pain prevalence estimates fit well into the range of estimates of the individual samples included in the present meta-analysis, we assume that these samples would not have changed the present results. This reinforces the conclusion that the current study provides a robust and reliable pain prevalence estimate in adults with CP. Second, all included studies were conducted in developed countries (North America, Western Europe, West Asia or Australia, see Table 1), which prevents the generalizability of the results to low-resource countries. Outlying samples have the potential to bias results. The two most outlying estimates of pain prevalence arose from potentially selective samples. The lowest estimate of pain prevalence (38%) was in a Turkish sample [18], in which individuals with unilateral CP and GMFCS level I were overrepresented. The highest pain estimate (89%) was from Norway [32], with more women than men, and an overrepresentation of GMFCS level II. Excluding these samples from the meta-analysis did not substantially alter the results. Including a variety of measurement procedures in a meta-analysis is another potential limitation (see Appendix II). Primary outcome measurements varied between samples, from assessing current pain, to pain up to 3 months or longer. We assume this effect to be small, because sensitivity analyses excluding samples that explicitly assessed pain up to 3 months and longer [33,34] showed similar results, and pain in CP often lasts more than 1 year [12,15]. Pain type was not analyzed because this characteristic was studied by only one group [16], which limits unravelling pain mechanisms. Pain severity and pain interference were assessed by a variety of scales and required conversion to a common scale. In one third of adults with intellectual disability, pain was reported by proxy, potentially resulting in a misjudgment of pain in this subgroup [49]. This effect is assumed to be minimal because results were unchanged when excluding individuals with intellectual disability. The high level of heterogeneity reflects the substantial variation in outcomes between studies. To account for between-studies heterogeneity, pooled prevalence estimates were obtained with random-effects models. Multivariable subgroup analyses revealed some subgroups at increased risk for pain; however, these results should be interpreted with caution because of few observations in some subgroups (e.g., age 65–84 years or in GMFCS level V).

The high prevalence of pain in adults with CP indicated by this meta-analysis is a plea for strategies to strengthen health services and scientific research for individuals with this lifelong disability. There is need for routine clinical follow-up, including screening and treatment of pain in adults with CP. The range of measurement instruments used in this review emphasizes the importance of using common outcome measures specific to pain internationally. Further research should explore causes of pain to increase insight into multifactorial aetiologies and potential targets for treatment and management. More knowledge is needed on the influences on pain in CP by motor patterns and physical behaviour as well as psychological factors and also on the mechanisms of how pain affects other domains within the biopsychosocial model. Moreover, we need to investigate pain management and treatment, such as approaches of therapy and surgery, and pharmacological treatment [50,51]. Use of medication is known to increase with age, and high levels of medication are prone to the risk of polypharmacy [52]. Furthermore, long-term effects could be

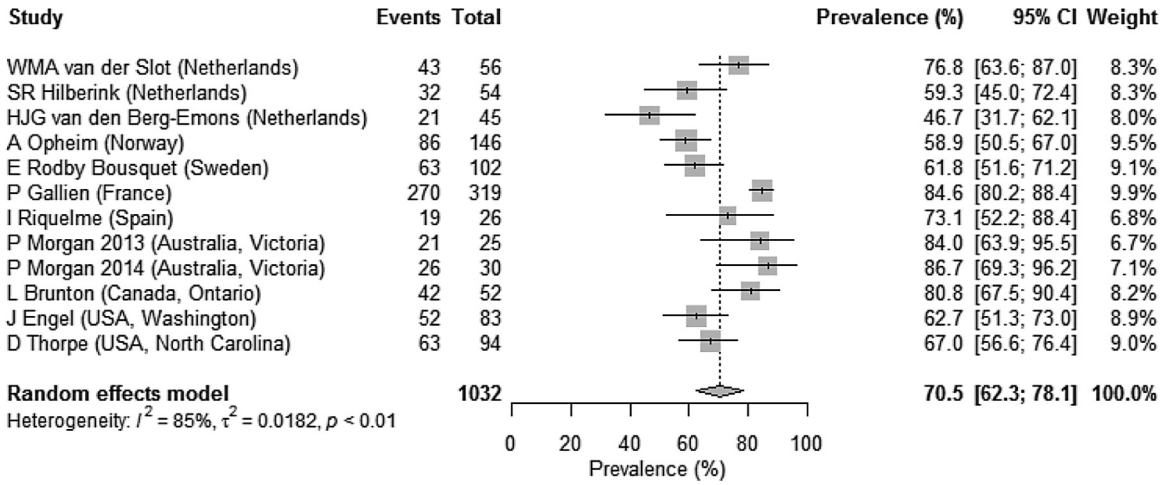

Fig. 4. Forest plot of sensitivity analysis (N = 1032) excluding the 2 samples [18,32] with the most deviating pain prevalence estimates compared to the other samples.

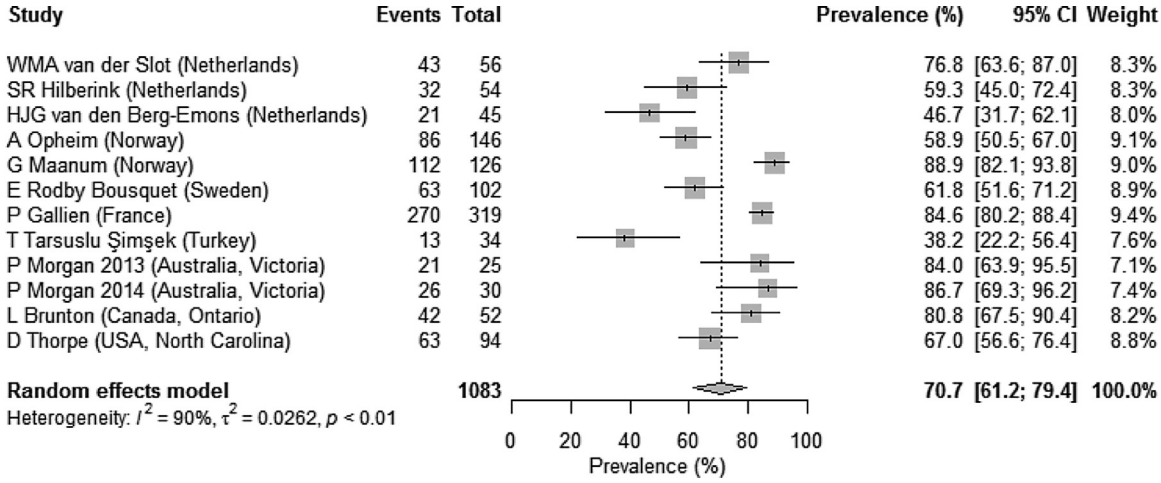

Fig. 5. Forest plot of sensitivity analysis (N = 1083) excluding the 2 samples that assessed the pain 3 months or longer [33,34].

studied in follow-up programs (e.g., CP registries) continuing into adult age [41].

In conclusion, most adults with CP experienced pain. Pain was mostly located in the legs but was also common in the neck/back and arms. Subgroups at increased risk for pain were women, adults with GMFCS levels II and IV, those with GMFCS level III for leg pain, and individuals aged over 45 years for pain in the arms. The present meta-analysis provides a reliable estimate of pain prevalence in adults with CP and highlights the need for routine pain screening in people with CP.

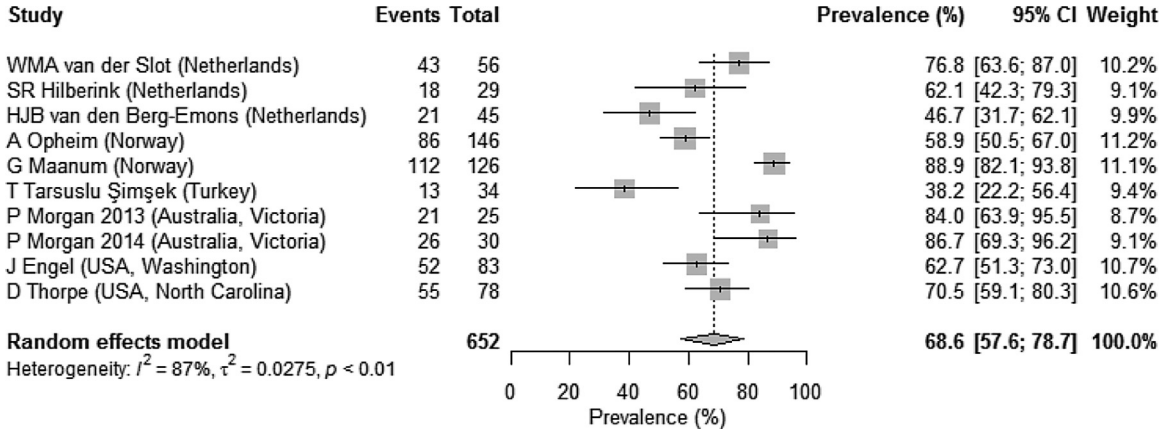

Fig. 6. Forest plot of random-effects meta-analysis for mean prevalence of pain in adults with CP without intellectual disability. Number of samples = 10. Eight samples included only individuals without intellectual disability (N = 540) [12,14,15,18,32,33,42,54]. Three other samples included a traceable number of individuals without intellectual disability (N = 118); Hilberink (N = 29; 54%), Riquelme (N = 6; 18%), Thorpe (N = 83; 83%), of which the subsample of Riquelme was too small (< 10) to include in this analysis [16,34,53] N = 652.

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Contributions

The study was coordinated and designed by WS and MR. The screening of articles was performed by JB and MR and the methodological quality assessment by JB, SH and MR. GP, JB and WS had full access to the study data from all contributing studies. A statistician was involved for the duration of the project (GP). GP, JB and WS analyzed and GP, JB, WS and MR interpreted the data. LB, JE, PG, SH, GM, PM, AO, ER, IR, TŞ, DT, RB and LV provided the data of the original studies, interpreted the results of the meta-analysis and reviewed the manuscript. The manuscript was written and prepared by WS, and all authors have seen and approved the final version.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2019.12.011.

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