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Comprehensive review

Prevalence and natural history of pain in adults with multiple sclerosis: Systematic review and meta-analysis

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ABSTRACT

The prevalence, associations, and natural history of pain in multiple sclerosis (MS) are poorly understood. The objective of this work was to study the prevalence of pain syndromes in MS both cross-sectionally, and longitudinally during the MS disease course. We systematically identified prospective studies detailing pain prevalence in definite MS. We used pooled prevalence estimates, explored heterogeneity using meta-regression, and analysed prevalence during the disease course using both estimates at disease milestones and longitudinal studies. Twenty-eight articles (7101 subjects) describing overall pain, or pain syndromes, met inclusion criteria. Pooled overall pain prevalence (17 studies, 5319 subjects) was 63% (95% confidence interval [CI] 55–70%). Marked heterogeneity in this estimate was not significantly explained by selected study design variables (use of outpatient sample, timeframe prior to study over which pain was assessed) or sample demographic variables (mean Expanded Disability Status Scale, mean disease duration, proportion of female sex, and proportion with progressive MS). We quantified prevalence of headache (43%; 95% CI 33–52%), neuropathic extremity pain (26%; 95% CI 7–53%), back pain (20%; 95% CI 13–28%), painful spasms (15%; 95% CI 8.5–23%), Lhermitte sign (16%; 95% CI 10–25%), and trigeminal neuralgia (3.8%; 95% CI 2–6%) in included studies. Prevalence of pain at MS disease milestones (prior to onset, at onset, and at relapse) and during longitudinal follow-up was poorly described. Pain is common in MS, as are specific pain syndromes. The clinical associations and natural history of pain in MS require clarification. Future study could be enhanced by standardised study design.

1. Introduction

Pain is a key symptom in multiple sclerosis (MS). It has been rated by people with MS as one of their most important symptoms [17] and is often severe [20]. In addition, pain has frequently been linked to adverse disease outcomes including impaired quality of life [42] and disability [1], and is therefore potentially a highly important therapeutic target in MS [44].

Despite its clinical importance, however, many features of pain associated with MS remain poorly understood. Overall pain prevalence is unclear, with estimates ranging widely from 29% to 86% [6,41]. Studies examining relationships of pain prevalence to clinical variables use differing patient samples and study design, and report inconsistent conclusions. There is, therefore, limited understanding of which MS patient groups suffer most frequently from pain, or of the influence of study methodology on pain estimates. Lastly, the natural history of pain during the disease course is uncertain. One previous systematic review carried out in 2007 [31] usefully explored some of these issues. The authors did not, however, examine the literature published in languages other than English, and did not use weighted meta-analysis to calculate prevalence estimates. Therefore, confidence intervals for estimates are not available, and between-estimate heterogeneity has not been quantified nor formally explored.

Better understanding of the prevalence, and natural history, of MS-related pain could help to estimate the true extent of this problem, as well as to identify patient groups in which pain is most prevalent. Furthermore, better understanding of the epidemiology of pain in MS could improve understanding of symptom mechanisms,

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and potentially contribute to development of targeted treatment strategies. We therefore carried out a systematic review and meta-analysis of the prevalence, and natural history, of pain in MS. We firstly aimed to identify, assess, and synthesise cross-sectional studies of the prevalence of pain, and secondly to study longitudinal relationships of pain prevalence or incidence to disease course.

2. Methods

2.1. Literature search and selection criteria

We used a strategy based upon recent systematic reviews [19,25,28,29,50] (Appendix A, supplementary material) to search Medline (from 1977), EMBASE (from 1974), and the Cochrane Library (November 11, 2011). We used Cited Reference Search (Web of Science) to identify articles referencing identified publications (January 3, 2012). Searches were limited to only studies of humans. We hand-searched reference lists and contacted authors to identify unpublished data.

To achieve the most reliable ascertainment, we included only prospective studies characterising clearly defined pain in adults with definite MS. We considered the diagnosis of MS as definite where use of recognised contemporaneous criteria, including McDonald [27], revised McDonald [34], or Poser [35] was described, or, if diagnostic criteria were not specified, where the diagnosis was explicitly confirmed by a neurologist [1,9,33,46]. We excluded studies investigating pain attributed solely to a treatment or intervention, those where subjects were selected for symptoms including pain, those reporting insufficient data to calculate pain incidence or prevalence, studies of childhood-onset MS (because of possible epidemiological differences from MS with adult onset [37]), and re-published data (Appendix A). Where interventional trials described the presence of pain, we assessed baseline data only. We reviewed titles and abstracts of identified studies. Potentially relevant articles were then reviewed in full by two authors (P.F., B.L.) using a standardised data extraction form. Disagreements were resolved by consensus. Studies published in languages other than English were reviewed by fluent medically qualified volunteers.

2.2. Data extraction and analysis

We extracted methodological data including; pain types studied and excluded, assessment instruments used, and timeframe over which pain was assessed in relation to the study (termed here "pain timeframe"). We recorded demographic properties of the sample, the prevalence of pain overall, and, where available, prevalence of pain syndromes, including prevalence of "neuropathic" or "somatic" pain syndromes (after O'Connor and colleagues) [31] as reported by investigators. We selected pain syndromes according to availability of data, and clinical relevance. Headache subtypes could not be analysed because of overlapping groups [7].

We carried out quality assessment according to 4 criteria. We noted investigator blinding of any type (for instance clinical assessment blinded to pain status); use of, or reference to, externally available validated instruments (relevant to prevalence estimation); presence of control groups; and description of longitudinal follow-up (relevant to comparison with wider populations, and to longitudinal characterisation, respectively).

Ninety-five percent confidence intervals of proportions were calculated by the Clopper-Pearson method [30]. Pooled proportions were calculated by DerSimonian and Laird random-effects meta-analysis [8]. Where study numbers allowed, we stratified pooled proportions by pain timeframe into studies examining pain within 1 month prior to assessment, and studies examining pain over longer periods. We chose the threshold of 1 month to balance study numbers in each stratum. We used the I^2 statistic to estimate heterogeneity. We visually inspected funnel plots, and used Egger and Begg-Mazumdar tests to estimate risk of bias.

We used meta-regression – in the absence of individual patient data – to explore study and demographic variables that might influence estimate heterogeneity. Seventeen estimates of overall pain [1–3,5,9,11,13,14,18,20,21,32,39,41,43,47,51] and 17 estimates of overall headache [1,2,7,10,14,18,20–22,33,36,38,43,45,48,49] were analysed. Study numbers were insufficient to allow meta-regression for other pain syndromes. We selected specific methodological characteristics of studies (investigator blinding, outpatient population studied, and pain timeframe used); as well as demographic characteristics of the sample (mean Expanded Disability Status Scale [EDSS], proportion female, proportion progressive MS, and mean disease duration) as independent variables based on availability of data, and on previously reported associations [31]. We did not distinguish between primary progressive and secondary progressive MS [26] in the primary analysis given low numbers of studies using this classification. Given limited study numbers, we used univariate analyses with significance threshold of $P < 0.05$, and Bonferroni correction for multiple comparisons. We also studied relationships between pain prevalence or incidence and the MS disease course using estimates at disease milestones (prior to disease onset, at disease onset, and at relapse) and longitudinal cohort studies of overall pain. We used StatsDirect v2.7.8b (StatsDirect Ltd, Cheshire, UK), and Stata v10 (StataCorp LP, College Station, TX USA).

3. Results

From 3674 abstracts we identified 28 studies, including 7101 subjects, which met inclusion criteria (Fig. 1).

3.1. Characteristics and quality assessment of included studies

Seventeen studies (5319 subjects) described overall pain and 11 (1782 subjects) described specific pain subtypes. The majority of these assessed headache (10 studies, 1581 subjects, one of which [10] included 2 patient samples). Study methodology and quality assessment are summarised in Table 1. In each sample, between 55% [41] and 96% [22] of subjects were female, between 30% [32] and 100% [10] had relapsing remitting MS, mean age was between 30.8 [10] and 54 [32] years, mean EDSS score was between 1.1 [10] and 5.3 [13], and mean disease duration was between 2.5 [5] and 23 [32] years (Appendix A). On quality assessment using our 4 prespecified criteria, only 8 studies described any control population (6 contemporaneous [13,22,36,38,43,45], 2 historical [20,23]), 4 described any blinding procedure [23,38,45,49], and 5 described follow-up [5,22,33,38,41]. Seventeen used at least one externally available validated instrument, of which 9 [10,22,33,36,45,48,49] were headache studies referring to International Headache Society Criteria [15,16]. Of overall pain studies, 2 studies [41,51] met one criterion, 4 [5,13,20,43] met 2, and none met more than 2. Of pain subtype studies, 5 studies [7,10,46,48] met one criterion, 3 [33,36,49] met 2, 3 [22,23,45] met 3, and one [38] met all 4.

3.2. Prevalence of pain overall, and of specific pain syndromes

Pooled overall pain prevalence from 17 estimates [1–3,5,9,11,13,14,18,20,21,32,39,41,43,47,51] was 62.8% (95% confidence interval [CI] 55.1–70.3%). Pain prevalence stratified by study pain timeframe (for studies examining pain within the last month prior to assessment, and studies examining pain over longer periods) was 61.8% (95% CI 51.6–71.5%) and 64.7% (95% CI 51.7–76.7%), respectively (Fig. 2).

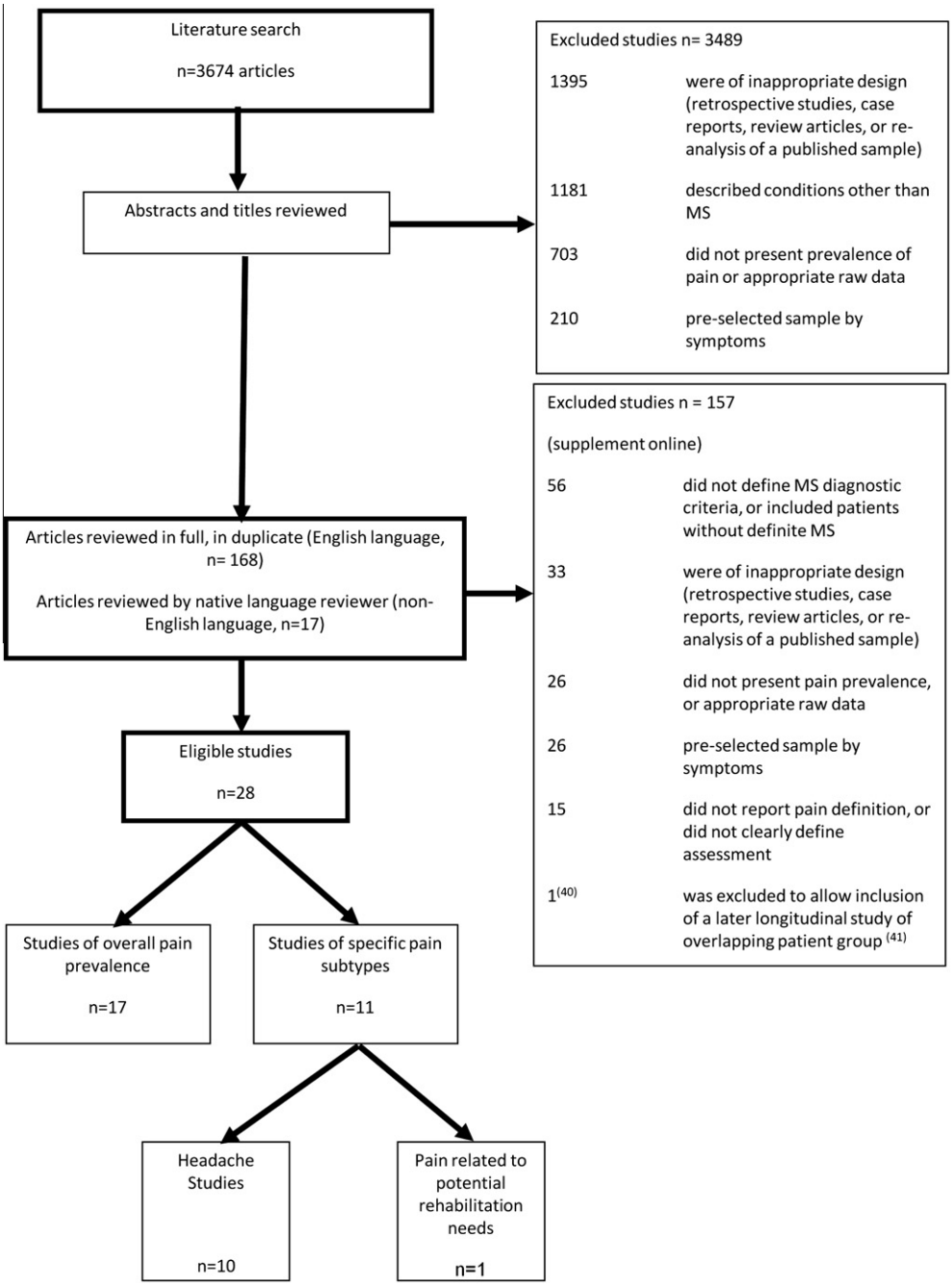

Fig. 1. Flowchart describing selection of studies.

From 17 estimates of headache prevalence [1,2,7,10,14,18,20–22,33,36,38,43,45,48,49], pooled prevalence was 42.5% (95% CI 33.2–52.1%). Headache prevalence stratified by study pain timeframe was 28.8% (95% CI 15.8–44.0%) for studies examining pain within the month prior to study, and 50.5% (95% CI 40.4–60.6%) for studies examining pain over longer periods (Fig. 3).

Pooled prevalences of specific pain syndromes were: neuropathic extremity pain 26.6% (95% CI 7–52.8%), back pain 20.0% (95% CI 13.3–27.7%), painful spasms 15.0% (95% CI 8.5–23.0%), Lhermitte sign 16.6% (95% CI 9.7–25.0%), and trigeminal neuralgia 3.8% (95% CI 2.0–6.0%) (Fig. 4). We found insufficient data to allow pooled estimates for other pain syndromes. Pooled overall prevalence of investigator-defined neuropathic pain was 28.5% (95% CI 23.5–33.8%), and of somatic/nociceptive pain, 18.2% (95% CI 14.0–23.0%) (Fig. 5). We found low risk of small study bias for all described estimates.

In an additional post hoc analysis, we further analysed pain prevalence in the few studies detailing the number of subjects with relapsing remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS) [26]. These data were available in 9 studies of overall pain [2,3,9,14,20,32,39,41,51] and 4 headache studies [36,45,48,49]. Of these studies, 5 studies of overall pain [3,9,14,39,51] presented pain prevalence separately for each disease subgroup. For these 5 studies, pooled pain prevalence in relapsing remitting disease was 50.0% (95% CI 35.4–64.5%) (5 studies [3,9,14,39,51], 2089 subjects with RRMS, I^2 97.1%). In SPMS, pooled pain prevalence was 69.8% (95% CI 54.7–83.0%) (5 studies [3,9,14,39,51], 673 patients with SPMS, I^2 92.6%); and for PPMS,

Table 1
Characteristics of included studies.

Authors	n = MS total	Overall proportion suffering pain	Quality assessment				Pain assessment details			
			Follow-up?	Controls?	Validated externally available assessment instrument?	Blinding?	Pain types studied	Instrument(s) used	Specific exclusions	Allocated pain timeframe stratum [a]
General pain prevalence studies										
Archibald et al. [1]	85	0.53	No	No	No	No	General	Structured interview	None recorded	Up to 1 month
Beiske et al. [2]	142	0.65	No	No	No	No	General	Structured interview	Primary headache	Up to 1 month
Boneschi et al. [3]	428	0.40	No	No	No	No	General	Semi-structured questionnaire	Chronic pain lasting < 6 months	Longer than 1 month
Brochet et al. [5]	68	0.74	Yes	No	Yes	No	Bodily pain	SEP-59	None recorded	Up to 1 month
Douglas et al. [9]	219	0.67	No	No	No	No	General	Piloted questionnaire booklet, interview	Everyday pain - minor headaches, sprains and toothache	Up to 1 month
Fryze et al. [11]	104	0.70	No	No	No	No	General	Authors' questionnaire	None recorded	Longer than 1 month
Grasso et al. [13]	128	0.48	No	Yes[b]	Yes	No	General	sfMPQ, VAS, component of SF36	VAS score < 3	Up to 1 month
Grau-Lopez et al. [14]	134	0.55	No	No	No	No	General	Semi-structured interview	None recorded	Up to 1 month
Indaco et al. [18]	122	0.57	No	No	No	No	General	Interview	Chronic headache, pain syndromes relieved by analgesics	Longer than 1 month
Kalia and O'Connor [20]	99	0.69	No	Yes[c]	Yes	No	Any chronic	VAS, sfMPQ, component of SF36	Chronic pain due to other diagnosis or trauma	Up to 1 month
Kassirer and Osterberg [21]	28	0.82	No	No	No	No	General	Questionnaire	None recorded	Longer than 1 month
Osterberg et al. [32]	364	0.57	No	No	No	No	General, particularly central	Postal questionnaire interview in person	Back pain, tension headache, migraine, optic neuritis	Longer than 1 month
Solaro et al. [39]	1672	0.43	No	No	No	No	General	Structured questionnaire	Headache, acute pain due to ON, somatic pain other than back pain, tendonitis, capsulitis	Up to 1 month
Stenager et al. [41]	49	0.86	Yes	No	No	No	General	Interview, examination	Headache, minor pain relieved by analgesics	Longer than 1 month
Svendsen et al. [43]	627	0.79	No	Yes[b]	Yes	No	General	MPQ	None recorded	Up to 1 month
Vermote et al. [47]	83	0.54	No	No	No	No	General	Questionnaire with elements of MPQ	Headache, visceral pain	Up to 1 month
Zajicek et al. [51]	967	0.70	No	No	Yes	No	General	Authors' questionnaire, SF36	None recorded	Up to 1 month
Specific pain subtype prevalence studies										
D'Amico et al. [7]	116	0.58	No	No	Yes	No	Headache	Authors' questionnaire[e]	Non-headache pain	Longer than 1 month
Ergun et al. (remission phase) [10]	34	0.74	No	No	Yes	No	Headache	Interview[e]	Trigeminal neuralgiaoptic neuritis, other cranial neuralgia	Longer than 1 month
Ergun et al. (relapse phase) [10]	18	0.39	No	No	Yes	No	Headache	Interview[e]	Non-headache pain	Up to 1 month
Katsiari et al. [22]	48	0.50	Yes	Yes[b]	Yes	No	Headache	Interview[e]	Non-headache pain	Longer than 1 month
Kister et al. [23]	204	0.64	No	Yes[c]	Yes	Yes	Migraine	Multiple questionnaires	Related to trauma, infection or medication	Longer than 1 month

(*continued on next page*)

Table 1 (*continued*)

Authors	n = MS total	Overall proportion suffering pain	Quality assessment				Pain assessment details			
			Follow-up?	Controls?	Validated externally available assessment instrument?	Blinding?	Pain types studied	Instrument(s) used	Specific exclusions	Allocated pain timeframe stratum [a]
Pöllmann et al. [33]	82	0.65	Yes	No	Yes	No	Headache	Standardised questionnaire[e]	Analgesic overuse headache	Longer than 1 month
Putzki et al. [36]	491	0.54	No	Yes[b]	Yes	No	Headache	Questionnaire[e]	Non-headache pain	Longer than 1 month
Rolak and Brown [38]	104	0.52	Yes	Yes[b]	Yes	Yes	Headache	Authors' interviews, psychiatric interview[f]	Optic neuritis, trigeminal neuralgia	Longer than 1 month
Vacca et al. [45]	238	0.51	No	Yes[b]	Yes	Yes	Headache	Semi-structured interview[e]	Non-headache pain	Longer than 1 month
Villani et al. [48]	102	0.62	No	No	Yes	No	Headache especially primary headaches	Authors' questionnaire[e]	Non-headache pain	Longer than 1 month
Villani et al. [49]	144	0.64	No	No	Yes	Yes	Headache especially primary headaches	Authors' questionnaire[e]	Probable migraine	Longer than 1 month
Vazirinejad et al. [46]	201	N/A[d]	No	No	Yes	No	Related to potential rehabilitation needs	NEADL, MSQOL54, own questions	None recorded	Up to 1 month

VAS, visual analogue scale for pain; MPQ, McGill Pain Questionnaire; sfMPQ, short-form McGill Pain Questionnaire; NEADL, Nottingham Extended Activities of Daily Living scale; SF36, short-form 36 scale; MSQOL-54, Multiple Sclerosis Quality of Life-54 scale; SEP-59, "Sclerose en Plaques-59" French Language scale derived from components of SF36 and MSQOL54.

[a] Period of interest over which pain occurrence was investigated, stratified into; up to and including 1 month before assessment, and longer periods before assessment (as described in text).

[b] Contemporaneous controls.

[c] Historical controls.

[d] Overall pain prevalence not available (pain subtype prevalence data presented).

[e] Based on International Headache Society Criteria (1988 or 2004 versions).

[f] Based on definitions of Ad Hoc Committee on Classification of Headache (1962).

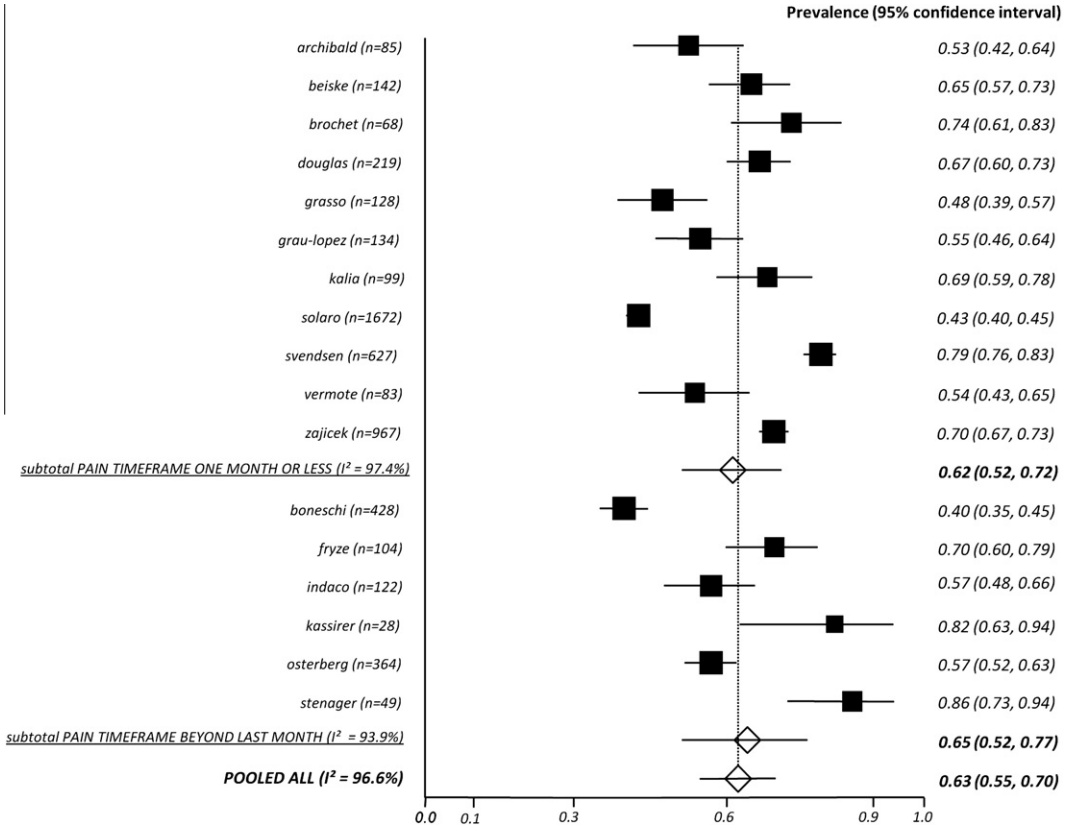

Fig. 2. Overall prevalence of pain, stratified by timeframe of assessment (17 studies).

pooled pain prevalence was 70.3% (95% CI 59.9–79.8%) (5 studies [3,9,14,39,51], 393 patients with PPMS, I^2 72.4%).

Of the 4 headache studies detailing the number of subjects with relapsing remitting, primary progressive, and secondary progressive MS [36,45,48,49], only 2 presented headache prevalence separately for each subgroup [48,49]. Given the low number of studies, we did not carry out weighted meta-analysis, however, in each study separately, headache prevalence in RRMS was 74.7% (83 subjects with RRMS, 95% CI 64.0–83.6%) [48] and 76.3% (118 subjects with RRMS, 95% CI 67.6–83.6%) [49]; and in SPMS 63.2% (19 subjects with SPMS, 95% CI 38.4–83.7%) [48] and 65.4% (26 subjects with SPMS, 95% CI 44.3–82.8%) [49]. No subjects in these 2 studies were classified as having PPMS. Although the limited number of studies and subjects included in this post hoc analysis did not suggest a difference in overall pain prevalence or headache prevalence according to disease subgroup, given the small number of studies reporting pain prevalence by MS subgroup, we cannot exclude a clinically important difference between groups.

3.3. Meta-regression analysis

We identified no studies of overall pain using investigator blinding of any type, and only one study of headache prevalence describing an inpatient population. We did not, therefore, assess the amount of estimate heterogeneity accounted for by these variables using meta-regression. For overall pain estimates, none of the prespecified methodological or sample demographic variables significantly explained estimate heterogeneity. For headache estimates, only the study pain timeframe accounted for a significant proportion of between-study heterogeneity. Timeframe of assessment of longer than 1 month prior to assessment was associated with higher headache prevalence than estimates assessing only headache in the preceding month (Table 2).

In an additional post hoc meta-regression analysis, examining the proportion of patients with SPMS and PPMS as independent variables did not significantly explain the observed heterogeneity in overall pain estimates (9 studies; SPMS: adjusted R^2 −10.19%, *P* value 0.586; PPMS adjusted R^2 17.91%, *P* value 0.172; threshold *P* value for both comparisons 0.0083 following Bonferroni correction). We did not carry out post hoc meta-regression analysis using these independent variables for headache studies, as insufficient study numbers were available.

3.4. Relationship of pain incidence or prevalence to MS disease course

(1) Pain incidence
We found no estimates of pain incidence.
(2) Pain prevalence prior to disease onset
We identified no prospective studies describing prevalence of overall pain prior to MS onset.
(3) Pain prevalence at disease onset
One study prospectively estimated pain prevalence soon after diagnosis (73.5% prevalence of any pain) [5]. Mean disease duration at assessment was 30.5 months (range 3–202 months).
(4) Pain prevalence at relapse
Only one study prospectively analysed pain at relapse, reporting headache prevalence of 38.9% (number of subjects with headache = 7: 5 primary stabbing headache, 2 migraine) [10].
(5) Pain prevalence during disease evolution
Only 2 studies prospectively examined overall pain evolution with disease progression [5,41]. Both describe a popula-

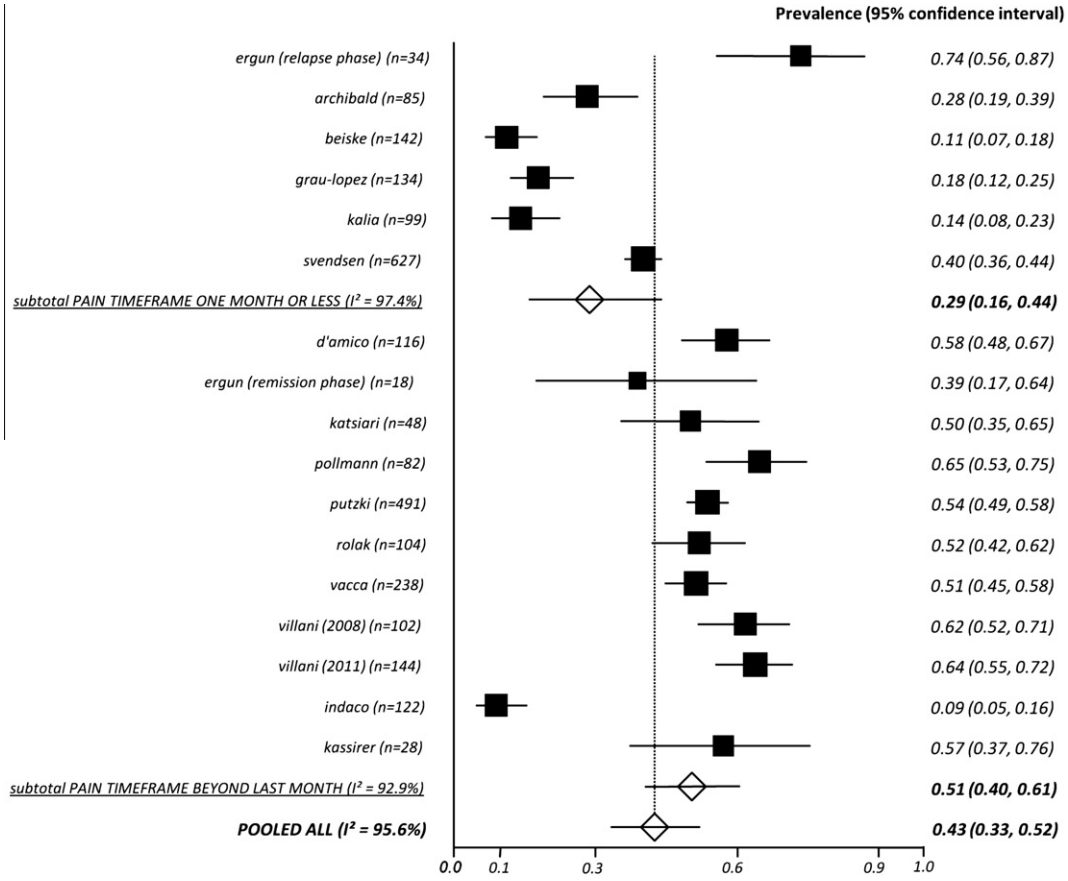

Fig. 3. Overall prevalence of headache, stratified by timeframe of assessment (17 estimates).

tion of mixed MS disease types. Brochet and colleagues [5] studied 68 subjects with early MS over 2 years; 33% of RRMS and 45% of PPMS subjects reported clinically significant pain at all time points. Pain prevalence appeared to decrease over time, however, this trend was not statistically significant. Stenager and colleagues [41] studied 70 subjects at baseline, and reassessed 49 of these after 5 years. They found a significant increase in prevalence of overall pain and of several pain syndromes, particularly in subjects with deteriorating EDSS. Brochet and colleagues report no loss to follow-up, whereas Stenager and colleagues report loss to follow-up of 30%.

4. Discussion

We have found that pain in MS is concerningly common, affecting around 63% of adults with the condition (95% CI 55–70%). Our results, in turn, support previous findings that pain in the MS population is heterogeneous, and includes several pain syndromes and mechanisms. We have found that headache, extremity neuropathic pain, back pain, painful spasms, Lhermitte sign, and trigeminal neuralgia are all common. Our findings quantify the prevalence of these syndromes in the MS population, and suggest that headache, followed by extremity neuropathic pain, are the most common pain syndromes, and trigeminal neuralgia the least common. Considerable uncertainty is, however, associated with these estimates, and prevalence of some painful syndromes (in particular, optic neuritis) remains unclear. Several pathophysiological mechanisms may be relevant to the identified pain syndromes, and our findings that both neuropathic and somatic/nociceptive pain mechanisms are prevalent in the included studies further highlight the complexity of pain in the MS population. Our findings additionally suggest that neuropathic pain mechanisms may be more prevalent than somatic/nociceptive mechanisms.

On comparison with previous estimates of pain prevalence, our analysis includes all studies used for prevalence estimates in a previous systematic review [31], with the exception of one [40] that we excluded in favour of a study examining an overlapping patient group [41]. By contrast, however, our estimates of overall pain prevalence (63%; 95% CI 55–70%) (17 studies, 5319 subjects), [1–3,5,9,11,13,14,18,20,21,32,39,41,43,47,51] and pain within the last month (62%; 95% CI 52–72%) (11 estimates, 4224 subjects) [1,2,5,9,13,14,20,39,43,47,51] vary significantly from previous estimates [31] of 50% for point prevalence (3 studies, 1872 subjects), [39,40,47] and 75% for pain within the last month (3 studies, 854 subjects) [1,2,43]. We believe that several factors, including the prospective design of all included studies, the larger number of included prospective studies (28 studies, 7101 subjects, in comparison to 9 prospective studies, 3311 subjects), and use of weighted meta-analysis, are likely to augment the accuracy of our estimates.

We have, in addition, highlighted the considerable heterogeneity in our pooled estimates, as evidenced by visual inspection of forest plots, and by I^2 statistics >75% for all pooled estimates (apart from for neuropathic pain, and somatic/nociceptive pain overall). We therefore explored sources of estimate heterogeneity in overall pain and headache using meta-regression. Regarding overall pain estimates, lack of studies employing investigator blinding precluded assessment of this variable by meta-regression. None of the remaining methodological variables (pain timeframe, or outpatient sample source), or sample demographic variables (mean EDSS, proportion of females, proportion progressive MS, or mean disease duration), however, significantly accounted for estimate

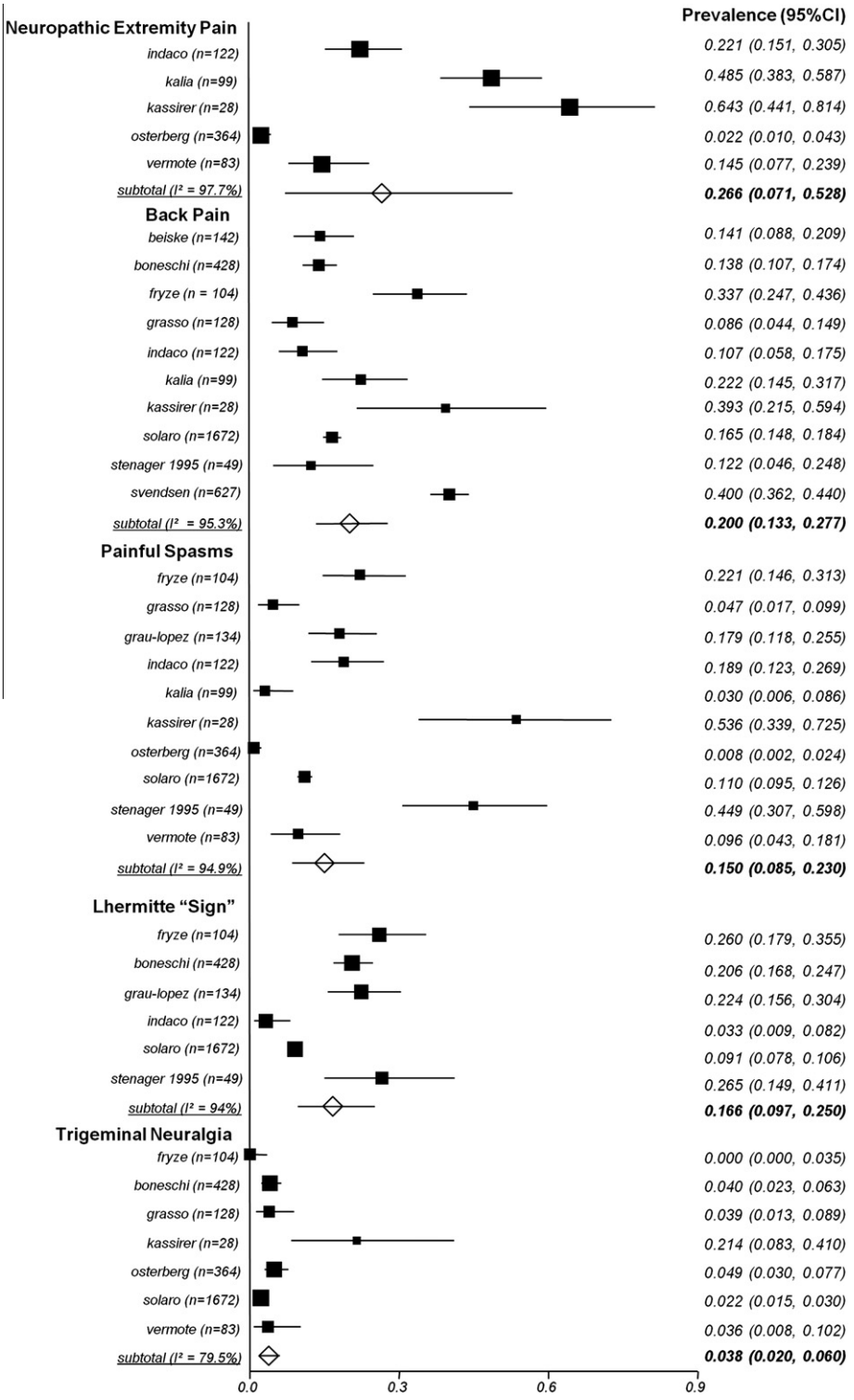

Fig. 4. Prevalence of specific pain syndromes.

heterogeneity. For headache estimates, lack of inpatient studies precluded meta-regression for this independent variable. Of the remaining variables, only pain timeframe significantly affected estimate heterogeneity (Table 2).

Post hoc prevalence estimates and meta-regression analyses did not, in addition, suggest a significant role of disease subgroup in the limited number of overall pain studies where relapsing remitting, primary progressive, and secondary progressive subgroups were specified. Post hoc prevalence estimates for headache studies likewise did not suggest a role of disease subgroup (although small study numbers precluded definite conclusions for all post hoc analyses).

These interesting results seemingly contradict previous findings that pain is more common with, for example, increasing disability and disease duration [3,9,14,39,41], and could be in keeping with studies finding no relationship [2,5,13,18], However, in our opin-

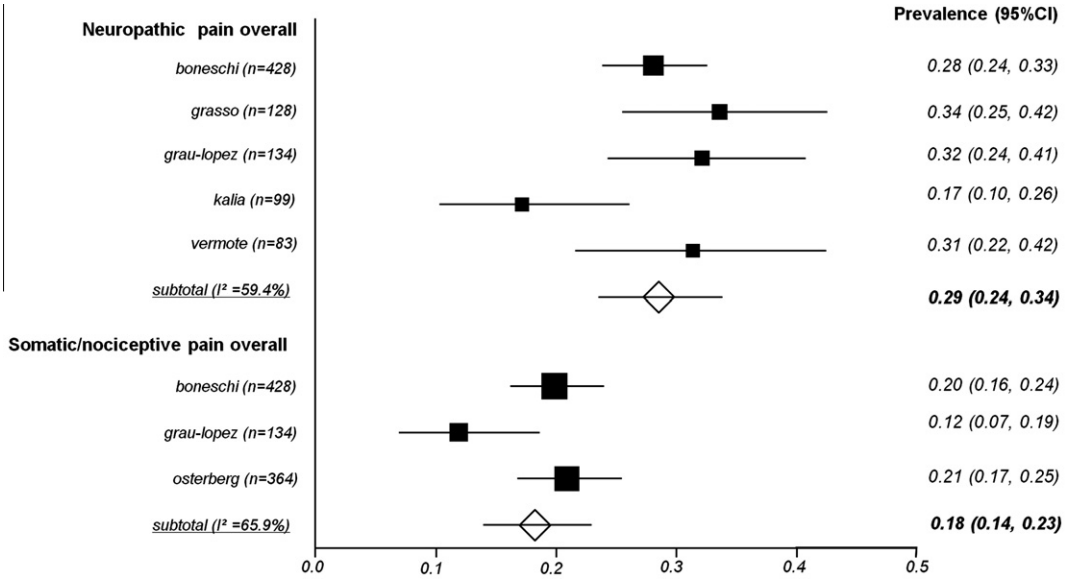

Fig. 5. Reported aetiology of pain syndromes.

Table 2
Meta-regression analysis of overall pain and headache prevalence studies.

	Studies analysing overall pain prevalence (total 17 estimates)			Studies analysing headache prevalence (total 17 estimates)		
	Number of studies where data available	Adjusted R^2 [c]	P value	Number of studies where data available	Adjusted R^2[c]	P value
Study variables						
Blinding	No blinded study identified, therefore meta-regression not carried out			17 3 blinding used, 14 blinding not used	0.73%	0.328[a]
Outpatient population studied	17 13 outpatient sample, 4 inpatient sample	−3.12%	0.497[a]	Only one inpatient study identified, therefore meta-regression not carried out		
Pain timeframe (pain within 1 month/longer than 1 month from time of assessment)	17 10 pain within last month only, 7 longer timeframe	−4.81%	0.506[a]	17 6 pain within last month only, 11 longer timeframe	32.13%	0.012[a]
Demographic variables						
EDSS (mean)	7	−16.22%	0.675[b]	10	43.86%	0.026[b]
Proportion female gender in population	16	−7.05%	0.868[b]	17	−5.02%	0.667[b]
Proportion progressive MS in population	13	−6.08%	0.617[b]	11	15.05%	0.145[b]
Disease duration (mean)	12	−10.30%	0.768[b]	12	28.12%	0.051[b]

EDSS, Expanded Disability Status Scale.
[a] Threshold significance value $P < 0.017$ for individual analyses, based on Bonferroni correction (3 comparisons) with $P < 0.05$ significance threshold.
[b] Threshold significance value $P < 0.012$ for individual analyses, based on Bonferroni correction (4 comparisons) with $P < 0.05$ significance threshold.
[c] Negative adjusted R^2 values may arise in the case of small sample sizes where R^2 value is less than expected by chance.

ion, even within a selected group of included studies, underlying effects could be masked by inconsistent use of diagnostic, inclusion, and exclusion criteria [31], or by low number of available studies. It is possible that the apparent significant effect of pain timeframe in headache studies, but not in overall pain studies, could reflect more consistent use of diagnostic [15,16], inclusion, and exclusion criteria in headache studies (Table 1). Higher adjusted R^2 values for other variables in headache studies as compared to overall pain studies could be explained similarly (Table 2). We also consider that significant correlates of pain may be unidentified, or inconsistently studied. Specifically, few studies quantified psychiatric or neuropsychological dysfunction.

Although we selected relatively high quality studies, we identified some methodological concerns in included studies. Investigator blinding, longitudinal follow-up, and control groups were all infrequently used, and externally available validated instruments were infrequently used in overall pain studies specifically (Table 1). Deficient blinding and use of varying diagnostic criteria may be most likely to influence prevalence estimates. Infrequent use of follow-up and of control groups may principally affect characterisation of the natural history of pain in MS, and assessment of differences between MS and other populations. In addition, all included studies were carried out in North America or Europe, which could limit wider generalisation of findings.

In order to study pain prevalence in relation to the MS disease course, we next sought characterisation of MS-related pain either at disease milestones, or longitudinally in evolving disease. We have found that the natural history of pain in MS is poorly characterised in the identified studies. Firstly, we found no studies of pain incidence. We also found no prospective studies of overall pain prevalence prior to disease onset (notwithstanding potential methodological challenges). In comparison, Vacca and colleagues [45] retrospectively found that headache was present prior to MS onset in 69.7% of MS headache patients, and that MS onset did not mod-

ify pre-existing headaches. Given descriptions elsewhere suggesting predisposition to chronic pain [12], these findings remain of interest.

We found only one prospective estimate of pain prevalence at disease onset [5]. Despite early recruitment, mean symptom duration was 30.5 months, and pain prevalence of 73.5% could be regarded as an estimate in early disease. Retrospective estimates from our included studies are lower (overall pain range 11–21%, headache range 1.7–6.7%) [7,18,20,32,38,45]. However, disease duration (where reported) for retrospective estimates ranged from 10.8 [20] to 23 years [32], and thus these figures are vulnerable to recall bias. The apparent discrepancy between prospective and retrospective results could suggest that retrospective estimates relatively under-report pain prevalence at disease onset. The role of data ascertainment methods in pain epidemiology studies remains under investigation [24].

Pain associated with relapse has similarly rarely been studied prospectively, despite clear potential clinical relevance. Several studies specifically excluded pain related to MS relapse [3,39], or did not separately report these data [1,21]. One prospective estimate [10] of headache prevalence in relapse was found (prevalence 38.9%), but no prospective studies of overall pain. In comparison, retrospective prevalence estimates ranged from 63% [43] for overall pain, to approximately 1% for headache or for central pain [32,33,38]. Katsiari and colleagues report no relationship between several headache subtypes and relapse activity, though methodology is not described [22]. Relapse-associated pain could be highly clinically relevant in informing immunomodulation decisions. The lack of prospective studies, and wide variation in estimates, suggest that further study is required.

With regards to longitudinal follow-up of pain syndromes, Stenager and colleagues [41] describe increasing prevalence of several pain syndromes with disease progression (initial mean EDSS 3.4). Brochet and colleagues [5] describe a statistically nonsignificant decrease in pain prevalence in less disabled subjects with early disease (median EDSS 2). Given the limited available data, including only 117 subjects and extending to a maximum of 5 years follow-up, it is not possible, in our opinion, to reliably describe any relationship of MS-related pain to disease evolution.

Our study had several limitations. Inclusion of a relatively low number of studies may have limited the power of our analyses, as discussed above. We have not studied pain severity, or quality of life, and have excluded pain related solely to MS treatment. Our findings therefore do not reflect these factors. A lack of control data precludes direct comparison of pain prevalence in MS groups with the wider population, or to other chronic neurological diseases, although chronic pain prevalence in the general population (Europe and Israel) has been estimated at around 19% [4]. Lastly, retrospective estimates of pain prevalence at disease milestones from our included studies are discussed in comparison to our prospective data, but we have not included all available retrospective estimates, as this was not the focus of our review.

4.1. Conclusions

We have found that prevalence of pain in MS is around 63%, and that it is composed of a variety of pain syndromes and mechanisms. There is significant uncertainty associated with prevalence estimates, though examined aspects of study design and sample populations did not significantly explain heterogeneity in overall pain estimates. It is most likely that variable study design and execution (even within our selected study group) contributes to this heterogeneity. We also found that characterisation of pain during the MS disease course is limited, and that incidence has not been studied. Therefore, while pain is common in MS, its relationships to disease course are poorly quantified.

Enquiry about pain should remain a priority for clinicians treating all patients with MS. Investigation of the temporal profile of MS-related pain, and characteristics of patients at risk – using standardised study design – should also be clinical research priorities. Better understanding of the epidemiology of pain in MS could contribute to investigation of its aetiology, management, and potentially, its prevention.

Conflict of interest statement

The authors declare no financial or other conflict of interest in relation to this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.12.002.

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