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Physical trauma and risk of multiple sclerosis: A systematic review and meta-analysis of observational studies☆

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ABSTRACT

Background: We aimed to examine physical trauma as a risk factor for the subsequent diagnosis of MS.
Methods: We searched for observational studies that evaluated the risk for developing MS after physical trauma that occurred in childhood (≤20 years) or "premorbid" (>20 years). We performed a meta-analysis using a random effects model.
Results: We identified 1362 individual studies, of which 36 case–control studies and 4 cohort studies met the inclusion criteria for the review. In high quality case–control studies, there were statistically significant associations between those sustaining head trauma in childhood (OR = 1.27; 95% CI, 1.12–1.44; $p < 0.001$), premorbid head trauma (OR = 1.40; 95% CI, 1.08–1.81; $p = 0.01$), and other traumas during childhood (OR = 2.31; 95% CI, 1.06–5.04; $p = 0.04$) and the risk of being diagnosed with MS. In lesser quality studies, there was a statistical association between "other traumas" premorbid and spinal injury premorbid. No association was found between spinal injury during childhood, or fractures and burns at any age and the diagnosis of MS. The pooled OR of four cohort studies looking at premorbid head trauma was not statistically significant.
Conclusions: The result of the meta-analyses of high quality case–control studies suggests a statistically significant association between premorbid head trauma and the risk for developing MS. However, cohort studies did not. Future prospective studies that define trauma based on validated instruments, and include frequency of traumas per study participant, are needed.

1. Introduction

Multiple sclerosis (MS) is a multi-factorial disease which results from complex interactions between susceptibility genes and environmental factors [1]. Whether physical trauma plays a causal role in the etiological pathway of MS has been debated since the earliest descriptions of the illness [2]. Some scientists argue that physical trauma, particularly involving the spinal cord and/or the brain may cause a disruption in the blood–brain barrier, which in turn could lead to the development of MS plaques in those who are already genetically at risk [3]. Thus, the controversy is not whether physical trauma in itself causes MS, but rather whether those with the genetic link with predisposing risk factors (such as Epstein Barr virus), who sustain significant physical trauma, may activate an otherwise dormant MS.

The majority of studies related to physical trauma and MS have either been case reports or smaller case–control studies, which have not only generated contradictory results but also produced effect sizes too small to resolve the hypothesis of an association between trauma and the eventual diagnosis of MS. Three record linkage studies [4–6] and one prospective cohort study [7] were published on the subject. One major review on the topic was published in 1999 [8], and a recent meta-analysis was conducted by Warren et al. in 2013 [9]. We feel it is necessary to report our results as the Warren study only included 13 case control studies, and three cohort studies, as opposed to our meta-analysis which reported on the pooled results of 36 case–control studies and four cohort studies. Furthermore, our results are classified more rigorously.

2. Methods

We followed the procedures for conducting systematic reviews and meta-analysis as outlined by the Cochrane Collaboration [10] and the reporting guidelines of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group [11].

2.1. Search strategy

Studies were identified by several methods. First, we searched for completed reviews in the Database of Abstracts of Reviews of Effects (DARE), the Evidence for Policy and Practice Information (EPPI) Centre,

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the HealthEvidence.ca website, and the Cochrane Database of Systematic Reviews. We searched for individual studies in the MEDLINE, Web of Science, PubMed, and the LILACS (Latin American and Caribbean Computer Library Center) databases. The Google Web search engine (www.google.com) and Google Scholar (scholar.google.com) were used to locate articles that may not have been included in the above databases. Gray literature was searched using OpenSIGLE, NTIS, Health Management Information, British National Bibliography for Report Literature, Proquest Dissertations and Theses, Dissertation Abstracts, CINHAL, and CyberTesis.

For the electronic search, we used the following search terms: (a) *multiple sclerosis* OR *demyelinating disease*; (b) *craniocerebral trauma*, *whiplash*, *hyper flexion*, *concussion*, *trauma*, *injury*, *accident*, *fracture*, *burn*, *contusion*, *sprain*, *spinal cord injury*, *cervical cord injury*, *skull fracture*, *unconsciousness*, and *loss of consciousness*; and (c) *etiologic factor*, *association*, *risk factor*, *causation*, *case–control*, *cohort*, *latent*, or *onset*. Reference lists of all relevant articles were examined for further pertinent studies. Forward citation searches of included studies and literature reviews were also done. Primary authors and experts in the field were contacted to identify additional published, unpublished, or 'in-progress' studies. The search was not limited by publication date, language, or publication status. All databases were last accessed in March 2013.

2.2. Inclusion criteria

We planned to include a broad range of observational studies: cohort, case–control, and cross sectional designs. As there were few primary studies, we also planned to include retrospective studies utilizing secondary data from healthcare databases. To be eligible for inclusion, studies needed to include patients with physician diagnosed MS (preferably using diagnostic criteria) and report original data. Studies were excluded if there was no control group. The primary outcome of interest was the development of MS following a past history of physical trauma (exposure variable). Due to the estimated mean latency period of MS, exposure categories were divided by age at the time of trauma: (1) age $\leq$20 years and (2) age >20 years (or premorbid).

2.3. Data collection and analysis

2.3.1. Selection of studies

One of the study investigators (CL) performed the initial search of all databases to identify potentially relevant citations. Where it was not possible to accept or reject the study, the full text of the citation was obtained for further evaluation. Following the screening of titles and abstracts, the full texts of potential articles were retrieved (and translated into English where required) and assessed for inclusion independently by two of the study investigators (CL, SF). If any differences in opinion occurred, they were resolved by consensus with a third reviewer.

2.3.2. Data extraction and management

Data were independently extracted by one unmasked reviewer (CL) using a standardized electronic data collection form and checked by a second reviewer (JKS) for accuracy. When raw data were not provided, the data were extracted from figures; where necessary, we attempted to seek additional information from first or corresponding authors via electronic mail. We attempted to extract the following information: source of cases and controls, eligibility criteria, sampling methods, participant demographics, MS diagnostic information, covariates adjusted for, outcome exposures, and results. Geographic latitude was assigned according to the latitude of the nearest major city to where the study was conducted or where the majority of study subjects lived. This method has been used by other researchers [12].

2.3.3. Quality assessment: risk of bias in included studies

After identification of articles meeting the inclusion criteria, two review authors (CL, JKS) independently assessed the methodological quality of studies according to the criteria of the Newcastle–Ottawa Quality Assessment Scale (NOS) as recommended by the Cochrane Collaboration for assessing the quality of non-randomized studies [13]. The NOS is based on a cumulative score in each of three broad categories: selection of study groups, comparability of their cases and controls, and their ascertainment of the outcome/exposure on cases and controls. If a study fulfills the criteria for an item, a score of 1 point is allocated, with the exception of comparability which can score up to 2 points, resulting in a maximum score of 9. Similar to other reviews, we considered studies that received a score of $\geq$6 on the NOS criteria to be of high quality. We specifically classified studies as high risk of bias (1–3 points), medium risk of bias (4–5 points), or low risk of bias (6–9 points). In the case of disagreement between reviewers, differences were to be resolved by discussion until consensus was achieved.

2.3.4. Dealing with missing data

When missing data were evident, we attempted to contact study authors. When data could not be obtained from authors, available data were extracted and missing data were imputed. For those studies reporting "no significance", with no additional statistical data, we assumed an odds ratio (OR) of 1.0 and estimated the confidence intervals (CIs) based on the number of reported MS cases [12]. Sensitivity analyses were performed to check the effect of imputation.

2.3.5. Assessment of heterogeneity and reporting bias

Heterogeneity between studies was examined visually using the I^2 statistic. Deeks and colleagues (for the Cochrane Collaboration) [14] suggest the following as a rough guide for interpreting the I^2 statistic:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Possible sources of heterogeneity were assessed by sensitivity analyses and described qualitatively in Table 1.

Stratified meta-regression, based on sub-groups including 10 or more studies, was performed to further examine heterogeneity. Odds ratios (β) and 95% CIs were calculated using the study level log OR and the standard error (SE) of the estimate by constructing univariate random effects (RE) meta-regression models in STATA 12 using the *megareg* command. A plot of ORs was done against NOS scores to determine if there was a linear relationship between the methodological quality of the studies and their results [15]. We also explored publication bias and other potential reporting biases, in those pooled comparisons with 10 or more studies, using funnel plots. We used the graphical approach for funnel plots as described by Peters et al. for assessing dichotomous outcomes with effects measured as ORs [16].

2.3.6. Subgroup analysis and investigation of heterogeneity

A priori, we planned to explore and address possible clinical heterogeneity as well as to investigate the magnitude and precision of effects by performing subgroup analyses based on the reported classification of "trauma". Unfortunately, the grouping of exposures reported in the epidemiological studies was problematic as the majority did not make explicit the type of trauma or the reported varying definitions of "trauma." For example, some studies included only severe cases of head trauma [6], others grouped head trauma with brain or spinal traumas [17], and some did not define the type of head trauma included at all [18]. We therefore aimed to group the studies together using the outcome name/term reported in the studies, e.g. "head trauma" and reported on the following classifications of trauma:

1. Head trauma, including the terms: "head trauma", "brain trauma", "loss of consciousness", and "concussion"
2. "Other trauma", including the general term trauma, and other terms such as "accidents" and "injuries"

3. Spinal injury
4. Fractures
5. Burns.

Sub-group analyses were also done based on population-level continuous variables (latitude, female-to-male case ratio, and mean age of MS onset) and various study-level variables (study quality [NOS score], language of publication [English vs. non-English], publication type [published vs. unpublished], number of matching variables, sample size [≤100 vs. >100], and number of MS cases [≤100 vs. >100]).

2.3.7. Effect measurement and data synthesis

Meta-analyses were performed using the Cochrane Collaboration software program Review Manager (Rev Man) Version 5.1 [19]. To estimate the strength of association between variables, data were pooled using the inverse variance (IV) approach to calculate the OR and 95% CIs and statistical significance was set at $p < 0.05$. When interpreting results of the forest plots for dichotomous data, the area to the right side of the forest plot graph (>1) favored the control group. Studies were weighted based on sample size and the number of events.

Meta-analysis methods were selected based on study heterogeneity and the number of studies included in the analyses. When the I^2 statistic was greater than 75%, we considered it substantial heterogeneity and pooled the study results using an RE model [20]. As we expected in statistical heterogeneity in the majority of outcomes, the RE model was used for all analyses.

2.3.8. Sensitivity analysis

We performed sensitivity analyses by examining the results of the meta-analysis under different assumptions and checked for robustness of the observed findings. A priori, the following sensitivity analyses were planned:

1. By limiting included studies in the analyses to those with the highest methodological quality (NOS score of ≥6), do the results change?
2. For studies in which the OR was reported as "not significant" and therefore had to be imputed, do the results of the pooled analysis change if these are excluded from the results?

3. Results

3.1. Characteristics of included studies

After excluding duplicate studies, we identified 1359 individual studies, of which 83 potentially relevant studies passed the first screening and were retrieved for closer examination. Of the 83 full text articles reviewed, 43 were excluded for the following reasons: 17 did not examine physical trauma [21–37]; 10 did not have a control group [38–47]; seven had a diagnosis other than MS [48–54]; seven were review articles [55–60]; one had insufficient data, and we were unable to locate study authors [61]; and in one study, trauma occurred after the diagnosis of MS was made [62]. Of the retrieved articles, 40 studies met the inclusion criteria for the systematic review [4–7,17,18,63–96]. Fig. 1 outlines the study selection process.

There were 36 case–control studies [17,18,63–96], one had insufficient data to be included in the majority of analyses [89]. The remaining four studies were cohort studies [4–7], three of which were record-linkages [4–6]. Six case–control studies had less than 100 participants in total, and 30 case–control studies had less than 100 cases included. Studies were published between 1965 and 2013 with the majority published in European countries [4,7,18,66,68–71,73,75,76,80–82,85,87,88,91,93], followed by North American [6,63,65,67,72,74,77–79,86,95,96], and Middle Eastern countries [64,83,90,92,94].

Twenty-two different trauma related exposures were reported in the 40 studies. With the exception of four studies [4–7], the risk for MS was reported as ORs while others simply reported whether the exposure risk for MS was "significant" or "not significant". The ORs ranged from 0.59 to 7.34. Fifteen independent studies reported statistically significant results for specific exposures [5,18,64,69,70,74–76,83,85,87,88,90,91,94], while the remaining 25 did not. Details of the 40 studies are summarized in Table 1 Characteristics of included studies.

3.2. Quality assessment

When stratified by study design, the mean NOS score for the 36 case–control studies was 4.8 (medium risk of bias) with seven of the case–control studies classified as having a high risk of bias (1–3 points) [18,65,69,70,72,73,76], 16 had a medium risk of bias (NOS score of 4–5 points) [17,63,64,66,68,74,79,81,82,84,87,90,93–96], and nine had a low risk of bias (NOS scores of 6–9 points) [67,77,78,80,85,86,88,91,92]. Four case–control studies could not be classified due to a lack of available data [71,75,83,89]. The mean NOS score for the cohort studies was 7.3 (low risk of bias). One cohort study was classified as medium risk of bias [6] while the three remaining studies were considered as low risk of bias [4,5,7].

3.3. Exposure results: case–control studies

The meta-analysis of case–control studies included data from all 36 included studies with 6664 MS cases and 7521 controls; there were twice as many females than males included in the studies and the mean age at MS diagnosis was approximately 29 years. See Table 2 for pooled trauma exposure results.

3.3.1. Head trauma

Of the 21 separate studies reporting on head trauma, eight examined head trauma occurring at ≤20 years, and 21 examined head trauma occurring before the diagnosis of MS or "premorbid". The eight case–control studies pertaining to head trauma occurring at ≤20 years [67,70,75,76,80,82,85,91] included 3695 cases and 3504 controls. The pooled RE model revealed a homogeneous sample ($I^2 = 0\%$; $p = 0.43$) with a statistically significant relationship between head trauma and MS diagnosis (OR = 1.26; 95% CI, 1.12–1.42; $p < 0.001$). We performed sensitivity analysis based on study quality (removing those studies with an NOS score <6). Removing the four studies [70,75,76,82] with an NOS score of <6 still allowed for a homogeneous sample ($I^2 = 0\%$; $p = 0.52$) and there were no changes in the direction or magnitude of the effect (OR = 1.27; 95% CI, 1.12–1.44; $p < 0.001$). Sensitivity analysis based on removing the one study where the OR was imputed [82] did not change the significance nor magnitude of the effect (OR = 1.28; 95% CI, 1.14–1.45; $p < 0.001$).

The 21 studies examining premorbid head trauma included 2574 MS cases and 2990 controls [17,18,63,65,67,70,73–76,78,80,81,84,85,87,88,93–96]. The pooled RE model displayed a homogeneous sample ($I^2 = 9\%$; $p = 0.34$) with a statistical difference between groups (OR = 1.65; 95% CI, 1.39–1.95; $p < 0.001$). When 16 studies [17,18,63,65,70,73–76,81,84,87,93–96] with an NOS score of <6 were excluded, the homogeneous results changed slightly as precision increased but p value decreased while still remaining significant (OR = 1.63; 95% CI, 1.10–2.42; $p = 0.01$). Sensitivity analysis based on removing the five studies [65,78,85,87,88] where the OR was imputed did not improve the heterogeneity ($I^2 = 27\%$; $p = 0.17$) nor change the significance and magnitude of the effect (OR = 1.66; 95% CI, 1.25–2.22; $p < 0.001$). See forest plot of the results presented in Fig. 2.

3.3.2. Other traumas

There were 20 discrete studies that examined "other physical traumas"; seven examined other traumas occurring in those ≤20 years and 16 examined other traumas in patients "premorbid". The seven studies reporting on "other traumas" in patient's ≤20 years [64,67,71,72,83,85,89], involved 595 MS cases and 1352 controls. The

Table 1
Characteristics of included case–control and cohort studies.

Author (year) country	MS cases (n)	Control group (n)	F:M ratio (MS cases)	Mean age at MS onset (y)	LAT	NOS score	MS Dx criteria	Timing of trauma	Matched variables	Name of exposure variable(s)	OR[a] (95% CI)
Case–control studies											
Al-Afasy (2013) Kuwait	101	202	1.80	–[b]	32	5	N	Pre	Age, sex, nationality, age at onset	Head trauma	2.6 (1.2–5.5)*
Alter & Speer (1968) USA	36	72	–[b]	–[b]	45	4	N	Pre	Age, sex, age at onset	Head trauma	1.37 (0.59–3.21)
Antonovsky (1965) Israel	241	964	1.10	–[b]	31	5	N	≤15 y, >15 y	Age, sex, age of onset, region of birth	Trauma	≤15 y: NS[c] >15 y: 1.82 (1.28–2.58)*
Bamford (1981) USA	82	82	–[b]	–[b]	32	3	K	Pre	Age, sex	(1) Trauma (2) Head trauma (3) Spine injury (4) Fractures	(1) 1.75 (0.74–4.12) (2) NS[c] (3) NS[c] (4) NS[c]
Berr (1989) France	63	63	2.70	30.8	42	5	P	Pre	Age, sex, residence	Trauma	1.17 (0.54–2.53)
Bobowick (1978) USA	10	8	–[b]	29.7	40	6	N	≤20 y	Age, sex	(1) Head trauma, (2) Trauma, (3) Burns	(1) 1.75 (0.13–23.7) (2) 7.0 (0.61–79.87) (3) 2.68 (0.10–75.1)
Casetta (1994) Italy	104	150	2.0	32.2	44	5	Mc	Pre	Age (>3 y), sex, residence	Trauma	NS[c]
Currier (1974) Ireland	60	60	1.4	26	53	3	A	Pre	Age, sex, social class, marital status	(1) Trauma (2) Burns	(1) 1.60 (0.78–3.31) (2) 3.50 (1.06–11.57)*
da Silva (2009) Brazil	81	81	2.10	–[b]	22	4	N	Pre	Age, sex, place of birth	Head trauma	1.36 (0.56–3.30)
de Gennaro (2009) Italy & Serbia	104	150	2.06	28	44	3	M	≤15 y, >15 y	Age, sex, residence	(1) Head trauma (2) Fractures (3) Spinal trauma	(1) ≤15 y: 1.89 (0.72–4.96), pre: 2.55 (1.40–4.64)* (2) Pre: 1.59 (0.96–2.64) (3) ≤15 y: 7.34 (0.35–154.51), pre: 1.52 (0.71–3.26)
Dokuchaeva (2006) Russia	178	178	2.80	–[b]	48	–[b]	–[b]	≤15 y, >15 y	Age, sex, ethnic origin	Trauma	NS[c]
Dolan (2003) USA	24	24	2.0	35.4	42	3	P	<20 y	Age, sex	Trauma	2.14 (0.63–7.33)
Fernandez (1990) Spain	43	41	1.69	28.3	45	3	P	Pre	Age, sex	(1) Head trauma (2) Spinal trauma (3) Fractures	(1) 1.95 (0.17–22.38) (2) 0.95 (0.06–15.75) (3) 0.95 (0.06–15.75)
Fraser & Lunny (2013) USA	493	493	1.45	39.7	42	5	N	Pre	Age, sex, age at onset	(1) Head trauma (2) Spinal trauma (3) Fractures	(1) 1.30 (0.84–2.00) (2) 1.75 (1.06–2.89)* (3) 1.25 (0.81–1.86)
Ghadirian (2001) Canada	197	202	2.17	–[b]	45	5	N	Pre	Age, sex	Head trauma	3.01 (1.06–8.53)*
Goncharova (2009) Russia	122	122	–[b]	–[b]	56	–[b]	–[b]	≤15 y, >15 y	–[b]	Head trauma	≤15 y: NS[c] >15 y: 2.13 (1.01–4.50)*
Gusev (1996) Russia	155	155	1.63	25.8	56	3	Mc	≤15 y, >15 y	Age, sex, residence, ethnicity	(1) Head trauma (2) Spinal trauma	(1) ≤15 y: 2.40 (1.10–5.25), * >15 y: NS[c] (2) ≤15 y: 1.51 (0.25–9.16), >15 y: 0.79 (0.21–3.02)
Helmick (1989) USA	22	22	3.4	29	25	6	P	Pre	Age, sex	Trauma	0.98 (0.34–2.85)
Hopkins (1991) USA	14	56	4.30	35.2	41	7	P	Pre	Age, sex, race	(1) Head trauma (2) Trauma	(1) NS[c] (2) NS[c]
Koch (1974) USA	7	7	2.50	29.3	46	4	N	Pre	None stated	Trauma	NS[c]
Koch-Henriksen (1989) Denmark	297	297	1.42	32	56	8	A	≤15 y, >15 y	Age, sex	Head trauma	≤15 y: 1.38 (0.72–2.64), >15 y: 1.30 (0.69–2.46)

Kurtzke (1997) Norway	23	127	1.55	30	62	5	Schum	Pre	Age, sex	(1) Head trauma	(1) 2.24 (0.72–6.98)
Lauer (1994) Germany	150	150	2.04	30.3	51	4	B	≤14 y	Age, sex, residence	Head trauma	NS[c]
Leibowitz (1973) Israel	70	70	–[b]	–[b]	31	–[b]	N	≤15 y, >15 y	–[b]	Trauma	≤15 y: 1.00 (0.51–1.96), >15 y: 2.04 (1.00–4.18)*
Martinez-Sobrepera (2001) Cuba	50	50	4.50	–[b]	21	5	P	Pre	Age, sex, ethnicity	(1) Head trauma (2) Burns	(1) 2.09 (0.36–11.95) (2) NS[c]
Materljan (1994) Croatia	36	72	1.8	24.4	45	6	P	≤18 y, pre	Age, sex, residence	(1) Trauma (2) Head trauma	(1) $p = 0.046$[d, *] (2) $p = 0.016$[d, *]
McAlpine (1952) England	250	250	1.86	29.6	51	3	N	Pre	Age, sex	Trauma	3.07 (1.58–5.94)*
Operskalski (1989) USA	145	145	2.45	30.1	47	9	N	Pre	Age, age at onset, sex, birthplace, residence, race	Fracture	0.91 (0.50–1.66)
Rudez (1998) Croatia	132	132	1.8	28	45	4	P	Pre	Age, sex, residence	(1) Head trauma (2) Trauma	(1) $p = 0.04$[d, *] (2) $p = 0.013$[d, *]
Sepcic (1993) Croatia	46	92	2.06	26.4	45	6	P	Pre	Age, sex, place birth, residence	Head trauma	Significant[d]
von Wilhelm (1970) Switzerland	36	36	–[b]	–[b]	51	4	N	≤20 y	Gender, age	Trauma (accidents and burns)	NS[c]
Westlund & Kurland (1952) Canada	112	123	1.43	30.3	49	5	N	Pre	Age, sex, age at onset	Head trauma	NS[c]
YosefiPour (2002) Iran	149	100	1.19	–[b]	32	4	N	Pre	Age, sex	Trauma	2.17 (1.06–4.43)*
Zaadstra (2008) Netherlands	2821	2550	2.30	–[b]	52	7	N	≤20 y	Age, sex, education, residence	Head trauma	1.24 (1.09–1.41)*
Zilber (1996) Israel	70	64	1.73	25.2	31	6	M	≤20 y, pre	1Age, sex	Trauma	NS[c]
Zorzon (2003) Italy	140	131	1.72	31.2	45	5	M	Pre	Age, sex	(1) Fractures (2) Head trauma	(1) 0.66 (0.38–1.16) (2) 0.96 (0.54–1.72)
Subtotal	6664	7521	2.0	28.8		4.8					

Cohort studies

Author (year) country (type)	Cohort size	F:M ratio (MS cases)	LAT	NOS score	MS Dx criterion	Mean follow up (y)	Adjustment	Exposure variable(s)	SIR[a] (95% CI)
Goldacre (2006) England (record linkage)	110,993	–[b]	51	8	Hospital admission for MS	16.7	Age, sex	Head trauma	1.12 (0.91–1.39)
Kang (2011) Taiwan (record linkage)	72,725	1.12	25	8	N	6	–[b]	Head trauma	1.48 (1.01–2.16)[e, *]
Pfleger (2009) Denmark (prospective/record linkage study)	150,868	0.56	56	7	A	22	Age, sex, year	Head trauma	0.94 (0.77–1.15)
Siva (1993) USA (record linkage)	819 (head trauma cases)	2.47	44	6	Workshop on the Diagnosis of MS	0.5	Residence	Head trauma	NS[c]
Subtotal	335,405	1.38		7.25					

A = Allison & Miller criteria, B = Bauer criteria, CI = confidence interval, Dx = diagnosis, F:M cases = ratio of female to male MS cases, K = Kurtkze criteria, LAT = latitude, LOC = loss of consciousness, Mc = McAlpine criteria, M = McDonald criteria, MS = multiple sclerosis, NOS = Newcastle–Ottawa Scale, N = neurologist diagnosed, NS = not significant, OR = odds ratio, P = Poser criteria, Pre: premorbid, age not specified other than surgery occurring before MS diagnosis, RR = rate ratio, Schum = Schumacher committee, Y = year(s).

* Indicates statistically significant results at $p < 0.05$.

[a] Standard incidence ratio (SIR) for risk of MS reported and/or inputted from study data using a random effects model.

[b] Data not reported/not available.

[c] Reported as "not statistically significant", no data provided.

[d] Reported as "statistically significant", no/or limited data provided.

[e] After adjusting for monthly income and geographic location.

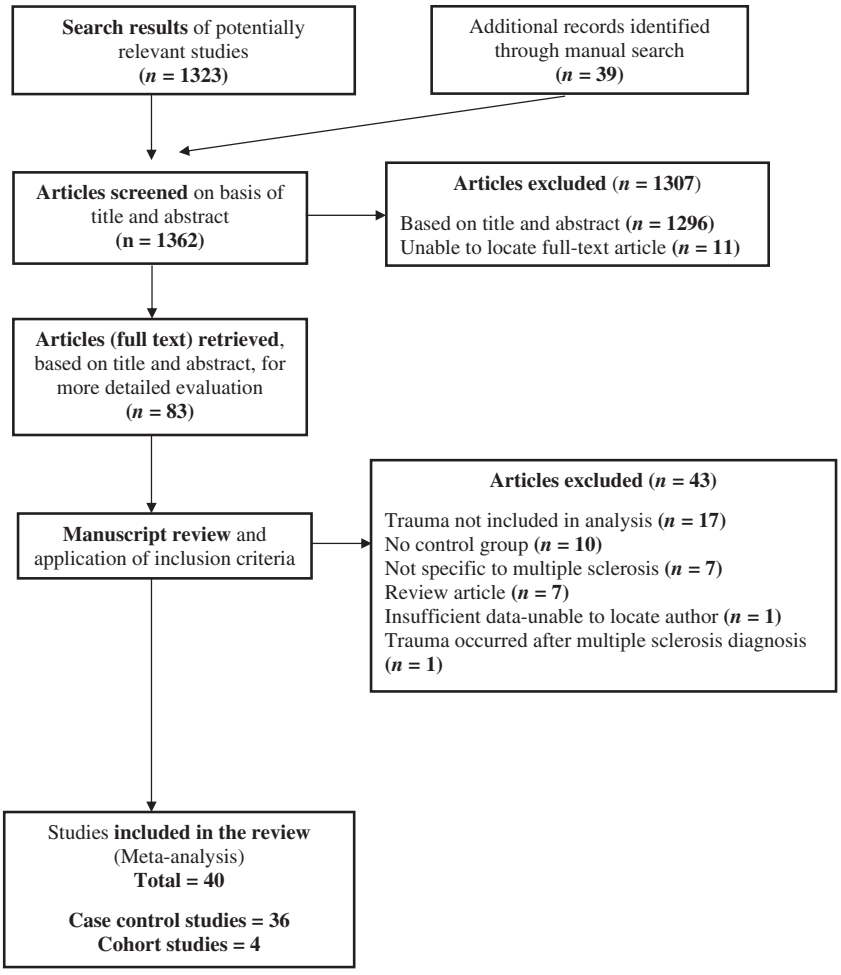

Fig. 1. Flow diagram of study selection.

pooled RE model revealed a homogeneous sample ($I^2 = 0\%$; $p = 0.43$) with no statistical difference between groups (OR = 1.12; 95% CI, 0.88–1.43; $p = 0.37$). Sensitivity analysis, based on removing those studies [64,71,72,83,89] with an NOS score of <6, significantly increased the magnitude of the effect size but not the precision of the result (OR = 2.31; 95% CI, 1.06–5.04; $p = 0.04$). Further sensitivity analysis,

Table 2
Rate ratios for pooled trauma exposures using a random effects model.

Exposure	All studies						Studies with NOS score ≥6		
	Incl. studies (n)	MS cases (n)	Controls (n)	Pooled OR (95% CI)	Level of heterogeneity I^2 (χ^2 p)	Test for overall effect Z (p)	Pooled OR (95% CI)	Level of heterogeneity I^2 (χ^2 p)	Test for overall effect Z (p)
Case–control studies									
Head trauma									
≤ Age 20 y	8	3695	3504	1.26 (1.12–1.42)*	0% (0.43)	3.89 (<0.001)	1.27 (1.12–1.44)*	0% (0.52)	3.66 (<0.001)
Premorbid	21	2524	2940	1.65 (1.39–1.95)*	9% (0.34)	5.77 (<0.001)	1.63 (1.10–2.42)*	0% (0.76)	2.45 (0.01)
Other traumas									
≤ Age 20 y	7	595	1352	1.12 (0.88–1.43)	0% (0.43)	0.91 (0.37)	2.31 (1.06–5.04)*	0% (0.35)	2.10 (0.04)
Premorbid	16	1475	2387	1.58 (1.28–1.94)*	16% (0.27)	4.34 (<0.001)	0.89 (0.53–1.51)	0% (0.53)	0.24 (0.67)
Spinal injury									
≤ Age 20 y	2	259	305	2.28 (0.48–0.74)	0% (0.38)	1.04 (0.30)	N/A[a]	N/A[a]	N/A[a]
Premorbid	5	877	921	1.51 (1.06–.14)*	0% (0.89)	2.30 (0.02)	N/A[a]	N/A[a]	N/A[a]
Fractures									
Premorbid	7	3747	3573	1.09 (0.95–1.24)	0% (0.43)	1.26 (0.21)	N/A[a]	N/A[a]	N/A[a]
Burns									
Premorbid	3	120	118	1.66 (0.49–5.55)	45% (0.16)	0.82 (0.41)	N/A[a]	N/A[a]	N/A[a]
Cohort studies									

Exposure	Included studies (n)	Pooled SIR (95% CI)	Level of heterogeneity I^2 (χ^2 p)	Test for overall effect Z (p)
Head trauma	4	1.07 (0.92–1.24)	39% (0.18)	0.85 (0.40)

CI = confidence interval, MS = multiple sclerosis, OR = odds ratio, Y = years.
* Indicates statistically significant results at $p < 0.05$.
[a] Studies had an NOS score of under 6; therefore analysis was not warranted.

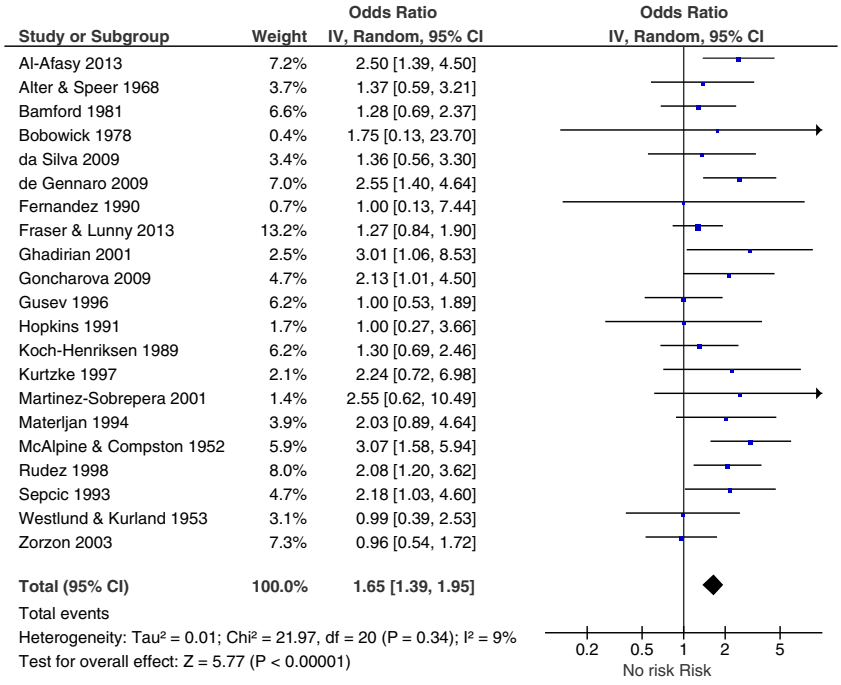

Fig. 2. Forest plot of 21 included studies reporting premorbid head trauma (occurring before the diagnosis of multiple sclerosis) in multiple sclerosis cases and controls. *Horizontal lines*, 95% CIs of each study; *squares*, odds ratios of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the pooled summary estimate; *solid vertical line*, null value. OR > 1 favoured the control group.

excluding those studies [64,71,83,85,89] that did not report a specific OR, also significantly increased the effect size but not the significance of the results (OR = 2.73; 95% CI, 0.91–8.17; $p = 0.07$). Due to so few studies included in both sensitivity analyses and the impreciseness of the results (wide CIs) in addition to the fact that the initial RE model was statistically homogeneous ($I^2 = 0\%$; $p = 0.42$), we choose to maintain all seven studies in the final analysis.

Of the 16 studies reporting on "other trauma" premorbid [18,64–69,71,77–79,81,83,87,90,92], there were 1475 MS cases and 2387 controls. The pooled RE results revealed a homogeneous sample ($I^2 = 16\%$; $p = 0.27$) and statistically significant differences between MS cases and controls (OR = 1.58; 95% CI, 1.28–1.94; $p < 0.001$). After removing those studies with an NOS score of <6, four homogeneous studies [67,77,78,92] remained and the results changed (OR = 0.89; 95% CI, 0.53–1.51; $p = 0.67$). Sensitivity analysis based on removing those studies [68,71,78,79,83,87,92] where the OR had to be imputed did not increase the magnitude of the effect or the precision of the result (OR = 1.84; 95% CI, 1.45–2.32; $p < 0.001$). As the initial pooled results including all 16 studies revealed a homogeneous sample, and the sensitivity analyses were less precise, all 16 studies were included in the final analysis.

3.3.3. Spinal injury

Five discrete studies examined "spinal injury"; two examined spinal injury occurring in those ≤20 [70,76] (259 cases and 305 controls) and five examined premorbid spinal injury [65,70,73,76,94] (877 cases and 921 controls). Pooled results for the ≤20 subgroup revealed a non-significant and imprecise result, whereas the spinal trauma premorbid subgroup revealed significant results. Specifically, for the group ≤20 years the OR was 2.28 (95% CI, 0.48–10.74; $p = 0.30$; $I^2 = 0\%$, I^2 $p = 0.38$) and the OR for the premorbid group was 1.51 (95% CI, 1.06–2.14; $p = 0.02$; $I^2 = 0\%$, I^2 $p = 0.89$). Sensitivity analysis for the premorbid group based on removing the one study [65] not reporting the exact OR, did not change the results (OR = 1.51; 95% CI, 1.03–2.22; $p < 0.03$). Sensitivity analysis based on study quality could not be done as all five studies had NOS scores <6; therefore, they were included in the final analysis.

3.3.4. Fractures and burns

The seven studies examining premorbid fractures [65,70,73,86,91,93,96] included 3747 MS cases and 3573 controls. The pooled results presented a homogeneous sample ($I^2 = 0\%$; $p = 0.43$) with no statistical differences between groups (OR = 1.09; 95% CI, 0.95–1.24; $p = 0.21$). All but one study [86] had an NOS score of <6 therefore sensitivity analysis based on study quality, could not be done. Further sensitivity analysis, excluding the one study [65] where a specific OR was not reported, did not improve heterogeneity ($I^2 = 15\%$; $p = 0.32$) nor significantly change the results (OR = 1.09; 95% CI, 0.91–1.30; $p = 0.36$).

The three studies reporting on premorbid burns [67,69,84] included a total of 120 MS cases and 118 controls. Premorbid pooled results revealed a statistically homogeneous sample ($I^2 = 45\%$; $p = 0.16$) and non-significant and imprecise results (OR = 1.66; 95% CI, 0.49–5.55; $p = 0.41$). As only one study [67] had an NOS score ≥6 sensitivity analyses based on study quality was not done. When we removed the one study [84] where the OR was imputed, the results became more homogeneous ($I^2 = 0\%$; $p = 0.88$) and significantly changed (OR = 3.40; 95% CI, 1.10–10.46; $p = 0.03$). As the p-value was of borderline significance, and the CI was very wide (imprecise) we choose to maintain the full more conservative initial model for the final analysis.

3.4. Exposure results: cohort studies

The meta-analysis of four cohort studies, examining premorbid head trauma [4–7], indicated moderate heterogeneity ($I^2 = 39\%$; $p = 0.18$) of the pooled RE model, with no statistical relationship between head trauma and MS diagnosis (OR = 1.07; 95% CI, 0.92–1.24; $p = 0.40$). Sensitivity analysis based on study quality was not warranted as all four studies had NOS scores ≥6; however, we did group the studies according to design. The one prospective/record linkage cohort study produced an insignificant result (OR 0.94, 95% CI 0.77–1.15, $p = 0.32$), whereas the three record-linkage studies when pooled produced moderate heterogeneity ($I^2 = 40\%$; $p = 0.19$), and a stronger yet still insignificant effect size (pooled OR 1.12, 95% CI 0.94–1.35, $p = 0.21$). We also conducted sensitivity analysis based on removing the one study

where the OR was imputed [6], but this did not improve homogeneity ($I^2 = 56\%$; $p = 0.10$) nor did it change the significance of the result (OR = 1.10; 95% CI, 0.89–1.38; $p = 0.34$). For that reason, we included all four studies in the final analysis. See Table 2 for pooled trauma exposure results.

3.5. Examining bias

To visually assess for heterogeneity, we plotted the ORs of high quality (NOS ≥6) versus low quality studies (NOS <6). The plot showed no distinct linear relationship between methodological quality of studies (NOS score) and ORs, with no obvious clustering, indicating a low risk of bias.

When funnel plots were examined for the case–control studies on the outcomes of premorbid head trauma and premorbid "other trauma", the plots looked symmetrical indicating a low risk of publication bias [97]. We further tested these two outcomes with the Peters test [16], which resulted in non-significant publication bias results ($p = 0.72$ and $p = 0.66$ respectively). There was also no evidence of publication bias with regard to premorbid head trauma and onset MS risk in cohort studies, as the Peters test was not statistically significant ($p = 0.97$). Given the small number of studies included in the other exposure subgroups (<10 studies), the interpretation of funnel plots must be undertaken with caution and are therefore not included here.

3.5.1. Meta-regression

Meta-regression was performed on the subgroups including at least 10 case–control studies, namely premorbid head trauma and premorbid "other trauma". Population-level continuous variables (geographic latitude, female-to-male MS case ratio, mean age of MS onset) and study-level dichotomous variables (language [English vs. non-English], publication type [published vs. unpublished], number of covariates adjusted for [≤2 vs. >2], total sample size [≤100 vs. >100], and sample size of MS cases [≤100 vs. >100]) for both trauma exposures did not significantly influence the effect sizes. However, significant heterogeneity was noted for both the continuous and categorical variables of the NOS score in the other trauma premorbid subgroup. That is, the risk for MS diagnosis decreased as the NOS score increased in those with premorbid other trauma. Results of the univariate meta-regression are presented in Table 3.

4. Discussion

In our systematic review and meta-analysis of 36 case–control studies involving 5922 MS cases and 6667 controls, we found a significant association between childhood and premorbid head trauma, other trauma premorbid, and spinal trauma premorbid and the subsequent risk for being diagnosed with MS. However, when the results were stratified by high quality (NOS ≥6), only head trauma during childhood and premorbid, other trauma childhood remained statistically significant. Furthermore, significant heterogeneity between high and lower quality study design was noted in meta-regression for premorbid other trauma; therefore, even the effect size of the higher quality studies should be interpreted with caution. The findings of the meta-analysis of case–control studies did not support an association between the other types of physical trauma studied, namely spinal injuries under 20 years of age, fractures, or burns occurring at any age and the subsequent risk for the diagnosis of MS.

In the meta-analysis of cohort studies, pooled results did not support a statistical association between head trauma and the later diagnosis of MS. Only the study of Kang et al. (2011) differed from the other three cohorts in showing an increased risk of MS after head trauma; however the difference could be attributed to the different phenotypes of MS in Asians, perhaps with a different susceptibility to head trauma.

Table 3
Sensitivity analyses and stratified meta-regression for assessing heterogeneity among case–control studies looking at the exposures premorbid head trauma and other trauma.[a]

Exposure variables	Head trauma — premorbid					Other trauma — premorbid				
	Studies		Sub-group	Meta-regression		Studies		Sub-group	Meta-regression	
	n	Total (*n*)	OR (95% CI)[b]	*p*	β (95% CI)[c]	*n*	Total (*n*)	OR (95% CI)[b]	*p*	β (95% CI)[c]
Population-level characteristics										
Latitude (geographic)	21	5464	1.65 (1.39–1.95)*	0.78	0.99 (0.97–1.02)	16	3862	1.58 (1.28–1.94)*	0.54	1.01 (0.98–1.03)
Female:male ratio (MS cases)	17	4930	1.68 (1.37–2.06)*	0.46	1.14 (0.78–1.68)	13	3540	1.51 (1.19–1.91)*	0.09	0.75 (0.54–1.05)
Mean age at MS onset	14	3984	1.58 (1.26–1.97)*	0.24	0.97 (0.91–1.02)	11	1748	1.47 (1.07–2.01)*	0.96	1.00 (0.85–1.17)
Study-level characteristics										
NOS score	20	5222	1.63 (1.36–1.94)*	0.54	0.95 (0.81–1.12)	14	3366	1.62 (1.30–2.02)*	0.03	0.78 (0.63–0.97)*
NOS score (<6 vs. ≥6)	20	5222	1.63 (1.36–1.94)*	0.91	0.97 (0.56–1.66)	14	3866	1.62 (1.30–2.02)*	0.03	0.49 (0.26–0.93)*
Language (English vs. non-English)	21	5464	1.65 (1.39–1.95)*	0.24	0.74 (0.44–1.24)	16	3862	1.58 (1.28–1.94)*	0.42	0.73 (0.32–1.66)
Pub type (published vs. unpublished)	21	5464	1.65 (1.39–1.95)*	0.51	0.76 (0.32–1.79)	16	3862	1.58 (1.28–1.94)		N/A[d]
Number of covariates[e] (≤2 vs. >2)	21	5464	1.65 (1.39–1.95)*	0.94	0.98 (0.63–1.53)	16	3862	1.58 (1.28–1.94)*	0.54	0.86 (0.52–1.42)
Sample size (≤100 vs. >100)	21	5464	1.65 (1.39–1.95)*	0.87	1.09 (0.37–3.22)	16	3862	1.58 (1.28–1.94)*	0.42	1.40 (0.58–3.37)
MS cases (≤100 vs. >100)	21	5464	1.65 (1.39–1.95)*	0.86	1.04 (0.65–1.66)	16	3862	1.58 (1.28–1.94)*	0.27	1.28 (0.80–2.04)

CI = confidence interval, MS = multiple sclerosis, NOS = Newcastle–Ottawa Scale, OR = odds ratio, Pub = publication, SE = standard error.

[a] All analyses weighted by sample size.

[b] OR (95% CI) were calculated using the random effects model in RevMan.

[c] β (95% CI) were calculated using the study level log OR and the SE of the estimate (calculated in RevMan) by univariate random effects meta-regression in STATA 12 using the *megareg* command.

[d] All studies were published — analysis not warranted.

[e] Number of potentially confounding variables adjusted for in individual studies.

* Indicates statistically significant results at $p < 0.05$.

The meta-analysis conducted recently by Warren et al. [9] found insignificant results in a general adult trauma exposure including 16 studies (13 case–control and three cohort studies). Their results must be viewed with caution as their classification of trauma was not as rigorous, as they included half the studies in our review, and they included children and adults in the same general category (specifically, the studies by Gusev [76], von Wilhelm [89], and Zorzon [93]). Furthermore, they grouped case–control studies examining head trauma [62,75,79,95] with case–control studies examining a more general trauma category as the exposure variable [17,64–66,68,73,88].

4.1. Quality of the evidence

When study participants self-reported an episode of head trauma, an increase in the risk of MS was observed, which did not persist after stratification by study design. The association between premorbid head trauma and MS diagnosis was weakest for the one prospective/record linkage cohort study (OR 0.94, 95% CI 0.77–1.15, $p = 0.32$), weak for the record-linkage studies (pooled OR 1.12, 95% CI 0.94–1.35, $p = 0.21$), strong for case–control studies with an NOS score of 6 or over (OR = 1.40; 95% CI, 1.08–1.81; $p = 0.01$), and strongest for all case–control studies (pooled OR 1.65, 95% CI 1.39–1.95, $p < 0.001$). Therefore, the strength of the association varies inversely with the strength of the study design. This may also suggest that event (trauma) recall bias and clinical heterogeneity (in the selection of study participants) may have produced a false or inflated association in the case–control comparisons.

It is unlikely though, that our results are prone to publication bias as the Peters test was not significant and significant relationships persisted during sensitivity analysis. However, since the sensitivity analyses for the cohort studies showed significant clinical and moderate statistical heterogeneity, investigation into the question of whether head trauma, other traumas, and spinal trauma indeed pose a risk for the diagnosis of MS should continue. We would therefore propose several recommendations for researchers who would take up the challenge.

The lack of a consistent and standardized definition of trauma was one of the main challenges of this review. All 40 studies included in the meta-analysis either did not explain how they defined trauma, or they defined trauma differently, which we consider a limitation in pooling of the results and may have introduced significant bias. In the future, if studies examine the effect of trauma on the risk for MS diagnosis, we suggest using validated severity grading tools for outcomes such as the traumatic brain injury scale [98]. Further, in case–control studies using self-report, medically validating the traumatic events would be ideal, and if this is not possible, having a parent or older sibling validate the event may minimize recall bias. In a meta-epidemiology study, Savovic et al. [99] found that average bias and increases in heterogeneity were driven primarily by trials with subjective outcomes, with little evidence of bias in trials with objective outcomes. When health records validate a patients' self-report, the subjective outcome event turns into an outcome which is objectively measured but potentially influenced by clinician or patient judgment (for example, hospitalizations) [99].

Despite the variety of outcomes reported in the studies, none reported on the effects of whiplash or cervical cord demyelination, which are both frequent events. Furthermore, none of the studies examined in this review considered the frequency of traumatic injuries sustained by each participant, which could be seen as a marker of severity and could then have been used to stratify results further.

4.2. Potential bias in the review process

The two review authors who assessed the methodological quality were not blinded for authors, journal, or institution. The potential bias caused by the non-blinded quality assessment was expected to be low as neither review author had a conflict of interest. Specifically, the review authors did not have any (financial or other) interest in positive or negative results. Furthermore, we searched the gray literature extensively for eligible studies, presented the search strategy and the inclusion criteria list, and all of the final results of the assessment, so that readers can make their own determinations of the results and our conclusions.

There is a possibility of publication bias or study selection bias in this meta-analysis, as was the case with the Warren meta-analysis that reported no publication bias, when this was clearly not the case. For example, by missing unpublished negative studies we may be over-estimating the association between prior trauma and the risk for developing MS. However, a comprehensive search of the published literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. This was followed by attempts to contact corresponding and first authors, as we recognize that unpublished or negative studies may exist.

From the results of our search, we suspect that there was selective reporting of some outcomes in epidemiology studies, depending on the nature and direction of the results. Epidemiology studies use differing outcomes in study questionnaires, and may only choose to report on some of them. We attempted to contact authors of epidemiological case–control studies to ask if they had examined trauma as an outcome, even though it was not reported; however given that most studies were published many years ago it would have taken a tremendous effort to contact all authors to ask them if they had included any trauma outcome which they had not reported on.

4.3. Theoretical possibility

Theories linking physical trauma to the onset or exacerbation of MS date back as far as the time of Charcot who defined MS in the mid 1860s [2]. Despite the accounts of several researchers, primarily documenting their observations in either anecdotal or case series reports, a proposed biological model linking physical trauma and MS has yet to be conclusively established [8]. Some scientists hypothesize that physical trauma, particularly involving the spinal cord and/or the brain may cause a disruption in the blood–brain barrier, which in turn could lead to the development of MS plaques in those who are already genetically at risk [3]. More specifically, when the blood–brain barrier is disturbed autoreactive immune cells are permitted to pass from the blood stream into the central nervous system where they contribute or activate MS lesions or plaques in those who are already at risk for developing the disease. Hence significant injury or trauma to the head, neck or spine may activate an underlying and possibly inherited defect in the small blood vessels of the brain [3]. Compston goes even further and regards penetration of the blood–brain barrier as a necessary initial primary process in the pathogenesis of MS [100]. Yet others note the high frequency of blood–brain barrier breakdown in MS patients *without* preceding trauma and the fact that many experience trauma and *do not* develop MS thus concluding a purely coincidental, rather than a causal association [101].

While anecdotal reports and case series have provided important medical insights into the science of medicine in general, we agree that conclusions of such inquiry are most useful in providing etiological clues and ought to be supported by more rigorous evidence. However, given the long latency period of MS and the unexpected nature of physical trauma, it is clearly a condition that cannot be studied using prospective randomized methods in a controlled setting. As a result, retrospective cohort studies, where a trauma cohort is defined in the past and followed forward to assess the outcome of MS, are the only feasible means of studying this condition further.

5. Conclusion

In the meta-analysis of the four cohort studies, pooled results did not support a statistical association between head trauma and the later diagnosis of MS. The result of the meta-analyses of high quality

case–control studies however, suggests a statistically significant association between premorbid head trauma and the risk for developing MS. More specifically, those with premorbid head trauma were significantly more likely to be diagnosed with MS in comparison to those controls of similar age and sex who had not sustained head trauma. Despite this significant finding, this in no way suggests or demonstrates causality, in that epidemiological studies can only provide etiological clues at best. More rigorous prospective studies, with high statistical power, are needed to convincingly establish an association between trauma and MS. Future prospective studies that take into consideration (a) the long latency period between the age of putative biological onset and clinical onset of MS, (b) define trauma based on validated instruments, (c) include frequency of traumas per study participant, and (d) include information on the site of trauma and MRI of the lesion are needed in order to definitively rule out any causal links between physical trauma and MS.

Conflict of interest

The authors have no financial, personal, or any other kind of competing interests with this paper.

Author contributions

Study concept and design: C Lunny, JA Knopp-Sihota, and S Fraser; acquisition and preparation of data: C Lunny; analysis and interpretation of the data: C Lunny, JA Knopp-Sihota, and S Fraser; risk of bias assessment: C Lunny and JA Knopp-Sihota; first draft of the manuscript: C Lunny. All authors critically reviewed the manuscript and approved the final version of the manuscript to be published.

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