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Original Article

The association between multiple sclerosis and fracture risk

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Abstract: Sever studies were performed to assess the association between multiple sclerosis (MS) and fracture risk. However, the results were inconsistent and inconclusive. In the present study, the possible association was investigated by a meta-analysis. Eligible articles were identified for the period up to August 2014. Pooled risk ratios (RR) with 95% confidence intervals (CI) were appropriately derived from random-effects models. Nine studies with more than 9,000,000 subjects were eligible. We found that MS was significant associated with fracture risk in overall population (OR = 1.58, 95% CI 1.36-1.84, $P < 0.01$). In terms of subgroup analyses by fracture sites, the associations were significant in femur (RR = 4.57, 95% CI 3.01-6.69, $P < 0.01$), hip (RR = 3.01, 95% CI 2.72-3.41, $P < 0.01$), tibia (RR = 2.72, 95% CI 2.22-3.32, $P < 0.01$), humerus (RR = 1.78, 95% CI 1.12-2.40, $P = 0.02$), pelvis (RR = 1.34, 95% CI 1.12-1.67, $P < 0.01$), and vertebrae (RR = 1.30, 95% CI 1.13-1.69, $P < 0.01$). This meta-analysis suggested that MS may be associated with fracture development.

Keywords: Multiple sclerosis, fracture, meta-analysis

Introduction

Multiple sclerosis (MS) is a neuroinflammatory disease which can affect all functions of the central nervous system. MS is the most common cause of non-traumatic disability among young and middle-aged adults in the western hemisphere, and as such, leads to high rates of disability and societal costs [1]. Various sociodemographic factors are associated with a higher risk for MS, such as female sex [2], place of residence during childhood [3], and low educational level [4].

Fractures represent a serious health risk in the elderly, with a significant associated morbidity and mortality. Approximately 13.5% of those who suffer a hip fracture die within 6 months and 24% within 1 year of the episode [5]. The identifiable risk factors for fracture are advanced age, female sex, osteoporosis, low vitamin D levels and calcium intake, and prior history of fractures [6]. Several studies found MS to be a risk factor in fracture, but other studies showed no association between MS and risk of fracture. These studies revealed an inconsistent conclusion [7-15]. Therefore, we conducted a meta-analysis to assess the association between MS and fracture risk.

Methods

Publication search

A computerized literature search was performed to identify the relevant studies from five electronic databases including PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals, and China Biology Medical literature database (CBM). The search terms were used as follows: (multiple sclerosis) and (fractures or fracture). All searched studies were retrieved and the bibliographies were checked for other relevant publications.

Inclusion and exclusion criteria

The following criteria were used for the literature selection: first, studies should concern the association of MS and fracture risk; second, studies must be observational studies (case-control or cohort); third, studies must offer the size of the sample, risk ratios (RRs) and their 95% confidence intervals (CIs). Studies were

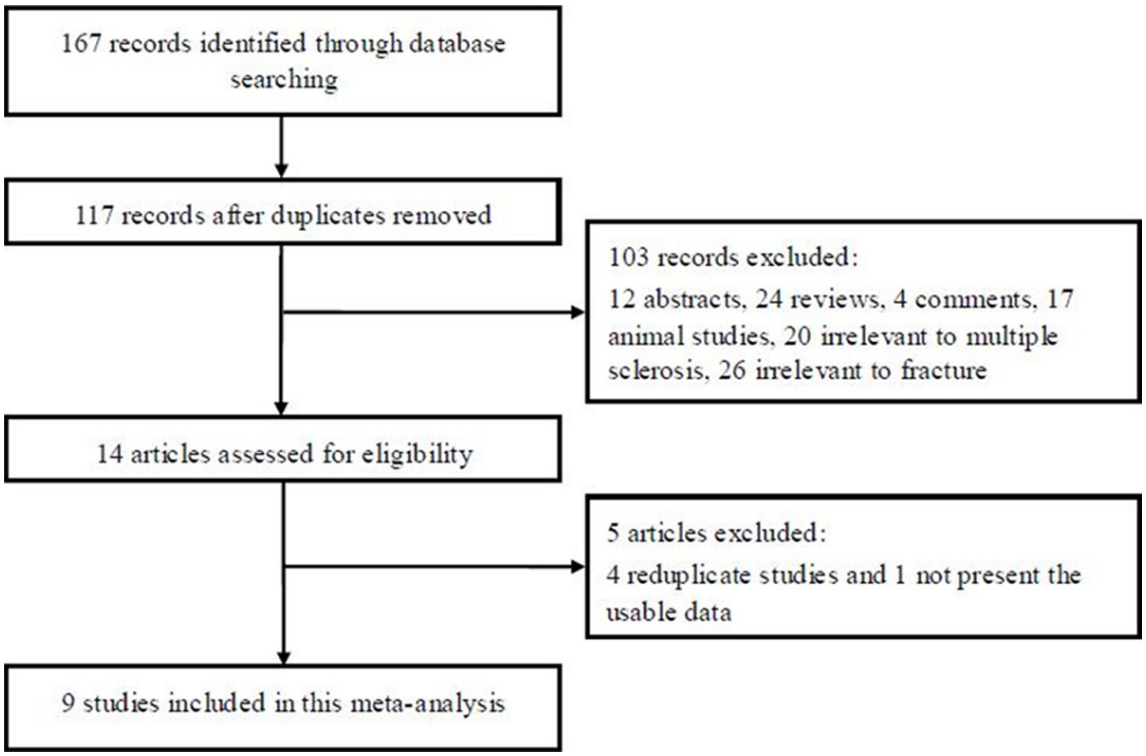

Figure 1. The flow diagram of search process.

excluded if one of the following existed: first, studies were not relevant to MS or fracture; second, no useful data were not reported; third, reviews and abstracts. As for the studies from the same institution, only the one with the largest sample size was included. No language restrictions were imposed.

Data extraction

Data were extracted by two authors independently. If encountered the conflicting evaluations, an agreement was reached following a discussion; if could not reached agreement, another author was consulted to resolve the debate. The following information was extracted from each study: first author, year of publication, ethnicity, age, gender, sample size.

Methodological quality assessment

Two authors assessed the study quality. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality [16].

Statistical analysis

We estimated the RR with 95% CI for fracture. A random effects model (the DerSimonian and Laird method) was used. Statistical heterogeneity among studies was evaluated using the Q and I^2 statistics. Subgroup analyses by site of fracture were performed. The publication bias was assessed using the Egger's linear regression test [17]. All statistical analyses were performed with the STATA software (version 12.0, Stata Corporation, College Station, Texas).

Results

Characteristics of studies

A flowchart of the process of study selection is shown in **Figure 1**. Based on the inclusion and exclusion criteria, a total of 9 articles were included in the meta-analysis after full-text review [7-15]. The main characteristics of included studies are presented in **Table 1**. All of the studies were conducted in Caucasians. Two studies used female subjects. The quality scores of the studies were more than 7, suggesting that the quality of the included studies was high.

Meta-analysis results

The results of this meta-analysis are shown in **Table 2**. We found that MS was significant asso-

Table 1. Characteristics of the studies

First author	Year	Race	Mean age	Gender	No. of participants	Quality score
Bazelier 1	2011	Caucasian	44.8	Mixed	38925	8
Moen	2011	Caucasian	37.1	Mixed	231	7
Bazelier 2	2012	Caucasian	43.6	Mixed	15056	7
Bazelier 3	2012	Caucasian	46.4	Mixed	68430	8
Bazelier 4	2012	Caucasian	36.9	Mixed	18399	8
Dennison	2012	Caucasian	NR	Female	52960	7
Ramagopalan	2012	Caucasian	NR	Mixed	7908570	9
Bhattacharya	2014	Caucasian	65	Mixed	1066404	9
Gregson	2014	Caucasian	≥ 55	Female	60393	7

NA, not reported.

Table 2. Results of meta-analysis and subgroup analysis

	RR (95% CI)	*P* Value	I^2 (%)
Overall	1.58 (1.36-1.84)	< 0.01	98
Femur	4.57 (3.01-6.69)	< 0.01	70
Hip	3.01 (2.72-3.41)	< 0.01	0
Tibia	2.72 (2.22-3.32)	< 0.01	55
Humerus	1.78 (1.12-2.40)	0.02	52
Pelvis	1.34 (1.12-1.67)	< 0.01	0
Vertebrae	1.33 (1.12-1.59)	< 0.01	0
Ribs	1.10 (0.71-1.58)	0.48	31
Radius/ulna	0.78 (0.56-1.03)	0.13	0

ciated with fracture risk in overall population (OR = 1.58, 95% CI 1.36-1.84, $P < 0.01$, **Figure 2**). In terms of subgroup analyses by fracture sites, the associations were significant in femur (RR = 4.57, 95% CI 3.01-6.69, $P < 0.01$), hip (RR = 3.01, 95% CI 2.72-3.41, $P < 0.01$), tibia (RR = 2.72, 95% CI 2.22-3.32, $P < 0.01$), humerus (RR = 1.78, 95% CI 1.12-2.40, $P = 0.02$), pelvis (RR = 1.34, 95% CI 1.12-1.67, $P < 0.01$), and vertebrae (RR = 1.30, 95% CI 1.13-1.69, $P < 0.01$).

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed effect model and random effect model) to evaluate the stability of the meta-analysis. All the results were not materially altered (data not shown). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible. There was no publication bias ($P = 0.24$).

Discussion

Although many studies analyzing the research results about MS and fracture risk, definite conclusions cannot be drawn. Therefore, we did this meta-analysis to estimate the relationship between MS and fracture risk. To our knowledge, this is the first meta-analysis regarding MS and fracture risk. The meta-analysis involved nine articles. The results from this meta-analysis showed that MS was significantly associated with increased fracture risk. When we performed the subgroup analysis by site of fracture, significant association with susceptibility for the development of fracture was found in femur, hip, tibia, humerus, pelvis, and vertebrae.

There might be some reasons could be explained why MS patients had an increased fracture risk. MS is associated with an increased risk of osteoporosis and reduced bone mass, which when combined with the functional impairments of the disease, augments the possibility of fractures [18]. The development of osteoporosis in MS patients can be related to the cumulative effects of various factors. Physical inactivity and reduced mechanical load on the bones (offsetting gravity) is likely the major contributing factor for osteoporosis in MS [19]. Other possible factors leading to reduced bone mass are low vitamin D levels, use of medications such as glucocorticoids and anticonvulsants, and the role of the inflammatory processes of the disease [20].

Our meta-analysis has several strengths. First, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, Egger's linear regression tests were used to assess publication bias. Third, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis.

This meta-analysis also had several limitations. First, there was only 9 studies investigated the association of MS and fracture risk. Therefore, more studies with large sample sizes are needed to further identify the association. Second,

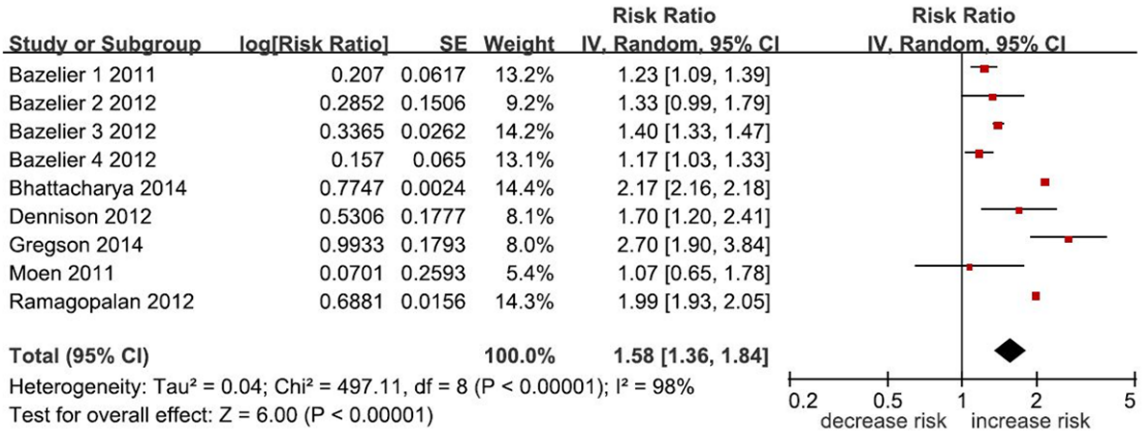

Figure 2. Meta-analysis between MS and fracture risk.

because small negative studies are less likely to published, the possibility of publication bias cannot be ruled out completely, even though the Egger's test did not provide the evidence of publication bias in this meta-analysis. Third, we did not evaluate the impact of lifetime corticosteroid use, nor examine specific doses of vitamin D.

In conclusion, this meta-analysis showed MS conferred significantly increased fracture risk. This result should be validated in the future studies.

Disclosure of conflict of interest

None.

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