Systematic Review and Meta-Analysis

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Factors associated with relapses in relapsing-remitting multiple sclerosis

A systematic review and meta-analysis

Yao Xie, PhD[a,b], Ziyu Tian, PhD[b,c], Fang Han, PhD[d], Shibing Liang, MD[c,e], Ying Gao, PhD[b], Dahua Wu, PhD[a,*]

Abstract

Background: The relapse is character of relapsing-remitting multiple sclerosis. The therapeutic goal is to reduce the risk of relapse. Factors associated with relapses can help to manage and prevent relapses. In addition, patients and doctors all pay attention to it. However, there are differences between studies. Our aim is to summarize factors associated with relapses in relapsing-remitting multiple sclerosis (RRMS).

Methods: PubMed, EMBASE, Web of science, Cochrane library, CNKI, Wanfang, SinoMed, and VIP were searched to identify risk factors about relapses in RRMS, which should be in cohort or case-control studies. This article was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The quality of studies was evaluated by the Newcastle-Ottawa Scale (NOS). Meta-analysis, subgroup and sensitivity analyses, and publication bias were all performed with Stata. This research has been registered on the international prospective register of systematic reviews (PROSPERO, CRD42019120502).

Results: 43 articles were included. Infection, postpartum period, risk gene, stress, and vitamin D were risk factors for relapses in RRMS. Pregnancy period was the protective factor. Among those, infection increased the risk of relapses in infection period (relative risk [RR], 2.07 [confidence interval (CI), 1.64 to 2.60]). Women in the postpartum period increased the risk of relapses compared with women before pregnancy (RR, 1.43 [CI, 1.19 to 1.72]), or women in pregnancy period (RR, 2.07 [CI, 1.49 to 2.88]). Women in the pregnancy period decreased the risk of relapses (RR, 0.56 [CI, 0.37 to 0.84]) compared with women before pregnancy. However, fewer studies, heterogeneity, and sample size were the limitations.

Conclusion: It is reliable to adopt results about infection, pregnancy period, and postpartum period.

Abbreviations: 95% CI = 95% confidence interval, CNKI = Chinese National Knowledge Infrastructure Databases, CNS = central nervous system, EDSS = the Kurtzke Expanded Disability Status Scale, HHV-6 =Human Herpes Virus-6, MS = multiple sclerosis, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = risk ratio, RRMS = relapsing-remitting multiple sclerosis, VIP = Chongqing Chinese Science and Technology Periodical Database.

Keywords: factor, multiple sclerosis, relapse, risk, systematic review

1. Introduction

Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system (CNS).[1] Approximately 85% of patients have a relapsing-remitting course from onset. Although a large expansion treatment options for MS have occurred in recent 20 years,[2] there is no curative treatment available, and the aim of current therapeutic strategy is to reduce

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This study fulfils compliance with ethical standards.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Neurology, Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine, Changsha, [b] Department of Neurology, Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine, [c] Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, [d] Office of Academic Research, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, Beijing, [e] College of Basic Medical Sciences, Shanxi University of Traditional Chinese Medicine, Taiyuan, China.

[*] Correspondence: Dahua Wu, Department of Neurology, Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine, Changsha 410006, China (e-mail: 547292206@qq.com).

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the risk of relapse.[3] It is of great significance to pathogenesis and prevention of MS by studying the factor associated with relapses. Such as risk factors in Framingham research, which changed clinical practice and evidence-based guidelines in cardiovascular disease.[4] Although many factors associated with relapses in MS have been reported, the results vary substantially between studies, and few systematic reviews consider more than 1 risk factor at a time.[5]

The aim of this article is to summarize factors associated with relapses in relapsing-remitting multiple sclerosis (RRMS), which were reported in observational studies, and examine the effect of these factors on relative risk of relapses in adult RRMS patients. Finally, it will help to manage and prevent relapses more effectively.

2. Materials and methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[6] As recommended by the PRISMA guidelines, this systematic review and meta-analysis was registered on the international prospective register of systematic reviews (PROSPERO, CRD42019120502).

2.1. Literature search

The following databases were systematically screened for literature: PubMed, EMBASE, Web of Science, Cochrane library, Chinese National Knowledge Infrastructure Databases (CNKI), Wanfang, SinoMed, and Chongqing Chinese Science and Technology Periodical Database (VIP), from January 1, 1983, to December 1, 2018. The search strategy used the terms "multiple sclerosis" or "MS" or "RRMS" or "relapsing multiple sclerosis", and "relapse" or "attack" or "recurrence" in combination with "risk" or "risk factor" or "factor" or "effect" or "influence" or "impact" or "prediction" or "predictor" or "predisposition".

2.2. Inclusion and exclusion criteria

This article included cohort and case-control studies that selected RRMS patients aged over 18 years, and their diagnosis met the Poster[7] or McDonald criteria.[8–10] This article also included studies, sufficient data in which were available to provide risk estimate (odds ratio [OR] or relative risk [RR] or hazards ratio [HR]), or construct 2×2 tables. Factors in literatures were clearly defined. Exclusion criteria were: patients with progressive multiple sclerosis in studies, or factors in studies which were drugs or treatment, or the literature is a review.

2.3. Study selection

One researcher (YX) screened titles of articles to exclude the obviously irrelevant studies, and obtained the full text of relevant studies. All abstracts and full-text articles of potentially relevant articles were independently screened by 2 researchers (YX, ZYT). Any disagreements were resolved by discussion or decided by a third researcher (SBL). When there was no available data, investigators of studies should be contacted by email.

2.4. Data extraction

The following data were extracted: publication, general information, study design, participant characteristics, diagnostic criteria, factors, the statistical method, adjusted parameters, outcome, duration of follow-up, effect value, etc. The data were evaluated and extracted independently by 2 researchers (YX and ZYT).

2.5. Quality assessment

Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of studies.[11] Cohort studies and case-control studies were assessed by 8 items, mainly including selection, comparability, exposure, and outcome. The full score of scale is 9 stars. This article graded quality as good (≥7 stars), fair (4–6 stars), poor (<4 stars).[12]

2.6. Statistical analysis

This meta-analysis calculated risk ratio (RR) and 95% confidence interval (95% CI) for factors in relation to relapses. The risk estimate (OR or RR or HR), or 2×2 tables data were extracted from included studies, then different data types were converted into risk ratio. If the odds ratio was described, the data was converted to a relative risk for meta-analysis ($RR=OR/([1 - pRef] + [pRef \times OR])$), where pRef is the prevalence of relapses in the reference group.[13] The following subgroups were planned to analyze: cohort studies versus case-control studies; corrected immunomodulatory therapy versus non-corrected immunomodulatory therapy; length of follow-up (<1 year versus ≥1 year). The random effects model (DerSimonian and Laird method) was applied in all meta-analysis, because the clinical and methodological condition differed to some extent in included studies. A random effects model is more conservative.[14]

Q-test has poor power to analyze heterogeneity in the situation of few studies.[15] Heterogeneity among the included studies were assessed by I^2. According to Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), the degree of heterogeneity was defined by I^2 value: might not be important (0%–40%), moderate heterogeneity (30%–60%), substantial heterogeneity (50%–90%), considerable heterogeneity (75%–100%).

Publication bias was assessed by the funnel plot and Egger test. The p value less than 0.05 was considered statistically significant. Sensitivity analyses were also undertook to analyze the stability of results in meta-analysis. All analyses were performed with Stata version 15.1.

3. Results

3.1. Characteristics of the included studies

A total of 21,965 records had been identified in the literature search, from which 318 full-text articles were assessed (Fig. 1). Of these, 43 articles were included (Table 1). This review included 9229 RRMS patients, 40 cohort studies, and 3 case-control studies.[16–58] Nineteen studies had adjusted the immunomodulatory therapy. The mean length of follow-up ranged from 2 months to 5 years. Factors included infection, pregnancy, postpartum, stress, vaccine, vitamin D, comorbidity, genes, smoking, obesity, age, lipid, gender, salt intake, temperature, the Kurtzke Expanded Disability Status Scale (EDSS). In these studies, 16 good quality studies, 25 fair quality studies, and 2 poor quality studies were identified by Newcastle-Ottawa Scale.

3.2. Results of the overall meta-analysis

Figure 2 presents the integrated meta-analysis results for factors associated with relapses in RRMS. Infection, vaccinations,

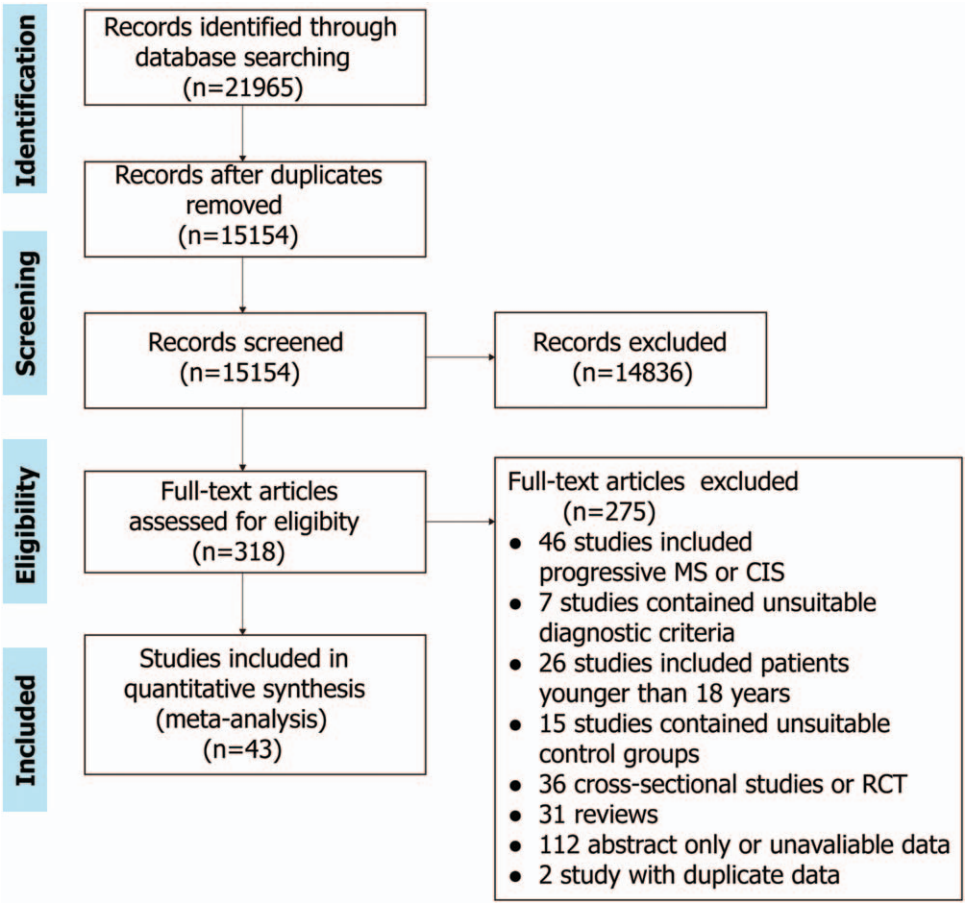

Figure 1. Flow diagram of publication searches and study selection.

pregnancy and postpartum, bread-feeding, stress, vitamin D, genetic risk factors, age, smoking, obesity were involved. Strong risk factors were infection, postpartum period, risk gene. Pregnancy period was the protective factor. Forest plots of each factor are displayed in supplementary figure, http://links.lww.com/MD/E508.

3.2.1. Infection. For virus or bacterial infection, 10 cohort studies and 2 case-control study had been included. Only 4 studies adjusted the immunomodulatory therapy, and 9 studies were followed over 1 year. The result of meta-analysis indicated it increased the risk of relapses in infection period (RR, 2.07 [confidence interval (CI), 1.64 to 2.60]) compared with RRMS patients in uninfected period. The heterogeneity showed small ($I^2=30.6\%$). A total of 7 studies defined the type of virus or bacteria, including influenza virus, chlamydia pneumoniae, Epstein–Barr virus, Human Herpes Virus-6 (HHV-6), adenovirus. The influenza virus and Epstein-Barr virus had 2 studies, the others only had 1 study. Only chlamydia pneumoniae increased the risk of relapses (RR, 2.15 [CI, 1.26 to 4.95]), and the meta-analysis of these 7 studies also showed it increased the risk of relapses (RR, 1.59 [CI, 1.01 to 2.50]) without any significant heterogeneity ($I^2=18.9\%$).

3.2.2. Vaccinations. Three cohort studies had been included. Only 1 study adjusted the immunomodulatory therapy, and all studies were followed more than 1 year. The result of meta-analysis indicated vaccinations had on effect on the risk of relapses (RR, 4.23 [CI, 0.86 to 20.74]). But the heterogeneity showed considerable ($I^2=76.7\%$). Of these studies, 2 studies were about H1N1 vaccine, and one study was about yellow fever vaccine. Although the yellow fever vaccine increased the risk of relapses (RR, 12.79 [CI, 4.29 to 38.18]), but the sample size was small.

3.2.3. Pregnancy and postpartum

3.2.3.1. Pregnancy period. There were 4 cohort studies for pregnancy period. All these were followed more than 1 year, and it did not adjust the treatment. In the meta-analysis, results showed women in the pregnancy period decreased the risk of relapses (RR, 0.56 [CI, 0.37 to 0.84]) compared with women before pregnancy. There was a tiny heterogeneity with $I^2=10.2\%$.

3.2.3.2. Postpartum period. Eight cohort studies were included. All of these were followed over 1 year, but only 1 study adjusted the treatment. The meta-analysis showed women in the postpartum period increased the risk of relapses compared with women before pregnancy (RR, 1.43 [CI, 1.19 to 1.72]), or women in pregnancy period (RR, 2.07 [CI, 1.49 to 2.88]). The heterogeneity of these studies was none ($I^2=0\%$).

3.2.3.3. Breast-feeding. Three cohort studies were included. The studies were followed more than 1 year, but only 1 study adjusted the treatment. In the meta-analysis, results showed

Table 1

Characteristics of 43 included studies.

Author	Year	Country	Sample size	Study design	Factors*	Adjusted data†	Follow-up (yr)
Andersen, O[16]	1993	Sweden	60	Cohort	Infection	N‡	2.6
Worthington[17]	1994	UK	37	Cohort	Pregnancy, postpartum	N	4.8
Gasperini, C[18]	1995	Italy	178	Case-control	Infection, stress	N	1
Buljevac, D[19]	2002	Netherlands	73	Cohort	Infection	N	/
Dragan, B[20]	2003	Netherlands	73	Cohort	Infection	N	1.7
Kriesel, J. D[21]	2004	America	16	Cohort	Infection	N	0.73
Dvan, B[22]	2005	Netherlands	54	Cohort	Infection	N	1.7
Álvarez-Lafuente, R[23]	2006	Spain	63	Cohort	Infection	N	1
Nathalia, T[24]	2006	France	1139	Cohort	Temperature	N	4
Jorge, C[25]	2006	America	60	Cohort	Infection	N	1.7
Maija, S[26]	2007	Finland	42	Cohort	Postpartum	N	1.5
Paavilainen, T[27]	2010	Finland	28	Cohort	Postpartum	N	1.5
Golan, D[28]	2010	Israel	156	Cohort	Stress	N	0.3
Potagas, C[29]	2008	Greece	37	Cohort	Stress, infection	Y§	1
Mervi, O[30]	2011	Finland	665	Case-control	Infection	Y	0.2
Annette, L. G[31]	2011	America	28	Cohort	Postpartum, breast-feeding	N	1
Farez, M. F[32]	2011	Argentina	7	Cohort	Vaccinations	Y	1.9
Neuteboom, R. F[33]	2012	Netherlands	35	Cohort	Pregnancy, postpartum	N	1.5
Sena, A[34]	2012	Portugal	132	Cohort	Contraceptive, smoking	Y	/
Pastò, L[35]	2012	Italy	349	Cohort	Breast-feeding, cesarean, epidural anesthesia	N	5
Jorge, C[36]	2013	Argentina	16	Case-control	Assisted reproduction technology	N	1.8
Fares, J[37]	2016	Lebanon	29	Cohort	Postpartum	N	5
Wawrzyniak, S[38]	2016	Poland	83	Cohort	Vitamin D	Y	1
Lai, W[39]	2018	China	14	Cohort	Pregnancy, postpartum	N	1
Wang, C[40]	2018	China	109	Cohort	Vitamin D, infection	Y	1
Hilven, K[41]	2018	Belgium	527	Cohort	Risk gene	N	3.95
Bsteh, G[42]	2016	Australia	221	Cohort	Age, gender, EDSS	Y	2
Marck, C. H[43]	2016	Australia	2399	Cohort	Comorbidities	Y	5
Tettey, P[44]	2016	Australia	198	Cohort	Comorbidities, obesity	Y	4
Simpson, S[45]	2015	Australia	119	Cohort	Risk gene	Y	2.4
Hellwig, K[46]	2015	Germany	201	Cohort	Breast-feeding	Y	1
Farez, M. F[47]	2015	Argentina	70	Cohort	Salt intake, age, gender, vitamin D, smoking, obesity	Y	2
Karp, I[48]	2014	Canada	677	Cohort	Pregnancy	N	4
Rui, L[49]	2014	Australia	145	Cohort	Risk gene	Y	2.3
Tettey, P[50]	2014	Australia	141	Cohort	Obesity, lipid	Y	2.3
Runia, T. F[51]	2012	Netherlands	73	Cohort	Infection, vitamin D	Y	1.7
Niall, S[52]	2012	Australia	145	Cohort	Vitamin D	Y	2.2
Mcnicholas, N[53]	2011	UK	30	Cohort	Vaccinations	N	1.3
Farez, M. F[54]	2012	Argentina	137	Cohort	Vaccinations	N	/
Jr, S. S[55]	2010	Australia	145	Cohort	Age, smoking, vitamin D	Y	2.3
Portaccio, E[56]	2011	Italy	302	Cohort	Postpartum	Y	1
Pittas, F.[57]	2009	Australia	198	Cohort	Smoking	Y	2.5
Mitsonisabcdbee[58]	2008	Greece	26	Cohort	Stress	N	4.7

* Factors were contained in one study.

† Whether some parameters, like drugs or baseline, were adjusted in the study.

‡ This study did not adjust any parameter.

§ This study adjusted at least 1 parameter.

'/' There is no data about this item.

breast-feeding had no effect on the risk of relapses (RR, 1.32 [CI, 0.89 to 1.96]). The heterogeneity showed small ($I^2 = 18.7\%$).

3.2.3.4. Other factors about pregnancy. Other factors were about assisted reproduction technology, oral contraceptive use, cesarean delivery, and epidural anesthesia, which respectively had 1 study associated with relapses. Only assisted reproduction technology (RR, 6.93 [CI, 3.36 to 14.27]) and oral contraceptive use (RR, 2.97 [CI, 1.24 to 6.54]) increased the risk of relapses. However, the sample size about assisted reproduction technology was small. The cohort study about oral contraceptive use included 137 RRMS patients, and it was assessed with good quality.

3.2.4. Stress. For stress, 3 cohort studies and 1 case-control study had been included. Three studies were followed more than 1 year, and 1 study adjusted the treatment. In the meta-analysis, results showed RRMS patients in the stress events increased the risk of relapses (RR, 4.89 [CI, 1.69 to 14.17]). However, the heterogeneity showed considerable ($I^2 = 79.3\%$).

3.2.5. Vitamin D. There were 6 cohort studies about vitamin D. All studies had adjusted the immunomodulatory therapy, and the length of follow-up were over 1 year. In the meta-analysis, the pooled data showed RRMS patients with lower vitamin D level increased the risk of relapses (RR, 1.85 [CI, 1.14 to 2.98]), but the

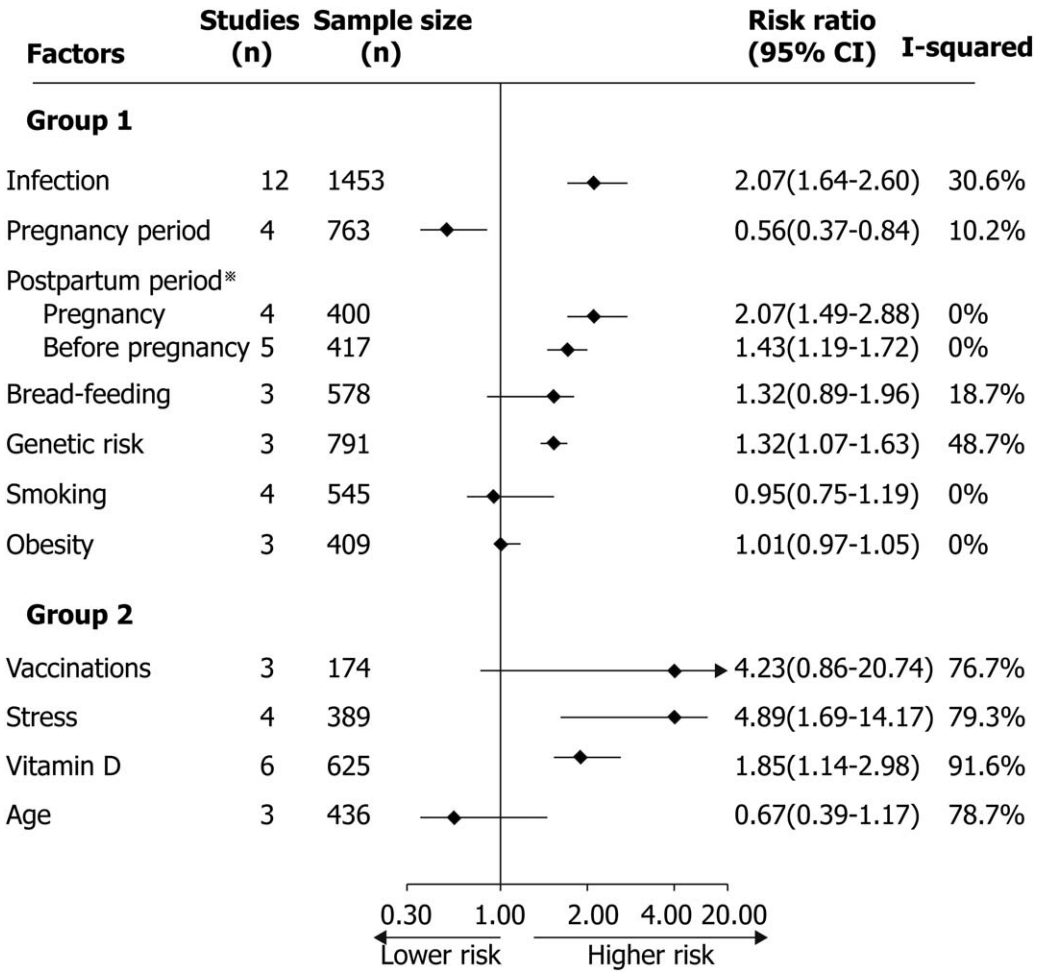

Figure 2. Meta-analysis results for factors associated with relapses in RRMS. Group 1: heterogeneity in risk factors were mild, or moderate. Group 2: heterogeneity in risk factors were significant. For postpartum period, studies respectively selected pregnancy period or period before pregnancy as the control group, and meta-analysis was performed according to different control groups.

heterogeneity was considerable ($I^2 = 91.6\%$), which showed considerable heterogeneity.

3.2.6. Genetic risk factors. Only 3 cohort studies were about gene. All studies were followed for more than 1 year, and 2 studies had adjusted the treatment. The pooled data of meta-analysis indicated risk genes brought the risk of relapses (RR, 1.32 [CI, 1.07 to 1.63]), and the heterogeneity was moderate ($I^2 = 48.7\%$).

3.2.7. Age. Old age as a risk factor, 3 cohort studies were included. All studies were followed over 1 year, and it had adjusted the immunomodulatory treatment. The result of meta-analysis indicated older age had no effect on relapses (RR, 0.67 [CI, 0.39 to 1.17]). However, the heterogeneity was considerable ($I^2 = 78.7\%$).

3.2.8. Smoking. Four cohort studies were included on smoking. Similarly, all studies were followed over 1 year, and these treatments were also adjusted. From merged data in meta-analysis, it showed smoking did not influence the risk of relapses (RR, 0.95 [CI, 0.75 to 1.19]). And there was no heterogeneity ($I^2 = 0\%$).

3.2.9. Obesity. There were 3 cohort studies on obesity. All studies were followed more than 1 year, and the treatment were also corrected. In the meta-analysis, obesity did not influence the risk of relapses (RR, 1.01 [CI, 0.97 to 1.05]). And it showed no heterogeneity ($I^2 = 0\%$).

3.2.10. Comorbidities. Only 2 cohort studies were included, and they were of fair quality according to Newcastle-Ottawa Scale. Two studies were followed over 1 year. Of these, 1 (Tettey, P 2016) included 11 defined comorbidities, in which rheumatoid arthritis and hay fever showed statistical significance after adjusting treatment, merged data of this study indicated comorbidities had no effect on relapse (RR, 1.26 [CI, 0.94 to 1.70]). Another study (Marck, C.H 2016) with 2399 RRMS patients showed that comorbidities can increase the risk (RR, 1.68 [CI, 1.30 to 2.18]) without adjusted parameter. In the meta-analysis of 2 studies, the result showed comorbidities increased the risk of relapses (RR, 1.33 [CI, 1.03 to 1.72]), and heterogeneity was moderate ($I^2 = 45.2\%$).

3.2.11. Other factors. Two studies were about gender, 1 study was respectively about lipid, salt intake, temperature, baseline EDSS. Only salt intake (RR, 3.37 [CI, 1.50 to 9.55]) increased the risk of relapses. Gender (RR, 0.92 [CI, 0.59 to 1.42]), lipid (RR, 1.06 [CI, 0.94 to 1.21]), temperature (RR, 1.14 [CI, 0.60 to 2.14]), and baseline EDSS (RR, 0.91 [CI, 0.78 to 1.06]) did not

influence relapses. Those factors, except temperature, were good quality cohort studies with adjusted treatment.

3.3. Subgroup analyses

The heterogeneity of postpartum period, smoking, and obesity were none ($I^2=0\%$), and the heterogeneity of pregnancy period was tiny ($I^2=10.2\%$), so this article did not perform the subgroup analysis for these factors. Meanwhile, factors for vitamin D and age, all of these were cohort studies and had adjusted the treatment, the length of follow-up were also over 1 year. Therefore, subgroup analysis of those were not carried out as planned. For infection, vaccinations, stress, genetic risk factors, and breast-feeding, the subgroup analysis were generally consistent with main results of meta-analysis, except for infection. In the subgroup analysis of infection, study design may be an important part of heterogeneity.

3.4. Sensitivity analyses

All studies were performed with sensitivity analysis. The results of sensitivity analysis were also generally consistent with the main result of meta-analysis apart from the following 4 exceptions. For pregnancy and genetic risk factors, the quality of studies may consist of the main heterogeneity. For vaccinations and age, the sample size was noted a significant component of heterogeneity.

3.5. Publication bias

Only infection, postpartum, and vitamin D were performed the funnel plots and Egger test, because of enough studies for it. The other factors were performed Egger test. The funnel plots of vitamin D showed obvious asymmetry, and Egger test indicated significant publication bias ($P=.019$). Studies for age also had evidence of publication bias according to Egger test ($P=.034$).

4. Discussion and conclusions

4.1. Principal findings

RRMS patients in infection period increased 2.07-fold risk of relapses, compared with these in non-infection period. The study design may be the major component of small heterogeneity. For specific viruses or bacteria, including influenza virus, chlamydia pneumoniae, Epstein-Barr virus, HHV-6, or adenovirus, no enough evidence was identified to influence relapses. The risk of relapses in pregnancy period were 0.56 fold than the period before pregnancy. However, the risk of relapses in postpartum period were 1.43 fold than the period before pregnancy, and 2.07 fold than the pregnancy period. Breast-feeding did not impact the risk of relapses. These results were reliable due to tiny or no heterogeneity. Assisted reproduction technology and oral contraceptive use may increase the risk, but no enough studies support it. Patients in stress events increased 4.89-fold risk for relapses. However, Considerable heterogeneity, poor and fair quality of studies make this result should be taken careful consideration. Lower vitamin D lever brought 1.85-fold risk of relapses, compared with higher vitamin D level. This result must be interpreted with caution because of significant publication bias. Some risk gene increased 1.32-fold risk for relapses, but there were different genes between studies. Vaccinations, obesity, age did not influence the risk of relapses in this meta-analysis, only the result of obesity was reliable, vaccinations and age need further verification. Some other factors, like comorbidities and salt intake, also increased the risk of relapses in RRMS, but there were not enough studies.

4.2. Definitions of factors

Infection, pregnancy period, postpartum period, risk gene, stress, and lower vitamin D level were identified as factors associated with relapses in this meta-analysis. Table 2 compares different definitions of risk factors in included studies. For 1 factor in those, the definition varied in different studies, but some studies have the trend to use the same definitions. A clear definition can help popularize these conclusions and promote more further research.

The definition of infection was based on symptoms or serological tests, which was consistent with clinical practice. At risk period mainly used Sibley's definition, extending from 2 weeks before the onset of infection to 5 weeks afterward.[59] Pregnancy period was during pregnancy, most studies chose 1 year before pregnancy as the control group, but 1 study selected the control group which different with others. For postpartum period, the control group was consisted of pregnancy or 1 year before pregnancy. And the length of postpartum period was from 6 months to 2 years. The criterion of stress[18,60–61] and risk genes varied between studies. And the time of stress life events was from 4 weeks to 3 months. The vitamin D level was all detected by serological test. The critical concentration was from 28 to 50 nmol/L, and less than 50 nmol/L was diagnosed with vitamin D deficiency.[62]

4.3. Strengths and limitations of study

An important strength of this article is to integrate all relevant factors in meta-analysis. To the best of our knowledge, this review is the first to quantitative assess all relevant factors associated with relapses in RRMS. Because relapses were the main outcome, this review only focused RRMS patients, and excluded the progressive MS. Study types at highest risk of bias for prognostic factor were also excluded, including cross-sectional and population-specific researches.[63] Therefore, doctors, patients, and medical decision makers can benefit from it. However, there were some limitations. Firstly, fewer studies were included after inclusion and exclusion, 6 factors only had 1 or 2 studies, the largest number of studies for 1 factor was 12. Only 3 or more studies can be used in meta-analysis.[64] Secondly, 5 factors in 11 factors indicated moderate or considerable heterogeneity, or publication bias. Finally, the sample size in most studies were not large.

4.4. Comparison with other studies

Although some previous reviews had reported factors about relapses. Several reviews or meta-analysis just focused on 1 factor. Or else, some reviews summarized many risk factors with qualitative description. D'hooghe et al[65] and McKay et al[66] respectively summarized factors about relapses without meta-analysis. The result of this article is consistent with those, but some factors not in this review, such as seasonal variation, menstruation, ethnicity, physical trauma, radiotherapy, and dietary habits. However, population, study design, diagnostic criteria, and unavailable data in above factors did not meet special criteria of this review. Meanwhile, some important

Table 2

The definition of factors.

Factors	Definition		Studies (n)
Infection	The presence of coryza, sore throat, flu-like symptoms, myalgia, fever, urinary infection, or diarrhea lasting more than 24 h	At-risk period: –2 to 5 wk *	5
	Definition was the same as the above	At-risk period: unknown	2
	Influenza A or B, or adenovirus infections	At-risk period: –2 to 5 wk *	2
	Acute chlamydia pneumoniae infection	At-risk period: 1 to 2 wk †	1
	EB positive in serological test	At-risk period: unknown	1
	HHV-6 positive in serological test	At-risk period: unknown	1
Pregnancy period	During pregnancy	Control: 1 yr before pregnancy	3
	During pregnancy	Control: non-pregnant RRMS patients	1
Postpartum period	6 mo after delivery	Control: pregnancy	3
	12 mo after delivery		1
	2 yr after delivery	Control: 1 yr before pregnancy	2
	1 yr after delivery		2
	9 mo after delivery		1
Stress	According to the method of Sibley [18]	Period: 3 mo	1
	War stressors	Period: 2 mo	1
	According to the Social Readjustment Rating Scale (SRRS) [61]	Period: 4 wk	1
	According to Brown's definition [60]	Period: 4 wk	1
Genetic risk factors	Associated with cerebrospinal fluid antibody responses in MS ‡	rs12988804*T allele §	1
	Genetic variation in PBMC-produced IFN-γ and TNF-α	rs522807 or rs25879	1
	A transcriptional repressor involved in cellular processes	rs2283792	1
Vitamin D	<50 nmol/L	3	
	<28 nmol/L	1	
	Every 1 ng was decreased	1	
	<40 nmol/L	1	

EB = Epstein-Barr virus, HHV-6 = Human Herpes Virus 6, PBMC = peripheral blood mononuclear cell, IFN = interferon, TNF = tumor necrosis factor.

* Adopted Sibley definition: 2 wk before the onset of infection to 5 wk afterward.

† 1 wk after positive serological test to 2 wk before negative serological test.

‡ The function of risk gene.

§ The detail name of risk gene.

studies[67,68] were also excluded. Vaccinations[69] and pregnancy[68] were researched by Confavreux et al, results showed vaccination did not appear to increase the short-term risk of relapse in multiple sclerosis, and the rate of relapse declined during pregnancy and increased during the first 3 months postpartum, which were also consistent with this article. But those were also excluded, because 2 studies all included progressive MS.

4.5. Future research

There are differences between RRMS and progressive MS in clinical course and pathology. Progressive MS is characterized by poor response to immunomodulatory treatments and an absence of new inflammatory demyelinating lesions, and hypocellular, gliotic core, and axonal swelling are contained in lesion.[69] So it is important to aim at RRMS patients for factor research. However, few studies and small sample size are current issues. Larger cohort studies with rigorous design are needed to verify and explore more factors. And registry cohort study will be the trend to explore it.[70,71] Meanwhile, verified factors will help to understand pathology and develop new treatment.

4.6. Conclusions

In conclusion, infection, postpartum period, genetic risk factors, stress, and vitamin D were all risk factors for relapses in RRMS. And pregnancy period was protective factor for relapses in RRMS women. Of those, it is reliable to adopt results about infection, pregnancy period, and postpartum period.

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Author contributions

Data analysis: Yao Xie.
Idea: Yao Xie, Ying Gao.
Manuscript drafting: Yao Xie, Fang Han.
Protocol: Yao Xie, Ziyu Tian, Shibing Liang.
Review & edit: Ying Gao, Dahua Wu.
Screen: Yao Xie, Ziyu Tian, Shibing Liang.
Search: Ziyu Tian.

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