Risk Factors for Relapsing Remitting Multiple Sclerosis

Commentary on: Xie Y, Tian Z, Han F, Liang S, Gao Y, Wu D. Factors associated with relapses in relapsing remitting multiple sclerosis: A systematic review and meta-analysis. Medicine (Baltimore). 2020;99(27):e20885-e.

Key Points

■ Acquired infection and the period post-partum may both be risk factors for relapse in relapsing remitting multiple sclerosis

■ The period of pregnancy may be a protective factor in risk of relapse in relapsing remitting multiple sclerosis

■ For the factors of vaccinations, stress, vitamin D and age, there was substantial unexplained heterogeneity

■ Future research should focus on developing standardised definitions of risk factors for relapse in relapsing remitting multiple sclerosis

Background to the reviews

Multiple sclerosis (MS) is a central nervous system disease and is classified by inflammation and demyelination of central nerve cells that leads to axon degeneration and physical disability (Reich et al, 2018). MS affects an estimated 2.2 million people globally (Collaborators, 2019), and is the most common neurological disability (Ghasemi et al, 2017). MS can be classified into several main types, which are progressive relapsing MS (PRMS), relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) (Loma and Heyman, 2011). RRMS is the most common type, affecting approximately 85% of all MS patients (Loma and Heyman, 2011). The cause of MS is unclear, but it is suggested that it is multi-factorial (McKay et al, 2015). Similarly, the cause of relapse has been attributed to multiple factors (McKay et al, 2017). However, despite this multifactorial relationship, previous systematic reviews have only assessed single factors at a time (McKay et al, 2017; Xie et al, 2020). Subsequently, the systematic review by Xie et al (2020) aimed to assess multiple factors associated with relapses in RRMS.

Aim of commentary

This commentary aims to critically appraise the methods used within the review by Xie et al (2020) and expand upon the findings in context to clinical practice.

Methods

A robust multi-database search was undertaken from January 1983 to December 2018. A broad inclusion criterion was used: only cohort and case control studies that included adults (over 18 years of age) with a RRMS diagnosis at the time of the study (Poser et al, 1983), or McDonald criteria (Polman et al, 2011). Initial screening of abstract and title was undertaken by a single reviewer. Secondary title, abstract and full paper screening were undertaken by two reviewers independently, with arbitration by a third reviewer. The exact process of data extraction and assessment of included study quality (Newcastle-Ottawa Scale) was unclear. An appropriate meta-analysis was undertaken using a random effects meta-analysis (DerSimonian and Laird method) to produce a summary estimate risk ratio (RR) and 95% confidence interval (95% CI). A range of subgroup analyses were planned for cohort studies versus case control studies; corrected immunomodulatory therapy versus non-corrected immunomodulatory therapy; and length of follow-up.

Results

This systematic review included 43 studies, of which 40 were cohort studies and three were case control design. Out of these 43 included studies, when using the Newcastle-Ottawa Scale, 16 were graded to be of good quality; 25 were fair quality; and two were deemed to be of poor quality. The included studies had a varying follow-up period ranging from 2 months to 5 years.

The findings of the systematic review identified that there was a statistical and clinically significant increase in risk of relapse between a period of infection compared to non-infection for adults with RRMS (RR 2.07, 95% CI: 1.64-2.60) (see Table 1 for all factors). There was a small amount of heterogeneity observed (I2 30.6%), and it was suggested that this small degree of variance in studies may be due to study design. Only seven studies out of the 12 included in this analysis reported any type of infection. These included adenovirus, chlamydia pneumoniae, Human Herpes Virus-6 (HHV-6), Epstein–Barr virus and influenza virus. Due to the limited number of studies for each of these viruses, it was not possible to undertake a subgroup analysis.

The summary estimate from eight studies demonstrated a statistical and clinical increase in risk of relapse for women in the postpartum period compared to before pregnancy (RR, 1.43 95% CI:, 1.19 to 1.72) and pregnancy period (RR, 2.07, 95% CI: 1.49-2.88). For the period of pregnancy, there was a statistical and clinically significant reduction in the risk of relapse compared to women before pregnancy (RR, 0.56 95% CI: 0.37-0.84). There was no notable heterogeneity for all pregnancy-related comparisons.

There was some evidence that the presence of genetic markers is positively associated with an increased risk of relapse; however, this was based on only three studies with statistically significant moderate heterogeneity. It was indicated that this variation in the study effects may be explained by the varying quality of the included three studies. There was no clear association in change of risk of relapse for factors such as smoking status, obesity and breastfeeding. For the remaining factors of vaccination status, stress, vitamin D levels and age, there was substantial unexplained heterogeneity and wide confidence intervals, which resulted in these associations being questionable. For the variables of vaccination status and age, the study size was noted as a significant component of heterogeneity.

Table 1. Factors associated with risk of relapse for adults with relapsing remitting multiple sclerosis

Factors	Number of studies	Sample size	Risk ratio (RR) 95% confidence interval (CI)	Heterogeneity I^2
Infection	12	1453	2.07(1.64-2.60)	30.6%
Period of pregnancy	4	763	0.56(0.37-0.84)	10.2%
Period post-partum compared to:				
Pregnancy	4	400	2.07(1.49-2.88)	0%
Before pregnancy	5	417	1.43(1.19-1.72)	0%
Breastfeeding	3	578	1.32(0.89-1.96)	18.7%
Genetic risk	3	791	1.32(1.07-1.63)	48.7%
Smoking	4	545	0.95(0.75-1.19)	0%
Obesity	3	409	1.01(0.97-1.05)	0%
Vaccinations	3	174	4.23(0.86-20.74)	76.7%
Stress	4	389	4.89(1.69-14.17)	79.3%
Vitamin D	6	625	1.85(1.14-2.98)	91.6%
Age	3	436	0.67(0.39-1.17)	78.7

Commentary

Using the Joanna Briggs Institute Critical Appraisal tool for systematic reviews, seven out of the 11 criteria were deemed satisfactory (Joanna Briggs Institute, 2017): review question, inclusion criteria,

critical appraisal tool, data extraction, data synthesis, assessment of publication bias and directives for future research. There were four criteria of quality within the review that remained unclear. First, despite the use of an appropriate critical appraisal tool, it was uncertain whether this was applied in an independent manner by two reviewers. Second, within the search strategy, it was not made evident why the date limit for publication was applied (1983 onwards). This may have had an impact on identifying relevant evidence. The search strategy may also be subject to language bias, due to only including studies that were reported in English or Chinese. Third, the sources used to search for evidence were deemed insufficient, as attempts were not made to undertake hand searching or identify unpublished studies. Finally, although it was stated that clinicians and policymakers could benefit from the review findings, no specific recommendations for practice were made.

Based on this quality assessment, it was deemed that the systematic review may not have identified all the relevant evidence for associated risk factors in RRMS. However, based on the evidence included within the review, it may provide an accurate summary of the results available.

Due to the limited evidence, wide confidence intervals and substantial heterogeneity, the factors of infection and post-partum pregnancy period are the only valid factors with a positive association for increased risk of relapse in adults with RRMS. These findings concur with previous systematic reviews (D'Hooghe et al, 2010; McKay et al, 2017). Investigation of these factors should be considered as a method for identifying patients who are at greater risk of relapse. There is also evidence to indicate that there is a negative association with the pregnancy period, which results in a reduced risk of relapse. This negative association is also supported by previous systematic review findings (McKay et al, 2017).

The association of vaccination status, stress, vitamin D levels and genetic risk factors is unclear, due to the wide variation of study findings. It is important that future research explores the possible causes of this heterogeneity, as there was some evidence to suggest that these are important moderators for increased risk of relapse for adults with RRMS. Future research should also ensure that standardised definitions are used for these moderating factors, as the variation of use may be causing additional heterogeneity. Moreover, further research should explore the different infection types, as there was some indication that the type of infection may influence the level of increased risk. Finally, there is the need for larger robust cohort studies as, for some of these factors, there was limited evidence; in many cases, these studies had small sample sizes.

CPD reflective questions

-What are the main strengths and weaknesses of the systematic review?

-What advice can be given to patients who may be at increased risk of relapse?

-How can we gain a greater understanding of the connection between infection during the post-partum period and the onset of RRMS?

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References

Collaborators GBDMS. 2019. Global, regional, and national burden of multiple sclerosis 1990-2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol. 18(3):269- 285.

D'Hooghe MB, Nagels G, Bissay V, De Keyser J. 2010. Modifiable factors influencing relapses and disability in multiple sclerosis. Multiple Sclerosis Journal. 16(7):773-785.

Ghasemi N, Razavi S, Nikzad E. 2017. Multiple sclerosis: Pathogenesis, symptoms, diagnoses and cell-based therapy. Cell journal. 19(1):1-10.

Loma I, Heyman R. 2011. Multiple sclerosis: Pathogenesis and treatment. Curr Neuropharmacol. 9(3):409-416.

McKay KA, Jahanfar S, Duggan T, Tkachuk S, Tremlett H. 2017. Factors associated with onset, relapses or progression in multiple sclerosis: A systematic review. Neurotoxicology. 61:189- 212.

McKay KA, Kwan V, Duggan T, Tremlett H. 2015. Risk factors associated with the onset of relapsing-remitting and primary progressive multiple sclerosis: A systematic review. Biomed Res Int. 2015:817238-817238.

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L et al. 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the mcdonald criteria. Annals of neurology. 69(2):292-302.

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. 1983. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Annals of neurology. 13(3):227-231.

Reich DS, Lucchinetti CF, Calabresi PA. 2018. Multiple sclerosis. N Engl J Med. 378(2):169-180.

Xie Y, Tian Z, Han F, Liang S, Gao Y, Wu D. 2020. Factors associated with relapses in relapsing-remitting multiple sclerosis: A systematic review and meta-analysis. Medicine (Baltimore). 99(27):e20885-e20885