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REVIEW ARTICLE

Seasonal and monthly variation in multiple sclerosis relapses: a systematic review and meta-analysis

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Abstract

Background Multiple Sclerosis (MS) relapses are episodes of transient disease exacerbation. There are contradictory findings regarding seasonal variation in MS relapses. In this systematic review and meta-analysis, we aimed to investigate the seasonal and monthly variation in relapse rates among patients with MS.

Methods We systematically queried PubMed, Scopus, and Web of Science for published papers until February 30, 2022.

Results A total of 24 studies were included in this systematic review and meta-analysis with a total of 29,106 patients with MS. We found that the relapse rate was significantly lower in fall compared to the average relapse rate in other seasons with a risk ratio (RR) of 0.97 (95% CI 0.95–0.98). Furthermore, patients with MS experienced a higher number of relapses in April (RR: 1.06, 95% CI 1.01–1.11) and March (RR: 1.08, 95% CI 1.00–1.16) compared to other months. Also, the risk of relapse was lower in August (RR: 0.92, 95% CI.85–0.98), September (RR: 0.97, 95% CI.94–0.99), October (RR: 0.92, 95% CI.89–0.96), and November (RR: 0.93, 95% CI.89–0.97).

Conclusion Our systematic review and meta-analysis confirm the temporal fluctuations in the relapse of MS through a comprehensive review of the existing literature, with a lower relapse rate during late summer and fall and a higher relapse rate during early spring.

Keywords Multiple Sclerosis (MS) · Relapse rate · Seasonal · Monthly

Introduction

Multiple Sclerosis (MS) is a neurological disease caused by chronic, inflammatory processes that lead to demyelination of the central nervous system (CNS), causing a wide range of physical and mental symptoms, including double vision, blindness, ataxia, urination disorders, and cognitive impairment. The pathogenesis of MS is not well known yet, but MS onset is correlated with impaired functioning of the immune system [1]. Both genetic and non-genetic risk factors have been incriminated in the pathogenesis of MS [1]. Episodes of transient exacerbation of MS, called relapses, are a key feature of MS [2]. A relapse is the clinical manifestation of acute inflammation and focal demyelination in a clinically eloquent region of the CNS [3, 4].

The effects of environmental risk factors in the onset of MS have been studied widely. Several environmental risk factors are suggested to contribute to MS, such as smoking, vitamin D deficiency, vascular risk factors, infectious

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diseases, such as Epstein–Barr virus (EBV) infection, obesity in childhood, and dietary habits [5–8].

There are clear seasonal physiological responses in animals, but the evidence supporting seasonality in humans is limited [9]. Some seasonal changes are observed in various human physiological processes, including nutrient intake [10], level of plasma cholesterol [11], blood pressure [12], and vitamin D metabolism [13]. Some of these factors also play a role in MS [13]. Moreover, several complex polygenic disorders, such as autoimmune [14], metabolic [15], and infectious diseases [16], exhibit seasonal patterns. At the molecular level, seasonal variation in the expression of a large set of genes in white blood cells is reported [17]. Despite these findings, the underlying mechanism of seasonality affecting human physiology is yet to be discovered.

A seasonal variation in relapses of MS has been demonstrated in some studies [18–20]; however, some other studies dispute these findings [21–23], where seasonal variation has been identified, peak frequencies in spring and summer, irrespective of latitude, have generally been observed [19, 20, 22, 24], and this pattern has also been supported by imaging findings [25]. The effect of seasonality on vitamin D metabolism might be one of the potential factors that causes seasonal and monthly patterns in relapse rates among patients with MS [26]. Seasonal relapse patterns might point the way for future studies on environmental variables linked to MS, as well as identifying potential pathways for relapse onset. In this systematic review and meta-analysis, we aimed to investigate the seasonal and monthly variation in relapse rates among patients with MS.

Methods

The Preferred Reporting Items for Systemic review and Meta-Analysis checklist was used to report the present systemic review and meta-analysis study [27].

Literature search

The following databases were systematically queried for published papers up to February 30, 2022: PubMed, Scopus, and Web of Science. The reference list of previous review studies was also reviewed to identify citations not captured in the initial search query. The following search strategy was adopted: (Multiple sclerosis) AND (season OR weather OR seasonality). Additional studies were identified through a manual search of the reference list of previous review studies.

Eligibility criteria

We included original research studies that reported the relapse rate of the MS population in different seasons or months. Non-English studies, case reports, case series, and letters were excluded.

Study selection

First, the title and abstract of the studies were reviewed by two independent investigators (M.Y, K.M) to identify relevant citations. Then the same reviewers screened the full text of identified citations for final selection.

Data extraction

The following data were extracted by the two investigators (M.Y, K.M): patient demographics, study design, follow-up duration, number of patients with MS, type of MS, EDSS score, and the relapse rate in different seasons or months.

Quality assessment

The Newcastle–Ottawa scale (NOS) was used as a tool for assessing the quality of the included studies. The quality of included studies was assessed in three domains including selection, comparability, and outcome using NOS which ranges from 0 to 8 [28].

Statistical analysis

We used a risk ratio (RR) with a 95% confidence interval (CI) to assess the risk of relapse in each season or month compared to other seasons or months. To do this, we compare the risk of relapse in a specific month or season versus total all other months or seasons. To measure the heterogeneity, Cochrane's Q test and I-squared (I^2) were used. A P value smaller than (< 0.10) and the I^2 value $> 75\%$ represent high heterogeneity. The random effects model was applied in statistical models. We used Stata 11.0 (College Station, TX) to perform statistical analysis.

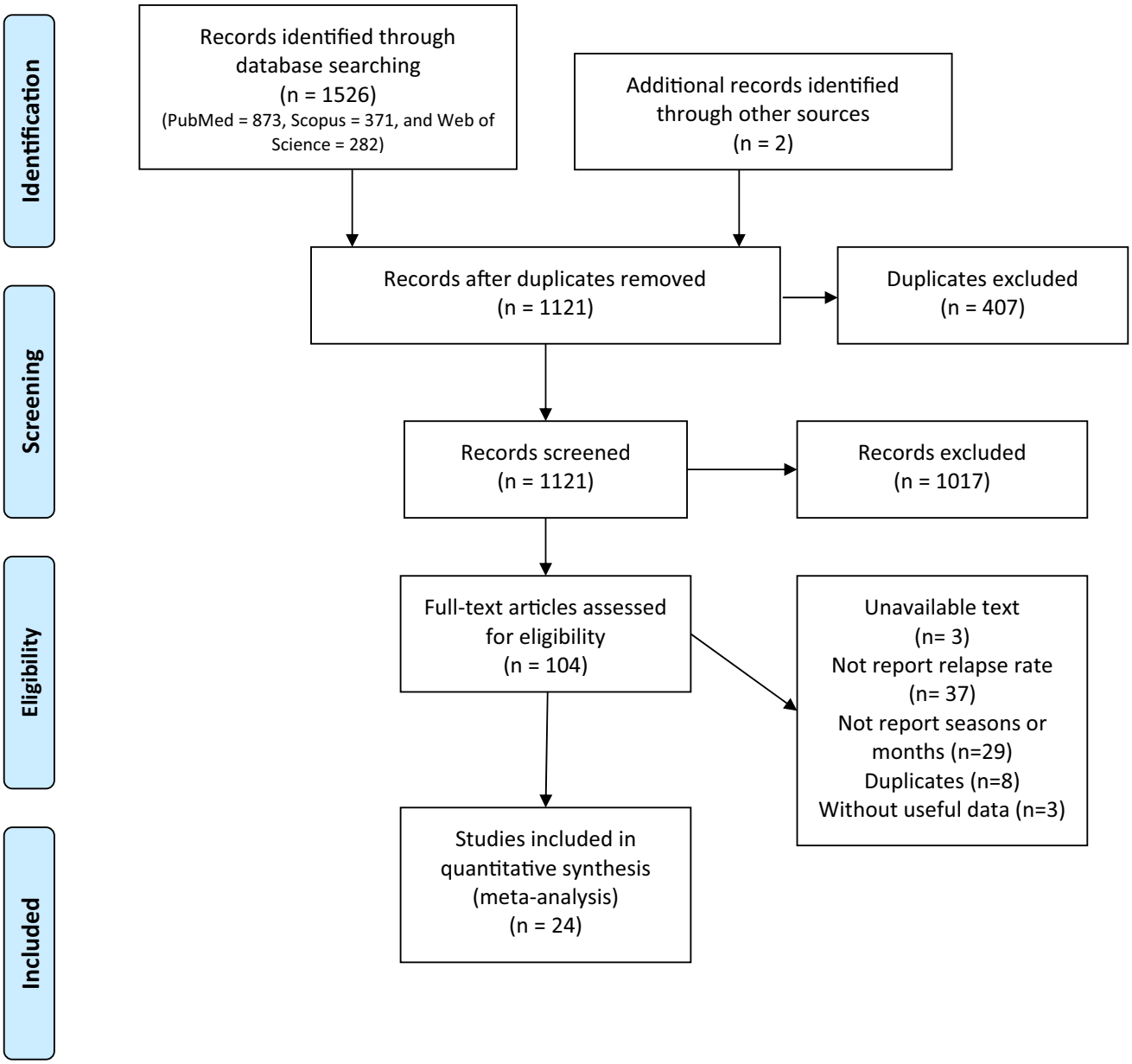

Fig. 1 PRISMA diagram of the selection process. PRISMA = Preferred Reported Items for Systematic Reviews and Meta-Analyses

Results

In total, our literature search and manual addition yielded 1121 articles. After title and abstract screening, 104 studies remained (Fig. 1). Finally, 24 studies entered our systematic review and meta-analysis after a full-text review [18–24, 29–45]. A total of 29,106 patients with MS were included in our study (Table 1). Among included citations, 14 were retrospective, two prospective, and two case–controls. Two papers were multicenter studies, three were from Italy, two from the UK, two from Iran, two from Italy, and one each from Japan, Brazil, Cuba, France, Germany, South Korea, Serbia, Israel, Ireland, Scotland, Portugal, Argentina, and Canada. The quality assessment showed that the mean score of NOS was 7.29.

Meta-analysis

Our analysis showed that the relapse rate is significantly lower in fall compared to the average relapse rate in other seasons with a RR of 0.97 (95% CI 0.95–0.98, Q value = 34.12, $P = 0.06$, $I^2 = 0.02\%$) (Figs. 2 and 3).

Table1 Demographic and clinical characteristic of included studies

Author	Country	Study design	Follow up duration	Number of MS cases	Type of Contentti MS	Mean age	NOS
Contentti et al. [30]	Argentina	Retrospective cohort	7.4 years	431	RRMS	31.2	7
Byun et al. [29]	South Korea	Case–control	7 years	1265	NR	41.1	8
Sistani et al. [42]	Iran	Prospective cohort	1 year	90	NR	NR	7
Harding et al. [33]	UK	HardingRetrospective cohort	7.8 years	2076	RRMS, SPMS, PPMS	54.2	8
Miclea et al. [38]	Germany	Retrospective cohort	2 years	40	RRMS, PRMS	44.1	7
Vojinovic et al. [45]	Serbia	Cross-sectional retrospective	5 years	101	RRMS	39.3	7
Shafa et al. [41]	Iran	Retrospective cohort	4 years	802	NR	32.69	8
Spelman et al. [43]	Multicenter	Retrospective cohort	8.3 years	9811	RRMS, SPMS	NR	8
Iuliano et al. [35]	Multicenter	Retrospective cohort	20 years	3941	NR	NR	8
Damasceno et al. [19]	Brazil	Retrospective cohort	NR	209	NR	NR	6
Iuliano et al. 2012	Italy	Retrospective cohort	20 years	189	NR	NR	7
Handel et al. [20]	Scotland	Retrospective cohort	13 years	7098	NR	NR	8
Saaroni et al. [39]	Israel	Retrospective cohort	3 years	235	RRMS	43.95	7
Salvi et al. [24]	Italy	Retrospective cohort	2 years	96	NR	38.5	6
Fundora-Hernández et al. [31]	Cuba	Retrospective cohort	3.7 years	21	NR	NR	6
Fonseca et al. [21]	Portugal	Retrospective cohort	4 years	249	RRMS	41.9	8
Tataru et al. [44]	France	Retrospective cohort	4 years	1139	NR		8
Koziol et al. [37]	USA	Retrospective cohort	1 years	24	RRMS	41 medians	7
Ogawa et al. [22]	Japan	Retrospective cohort	17 years	34	NR	31.4	7
O'Reilly et al. [23]	Ireland	Retrospective cohort	5 years	87	RRMS, PRMS	34.7	7
Goodkin et al. [32]	USA	Prospective cohort	4 years	425	RRMS	NR	8
Bamford et al. [18]	USA	Case–control	5 years	178	NR	NR	8
Schapira et al. [40]	UK	Retrospective cohort	NR	514	NR	NR	8
Hopkins et al. [34]	Canada	Retrospective cohort	4 years	51	NR	NR	6

NR not reported, *EDSS* expanded disability status scale, *RRMS* relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *PRMS* progressive relapsing multiple sclerosis, *NOS* Newcastle–Ottawa scale

Furthermore, there was no statistically significant higher or lower risk of relapse in total other seasons (Supplementary 1).

Evaluating the risk of relapse in different months revealed that MS patients experienced a higher number of relapses in April (RR: 1.06, 95% CI 1.01–1.11, Q value = 30.18, $P = 0.05$, $I^2 = 40.74\%$) and March (RR: 1.08, 95% CI 1.00–1.16, Q value = 49.16, $P = 0.00$, $I^2 = 74.37\%$) compared to total relapse rate in other months (Figs. 4 and 5). Also, it seems that the risk of relapse is lower in August (RR: 0.92, 95% CI 85–0.98, Q value = 38.25, $P = 0.01$, $I^2 = 65.87\%$), September (RR: 0.97, 95% CI 94–0.99, Q value = 28.01, $P = 0.08$, $I^2 = 0.00\%$), October (RR: 0.92, 95% CI 89–0.96, Q value = 18.82, $P = 0.40$, $I^2 = 19.68\%$), and November (RR: 0.93, 95% CI 89–0.97, Q value = 23.66, $P = 0.15$, $I^2 = 24.31\%$) (Fig. 6). There was no statistically significant difference in risk of relapse in other months versus the total average in all other months (Supplementary 2).

Discussion

It is evident that several environmental factors, including climate and latitude, play a role in the development and activity of MS [6, 46]. Thus, relapse rates in MS may also be subject to seasonal and monthly variations. Studies have found conflicting results regarding this matter, and a more comprehensive investigation is needed before a definitive conclusion can be made. In this systematic review and meta-analysis, we included 24 studies to evaluate the seasonal and monthly fluctuations in the frequency of relapses. Jin et al. performed a meta-analysis on seasonal variation in relapse rate among MS patients [47]. However, our study is the first systematic review and meta-analysis that investigates the seasonal and monthly patterns of relapses based on a comprehensive review of the previous literature.

According to our study, fall shows a significantly lower risk of relapse than other seasons. With a minimum

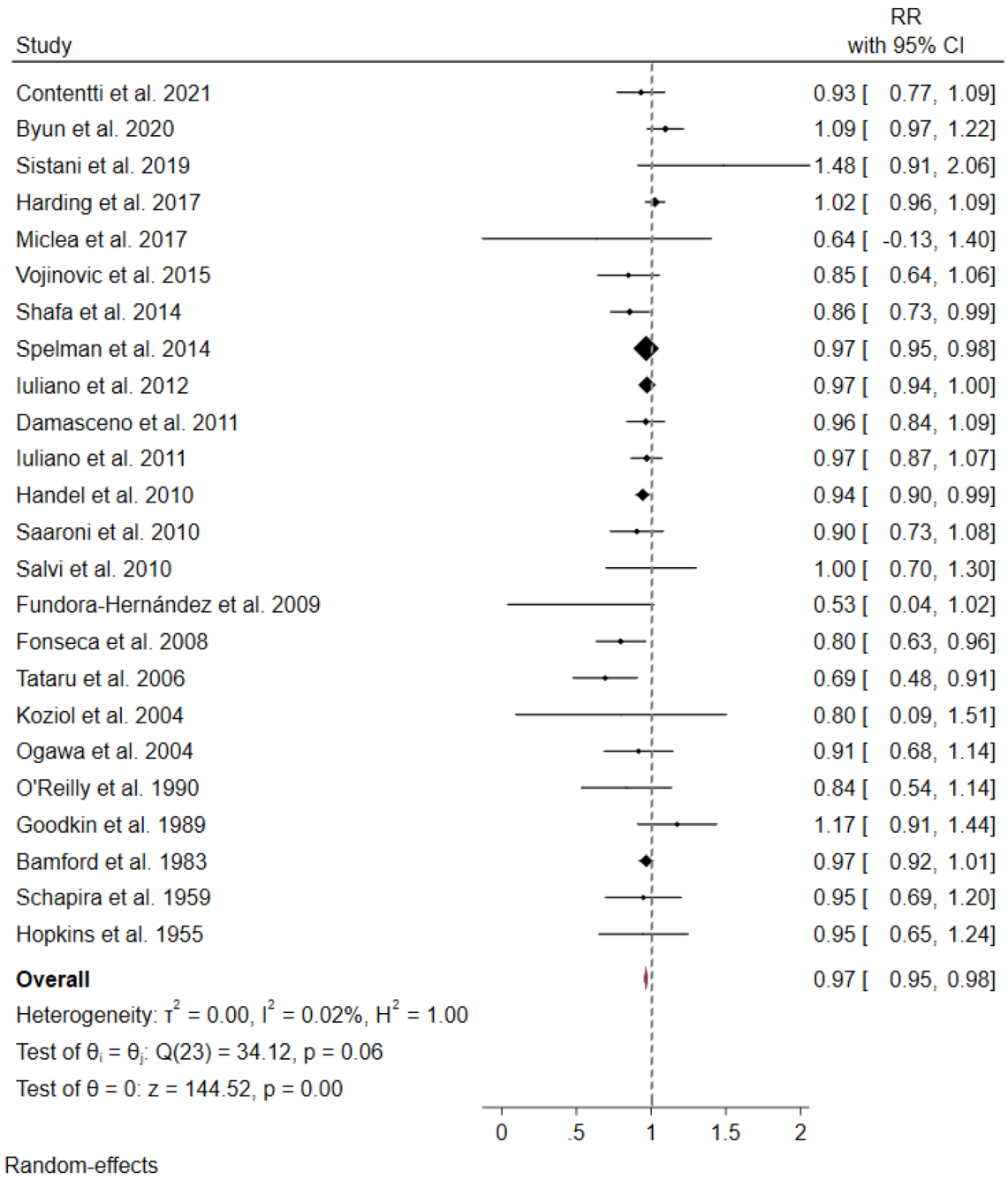

Fig. 2 Graphical representation of the relapse risk in fall versus total all other seasons

heterogeneity, this finding is in line with most of the existing literature. Moreover, this meta-analysis reveals that relapse rates vary by month, ranging from higher rates in April and March to lower rates in August, September, October, and November compared to other months.

In the previous literature, MS has been frequently associated with seasonal patterns. Although the exact mechanisms underlying seasonal variations in MS outcomes remain unclear, several theories have been proposed to explain this phenomenon. These theories include fluctuations in vitamin D levels, melatonin levels, infections, sodium consumption, and air pollution. Each of these factors is proven to be an independent factor affecting MS relapses, and their potential role in the observed temporal pattern will be discussed later.

Further to MS relapses, other similar neuroinflammatory disorders, including Neuromyelitis Optica Spectrum Disorder (NMOSD), also demonstrate seasonal patterns, suggesting that the seasonal changes could probably have roles in

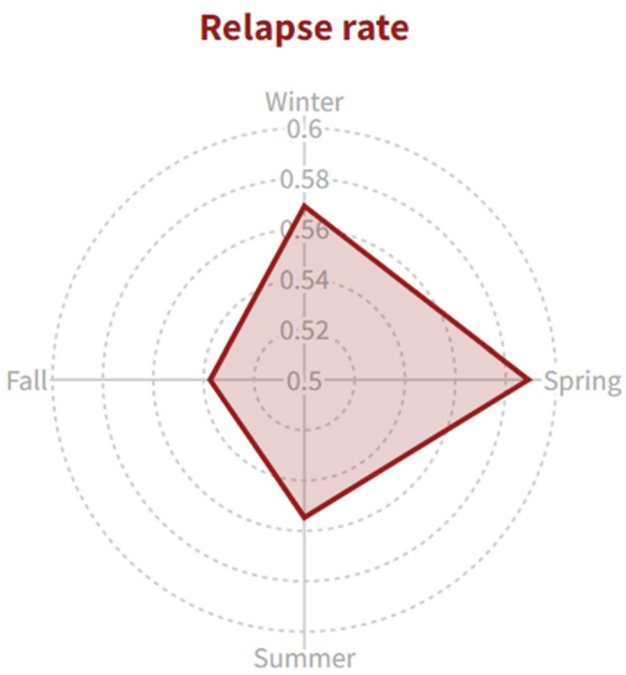

Fig. 3 Graphical representation for the relapse rate in different seasons

the pathophysiology of these diseases [43, 48]. Interestingly, an association has been observed between the month of birth and MS prevalence [49]. Children born in the winter months are less likely to develop MS later in their life [50]. The epigenetic effects of vitamin D in certain months of gestation might explain this correlation [51]. Moreover, MS is a neuroinflammatory disease affected by the release of cytokines, which also follow a seasonal pattern [52].

Vitamin D levels have been the focus of most studies among the aforementioned potential factors. Excluding supplementary multivitamin consumption, the most crucial factor in serum vitamin D levels is sun exposure, affecting vitamin D levels more than the dietary intake. Vitamin D exerts anti-inflammatory effects by influencing T helper 17 (Th17) cells, IL17 pathways [53], and IFN-beta activity [54, 55], all playing an essential role in the pathophysiology of MS, and are targets for immunotherapies. Several studies have confirmed the effect of vitamin D on MS, stating that higher vitamin D levels are associated with lower incidence and better prognosis of MS [56, 57]. similar findings are observed in neuroimaging studies [58, 59]. Furthermore, in animal studies, vitamin D demonstrates a protective effect on autoimmune encephalitis, an animal model for MS [60]. However, this theory is subject to debate. In most studies, MS relapses are less frequent in autumn and winter, during which sun exposure and vitamin D levels are lower compared to other seasons. This observation is called the "seasonal paradox" [61]. To explain this phenomenon, some researchers state that MS seasonality is mainly attributed to factors other than vitamin D, including melatonin levels [61]. Another theory is that there is a time lag between the maximum and the minimum sun exposure and its effect on MS activity, and the length of this lag varies between 30 and 60 days depending on the geographical latitude [43]. According to this theory, maximum sun exposure occurs in

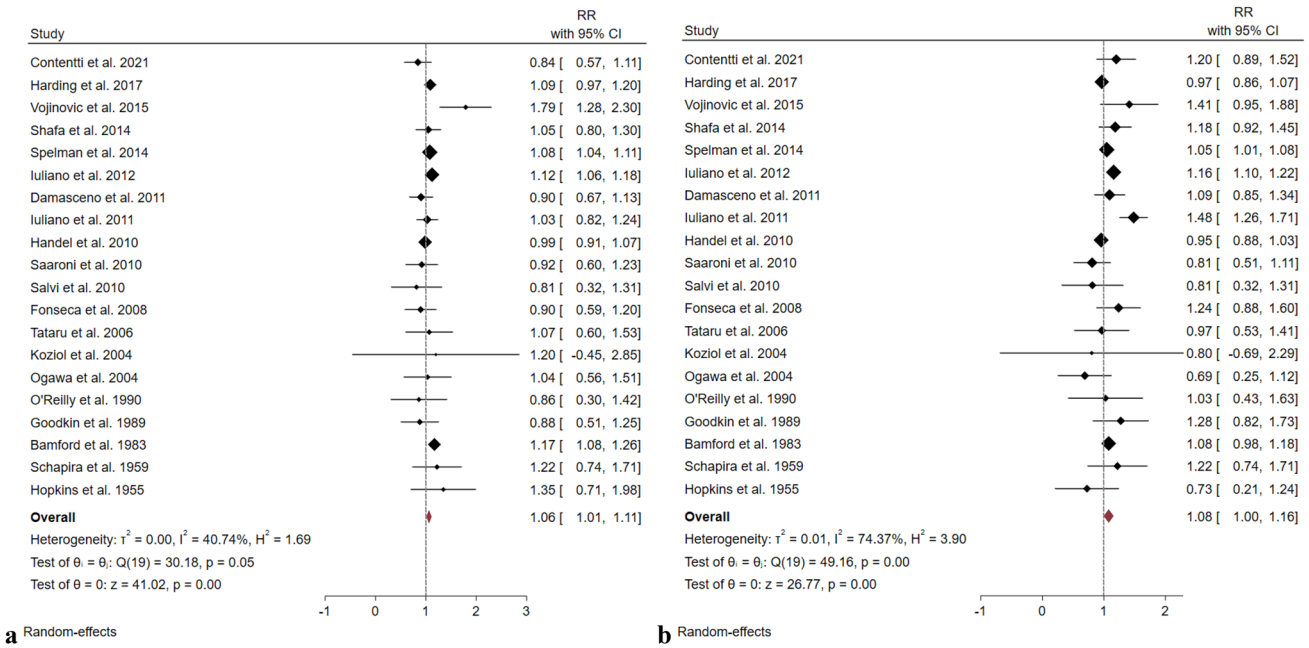

Fig. 4 Graphical representation of the relapse risk in April (**a**) and March (**b**) versus total all other months

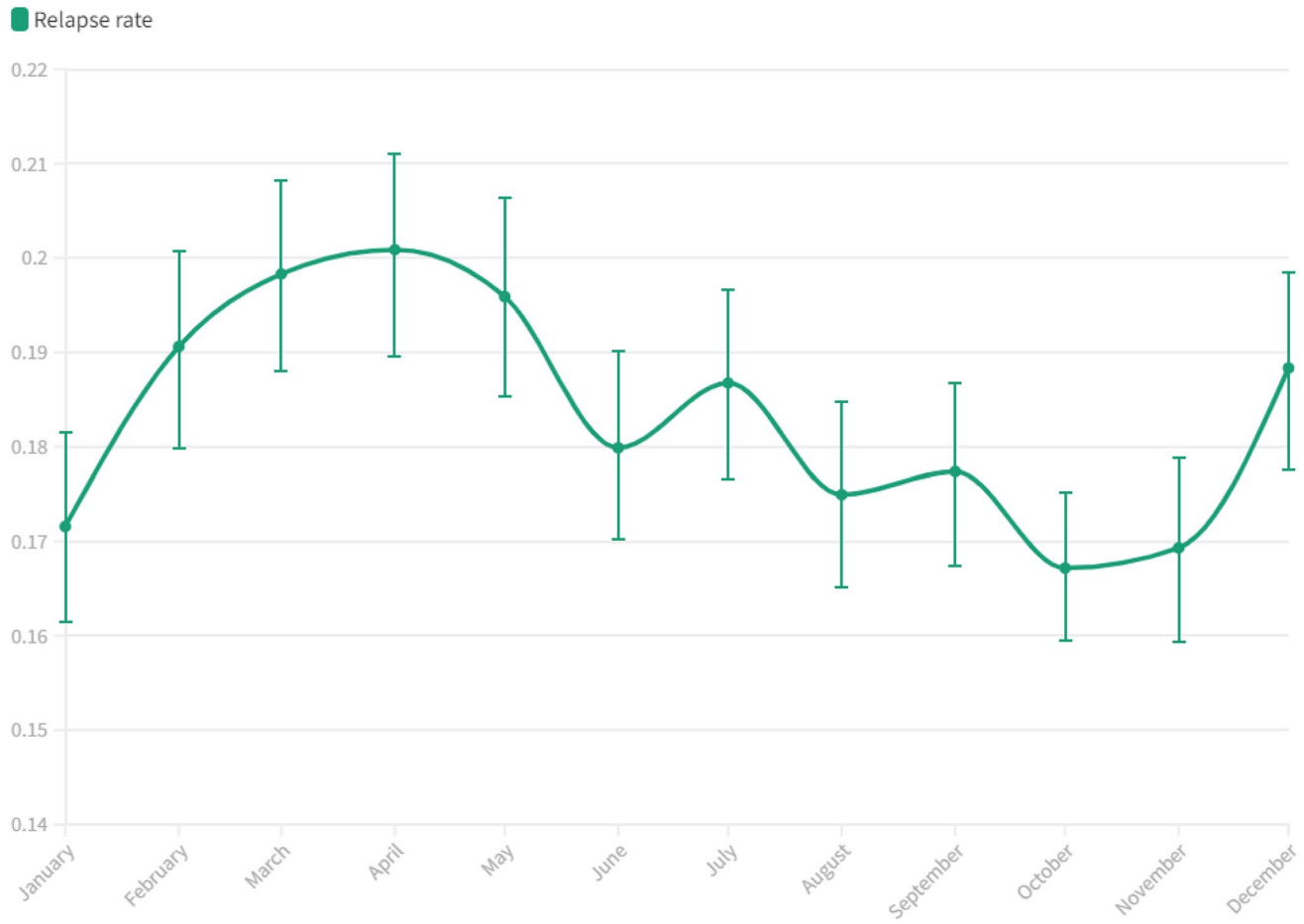

Fig. 5 Graphical representation of the relapse rate in different months

midsummer, creating a protective effect in late summer and early autumn. On the other hand, the minimum sun exposure in winter triggers relapses in early spring. The results of our meta-analysis are more consistent with the second theory.

Moreover, it has been observed that sun exposure itself is a factor affecting MS activity, independent of vitamin D levels [62]. Thus, both vitamin D and non-vitamin D pathways seem to be involved in the protective effects of sun exposure. As stated before, another possible reason for the seasonality is the melatonin level, which is controlled by night darkness duration. Melatonin follows a seasonal pattern, peaking in autumn and winter, and is an independent factor in MS exacerbations and their seasonality [61]. Unlike vitamin D levels, there is no time lag or seasonal paradox in the association between melatonin levels and MS relapses [63]. Melatonin is also associated with lower autoimmune encephalitis activity by regulating Th17 and regulatory T cells type 1 (Treg1) [61].

Furthermore, there is a positive relationship between MS exacerbations and infectious diseases, especially upper respiratory tract infections [64]. Minor viral infections of the upper respiratory tract can trigger MS relapses and are more common in winter [49, 65]. Another possible factor is NaCl ingestion, which affects Th17 cells and might trigger autoimmune diseases [66]. There is evidence of a seasonal pattern in sodium consumption, with a peak in winter [67]. MS has also been linked to air pollution [68]. Particulate matter and NOx pollution are associated with MS relapses and are higher in winter [45, 69], which could be one of the potential explanations for the observed seasonal pattern in the relapses.

Limitations

Our study has some limitations: First, the absence of a specified definition for relapse is potentially a significant source of bias in our results. Of 24 studies included in this meta-analysis, some were retrospective and relied on self-reported data with regard to (or to identify) the relapses, which brings a risk of recall bias, while others relied on physician reports. Second, the geographic diversity among the study locations

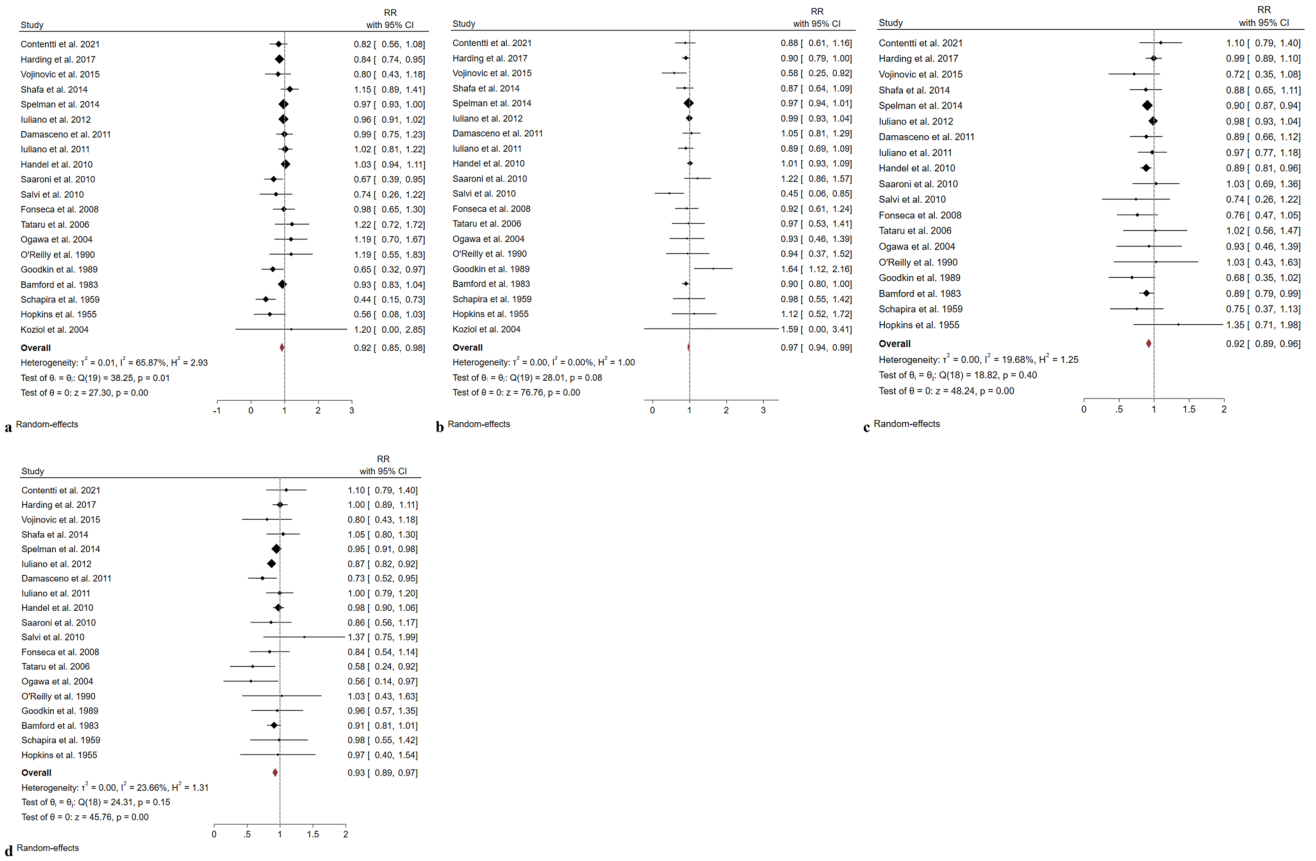

Fig. 6 Graphical representation of the relapse risk in August (**a**), September (**b**), October (**c**), and November (**d**) versus total all other months

is another potential confounding factor in our meta-analysis, which can affect the accuracy of our findings. Studies conducted in various locations have demonstrated different relapse patterns based on environmental and climatic factors. According to a multinational study, the temporal variation in the frequency of MS relapses also depends on the latitude of the study center [43]. Due to a low number of studies performing the sub-group analysis based on climate region or northern hemisphere or southern hemisphere was impossible. Thus, future studies should be performed to give a better understanding by adjusting for climate regions. Another limitation was the lack of complete details on the treatments used by the patients and also, several included studies did not report the type of MS among the participating individuals.

Conclusion

Our systematic review and meta-analysis confirm the temporal fluctuations in the relapse of MS through a comprehensive review of the existing literature, with a lower relapse rate during late summer and fall and a higher relapse rate during early spring. Several explanations have been proposed to influence the seasonal patterns observed in MS outcomes, including sun exposure, vitamin D levels, melatonin levels, air pollutants, allergens, and viral infections. However, further studies are required to determine the effect of each factor on the seasonal pattern of MS relapses.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-022-02103-y.

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