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Seasonal patterns in optic neuritis and multiple sclerosis: a meta-analysis

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Abstract

To quantify and characterize seasonal variation in monosymptomatic optic neuritis (MON) onsets, multiple sclerosis (MS) onsets and MS exacerbations (MSE), a meta-analysis was performed, using established methods and pooling weighted information obtained from nine reports on MON, six reports on MS onsets and nine reports on MSE, which fulfilled specific criteria for report quality and data homogeneity. The results suggested that MON, MS onsets and MSE in the Northern hemisphere present a similar pattern with highest frequencies in spring and lowest in winter. These differences were highest for MS onsets, 45% with 95% CI 36–55%, and lowest for MSE, 10% with 95% CI 7–13%, statistically significant and robust, insensitive to an alternative seasonal definition, not unduly influenced by any single primary study, and supported by fail-safe *N* calculations. Random variation, misclassification and publication bias were less likely to account for the reported generalized seasonal patterns.

Keywords: Meta-analysis; Seasons; Epidemiology; Optic neuritis; Multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic, progressive demyelinating disease with frequent episodes of worsening, denoted as bouts or MS exacerbations (MSE). Patients affected by MS are often in their most productive years, just as they start their professional careers and assume family responsibilities. Despite intensive research over decades and the identification of susceptibility genes [1], the etiology of MS remains enigmatic. Monosymptomatic optic neuritis (MON) is an acute disease of the optic nerve, attributed to focal inflammation associated with demyelination not attributable to concomitant systemic diseases or to lesions in the vicinity of the optic nerve. Multiple observations [2–10] suggest that MON is closely related to MS. Some authors believe that MON is a *forme fruste* of MS [11,12] and that optic neuritis (ON) frequently corresponds to an exacerbation of MS [2,9,13,14]. HLA-Dw2 phenotype, a genotype known to be associated with MS, constitutes a risk factor for MON, present in 47% of MON patients [15]. In contrast, etiological environmental factors of MON and/or MS have not been identified. Epidemiological research may reveal such factors.

Seasonality vis-à-vis clinical onset is a feature frequently studied in MON and MS, and might constitute a risk factor for disease progression in particular, were similar seasonal variations to be observed for onsets of MON, MS or MSE. Observations from a large study conducted in Switzerland [16] point to a similar seasonal pattern for MON, MS onsets and MSE. An ubiquitous seasonal pattern for MON was suggested from a recent informal review of MON seasonality, but relevant problems barring the way to any firm conclusions were also pointed out [17].

The purpose of this paper was to undertake a systematic

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analysis of studies reporting data on MON and MS with the specific aim of quantifying and characterizing any seasonal variation in MON onset, MS onset and MSE worldwide.

2. Materials and methods

Principles for meta-analysis proposed by Greenland [18], Friedenreich [19] and Abramson [20] were followed.

2.1. Study identification and selection

We collected a total of 41 reports [4,5,13,16,17,21–55] with seasonal information, drawn from a Medline search dating back to 1966 and the authors' personal files (one retrieved from both sources). These reports broke down as follows: 16 for MON or retrobulbar neuritis (RN) onset, 21 for MS onset and 25 for MSE. Two reports in Russian [22,38] and two in Romanian [39,40] were excluded due to our lack of language knowledge. Similarly excluded from the systematic review were a further 17 reports for failure to fulfill the following arbitrarily chosen quality criteria, applied independently by two of the present authors (YPJ and JP): (1) seasonal occurrence of at least one of the following three outcomes — ON/RN onset, MS onset or MSE — to be separately reported, thereby rendering data for at least one of the three available [16,26,35–37]; (2) primary ON to be explicitly differentiated from secondary ON [21,25]; (3) reported proportion of ON episodes with onset at ages 50 years and over, to be less than 20% [27]; (4) absolute seasonal figures for the event under study, or frequency counts capable of generating absolute numbers, to be furnished by table, text or graph in the published report [16,26,32,35–37,42,48,54–56]; (5) any study not explicitly defined as population-based to include a minimum of 30 cases or more; (6) proportion of ON and MS onsets lacking information on seasonality to be lower than 50% [34,51]; (7) studies not to focus on highly selected populations [41]. In the selection of reports, no limitations were considered as regards: study place; study period; prospective versus retrospective studies; population-based versus hospital-based studies; or criteria for definition of ON, MS-onset and MSE entities. When studies were replicated at the same place [13,49,31,50], only that one which proved most informative for our purposes was included [13,50]. In all, nine reports on MON/RN onsets [4,5,13,17,23,24,45–47], six reports on MS onsets in seven study places [13,28–30,33,50] and ten reports on MSE [13,28–31,43,44,51–53] were reviewed.

2.2. Data extraction

The seasonal and, where possible, the monthly number of study events was obtained from the selected reports. Four consecutive-3-month seasons were considered, namely, spring, summer, autumn and winter. All the studies were from the Northern nemisphere and so, where monthly data were available, the seasons were defined by taking spring as beginning in April. In cases where monthly data were not available and a definition of season was not given, seasonal figures as reported in the study were used.

2.3. Specifying the study outcome, exposure and characterization of effects

Onsets of MON/RN, MS and MSE were specified as the study outcomes in the present review, and the seasonal time periods were specified as the study exposures. The proportion of events occurring in any one season was denoted as the seasonal proportion and taken as a measure of seasonal effect. The ratio of highest to lowest seasonal proportions, denoted as HL ratio, was chosen as the quantitative measure of seasonal effect. A total of 95% confidence intervals (CI) of the HL ratio were assessed, using the logarithmic method [57]. The shape of the graphical depiction of proportions of cases in each season and the structure of the HL ratio were chosen as qualitative identifiers of seasonality. For example, an HL spring/winter ratio=46/25=1.84 (1.13–3.01) denotes that, of a total of 147 cases, the largest seasonal number of events, 46 cases, was observed in spring and the lowest, 25 cases, was recorded in winter, giving a ratio of 1.84 with a 95% CI (1.13–3.01).

2.4. Homogeneity of effects

To explore whether the differences existing as between different studies were small enough to be reasonably ignored for pooling results, we used the following strategies to examine the homogeneity of seasonal variation. (1) The results were grouped in three categories by outcome — MON/RN, MS onset, and MSE — in order to be separately examined for homogeneity. (2) In each primary study, we conducted a visual examination of the seasonal pattern so as to determine whether or not the shape of the graphical display of the proportion of cases in each season for the same outcome was similar. (3) Using the so-called ''funnel display'' as instrument for visual analysis [20], the HL ratio and 95% CI for single outcomes was plotted against the number of events in each study to identify divergent results. Where the 95% CI of the HL ratio in a any given study failed to overlap the CIs of the HL ratio in the remaining studies with the same outcome, the HL ratio in question was considered to be heterogeneous due to the contribution of said study, and the study was then considered for exclusion before pooling the data [20]. (4) The heterogeneity of HL-ratio magnitude variation within each outcome group was tested using the modified formula $X_h^2 = \Sigma w_i^* [\ln(\text{HL ratio})_i - \ln(\text{HL ratio})_p]^2$, with degrees of freedom equal to one less than the number of studies [18,56,57]. In this formula: $w_i = 1/v\text{ar}[\ln(\text{HL ratio}_i)]$ was

the weight; $v\text{ar}[\ln(\text{HL ratio}_i)] = (X_{hi} + X_{li})^2/(n_i^* X_{hi}^* X_{li}/2)$ was the variance of ln(HL ratio$_i$) in the ith primary study [57]; X_{hi} and X_{li} were the highest and lowest observed events in four seasons of equal length in the ith study, respectively; n_i was the ith total number of cases; ln(HL ratio)$_i$ was the natural logarithm of HL ratio in the ith study and $\ln(\text{HL ratio})_p = \Sigma[w_i^* \ln(\text{HL ratio}_i)]/\Sigma w_i$ [58]. (5) We examined the seasonal structure of the HL ratios, with attention first being paid to numerators and then, independently, to denominators. Homogeneity of seasonal structure was considered to be present when the majority of statistically significant HL ratios exhibited similar numerators and denominators, with 'similar' being defined here as season adjacent in time, e.g., highest proportion in spring or summer, and lowest in winter or autumn. (6) Where random variation was judged not to underlie differences in magnitude or seasonal structure for HL ratios of single outcomes, a search was made for methodological differences capable of explaining the above-mentioned variation; for instance, a systematic methodological error might lie in a different definition of seasonal intervals for a specific outcome or a potentially unnoticed combination of entities in the reported outcome. In cases where significant heterogeneity was detected by the above procedures, consideration was then given to subgroup analysis, e.g., prospective versus retrospective, or hospital-based versus population-based studies. If subgroup analysis proved difficult, the most divergent results were marked for possible exclusion from pooled data.

2.5. Pooling

Data were pooled only where predominant patterns had been identified and no substantial heterogeneity had been demonstrated after exclusion of the above-mentioned outliers. A weighted approach, with weights equal to w_i, was used to combine the results and to quantify the overall summary; for example, the pooled number of events in spring was the sum of number of events in each primary study in spring multiplied by the corresponding w_i.

2.6. Sensitivity analysis and influence analysis

To assess the robustness of the seasonal pattern obtained from an eventual pooled analysis, we conducted a sensitivity analysis by re-defining spring as beginning at a different time point, namely, from March, and re-analyzing the data and comparing the results against those yielded by the preceding analysis. In order to assess whether the results depended overly on any particular study, influence analysis was performed by re-analyzing and comparing the pooled results, after each of the primary studies had been separately dropped. In addition, to assess the resistance to the ''file drawer'' threat by an eventual selective publication of studies with positive results, a fail-safe N was calculated [59]. A number of fail-safe N equal to or larger than five times the studies combined plus ten, i.e. $5k+10$, was adapted as the tolerance for null results as suggested by Rosenthal [59]. Furthermore, the contribution of monthly numbers of events to the corresponding seasonal pattern for each outcome and the presence of a specific profile for MON, MS onsets and MSE were explored by examining the monthly distributions of pooled data for a subset of the selected studies providing such information.

3. Results

Summary characteristics of the reports on MON/RN, MS onsets and MSE selected for review are listed in Table 1. Study period, design, case-finding procedure, diagnostic criteria, and proportion of missing seasonal data all varied greatly, particularly in the MS studies. Of the seven MS onset studies, only one was explicitly denoted as population-based and clearly stated the diagnostic criteria employed, furnishing seasonal information from 74% of observed cases [33]. Five of the ten studies on MSE gave a definition for this outcome, but the definitions differed [29–31,43,53]. In contrast, all MON/RN studies, except for three reports (from Rochester, NE Ohio and Bydgoszcz, Poland, respectively), reported diagnostic criteria and had a high average number (95%) of records with seasonal information. While studies on MON/RN and MSE made use of both prospective [5,17,31,43,45,47,52] and retrospective [4,13,23,24,28–30,44,46,50,51,53] methods, all the MS-onset studies were retrospective.

The seasonal number of events for the three outcomes in each primary study was tabulated but not shown here (available upon request). The average numbers of events under study were as follows: MON/RN, 147; MS onset, 91; and MSE, 170. The seasonal pattern observed in each primary study is shown in Fig. 1. The pattern suggested in the case of MON/RN consisted of a spring or summer peak, declining to an autumn or winter low. Studies on MS onsets indicated considerable fluctuation, while the pattern for MSE was equivocal.

Fig. 2 shows HL structure and ratios on a logarithmic scale, plotted against indices of study size for separate outcomes. In this figure: (1) a funnel display was suggested for MON/RN, and less clearly for MS onset; (2) spring/winter, spring/autumn, summer/winter or summer/autumn structures were seen clearly in five of nine ON studies (numbers 1, 2, 5, 6 and 8), four out of seven MS onset studies (numbers 2, 5, 6 and 7), but in only two of ten MSE studies (numbers 4 and 10); (3) the lower limit of the HL-ratio 95% CI exceeded unity (i.e., $\ln > 0$) in approximately 50% of the study reports, namely, 5/9 for MON/RN, 4/7 for MS and 4/10 for MSE. The majority of statistically significant HL ratios had a predominant spring/winter or spring/autumn pattern: 4/5 for MON/RN, 2/4 for MS onsets and 0/4 for MSE. A less well-defined though similar pattern, marked by spring/winter,

Table 1
Summary features of the reports reviewed

Place and period	Entities on study (n/N)[a]	Case-finding and data-collection	Diagnostic criteria
SC, Sweden 1990–1995 [17]	MON[m] (147/147)	Patients prospectively referred from all ophthalmologists and neurologists in SC.	Explicit specific manifestations.
Lund, Sweden 1969–1981 [5]	MON (110/110)	Patients prospectively referred to the Dept. of Neurology at Lund University Hospital.	Explicit specific manifestations.
London, UK prior to 1978 [24]	MON[m] (144/146)	Retrospectively reviewed accessible notes at the Physicians' Clinic at Moorfields Eye Hospital.	Explicit specific manifestations.
London, UK 1963–1969 [45]	MON[m] (170/170)	Patients prospectively referred for hospitalized examination at a Medical Ophthalmology Unit.	Explicit specific manifestations.
N Ireland 1960–1974 [4]	MON[m b] (144/144)	Retrospectively reviewed medical records at all major hospitals in Northern Ireland.	Explicit specific manifestations.
Rochester 1937–1942 [46]	RN[m] (74/87)	Retrospectively searched medical records at the Mayo Clinic.	Not well defined.
ONTT 1988–1991 [47]	MON (338/388)	Patients prospectively referred to 15 clinical centers in USA for the ONTT study.	Explicit specific manifestations.
Bydgoszcz, Poland 1980–1986 [23]	ON[m] (85/85)	Retrospectively reviewed hospital records at an Ophthalmology Clinic.	Not mentioned.
NE Ohio 1941–1956 [13]	RN[m] (58/58) MS onset[m] (116/?) and MSE[m]	Retrospectively searched medical records at two hospitals at NE Ohio.	RN: not mentioned. MS: not mentioned. MSE: not mentioned.
Arizona, USA prior to 1981 [50]	MS onset (128/146)	Retrospectively self-administrated questionnaire completed by patients in two MS centers.	MS: not mentioned.
Ontario, Canada prior to 1981 [50]	MS onset (136/146)	Retrospectively self-administrated questionnaire completed by patients in two MS centers.	MS: not mentioned.
NE Italy 1972 [33]	MS onset (90/122)	Retrospectively searched medical records from multiple sources.	MS: Allison and Millar's criteria [60] including probable MS only.
Holstebro, Denmark 1973–1986 [28]	MS onset (45/45?) and MES	MS records in the study period were retrospectively reviewed.	MS: McDonald's criteria [61]. MSE: not mentioned.
S England prior to 1986 [30]	MS onset[m] (92/92?) and MSE[m]	Retrospectively searched MS records kept by general practitioners.	MS: McAlpine's critera [62], including definite and probable MS. MSE: evidence of increased severity or an extentioned of neurological involvement.
Scotland prior to 1986 [29]	MS onset[m] (32/32?) and MSE[m]	Retrospectively searched MS records kept by general practitioners.	The same as it in the study of S England.
Arizona, USA 1976–1980 [31]	MSE[m]	Prospectively studied MSE in MS patients constantly seen at MS Clinic.	MS: Rose's criteria [63] including probable MS and CDMS. MSE: new or accentuated symptoms lasting more than 24 h.
NE England prior to 1959 [51]	MS onset (246/700) and MSE[m]	Retrospectively studied the case histories of a large number of MS patients personally examined.	MS: not mentioned. MSE: not mentioned.

Table 1. Continued

Place and period	Entities on study (n/N)[a]	Case-finding and data-collection	Diagnostic criteria
N Dakota, USA 1984–1987 [43]	MSE[m]	Prospectively studied MSE in MS patients followed at MS Clinic.	MS: Poser's criteria [14] including clinical probable MS and clinically definite MS. MSE: new signs or worsening of existing signs lasting for a period of 5 days to 2 months.
Montreal, Canada 1950–1953 [52]	MSE[m]	Prospectively studied MSE in MS patients seen at Montreal Neurological Institute.	MS: not mentioned. MSE: not mentioned.
W Ireland 1981–1985 [53]	MSE[m]	Retrospectively reviewed medical records at Univ. College Hospital.	MS: McAlpine's criteria [64], including definite and probable MS. MSE development of new symptoms, or aggravation of existing symptoms.
Las Palmas, Spain prior to 1983 [44]	MSE[m]	Retrospectively reviewed medical records at two hospital MS clinics.	MS: Schumacher's criteria [65]. MSE: not mentioned.

[a] n: Number of cases with seasonal information; N: Number of cases investigated.
[b] Recurrent ON included. m: monthly number of events available. SC = Stockholm county; MON = monosymptomatic optic neuritis; RN = retrobulbar neuritis; MS = multiple sclerosis; MSE = MS exacerbations.

spring/autumn, summer/winter or summer/autumn structures, accounted for the large majority of the statistically significant HL ratios: 4/5 for MON/RN, 3/4 for MS and 1/4 for MSE. Lastly, (4) all the 95% CIs of the HL ratios overlapped across studies on MON/RN and MS onsets. The 95% CI for the smallest study ($n = 42$) — conducted

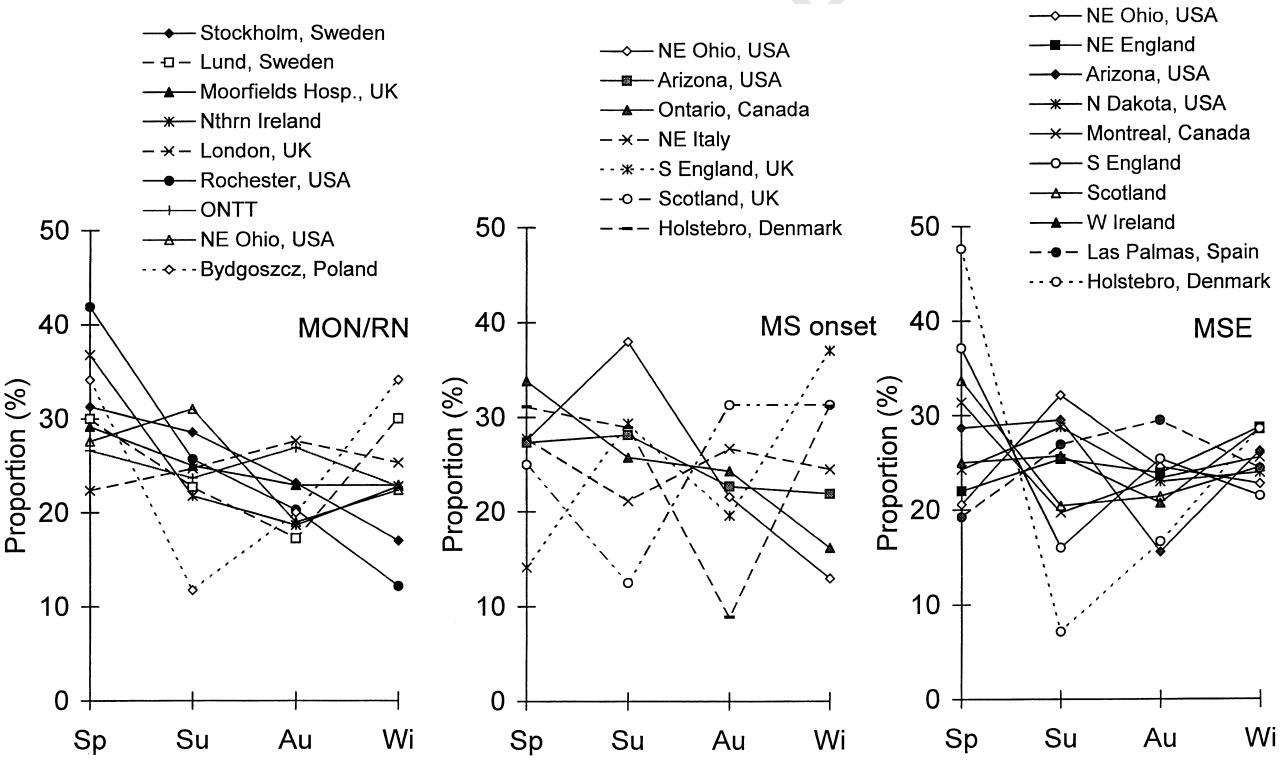

Fig. 1. Seasonal proportion of MON/RN, MS onsets and MSE in each primary study. ONTT = Optic Neuritis Treatment Trial; Sp = Spring; Su = Summer; Au = Autumn; Wi = Winter.

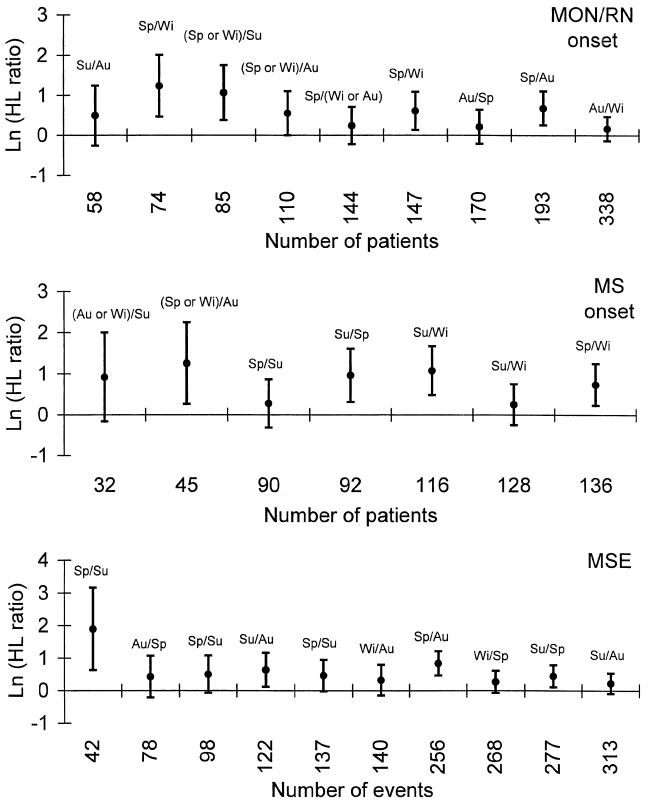

Fig. 2. HL ratio with 95% CI and HL structure in each primary study for each outcome and study size. Sp = Spring; Su = Summer; Au = Autumn; Wi = Winter; HL ratio = ratio of highest to lowest proportions.

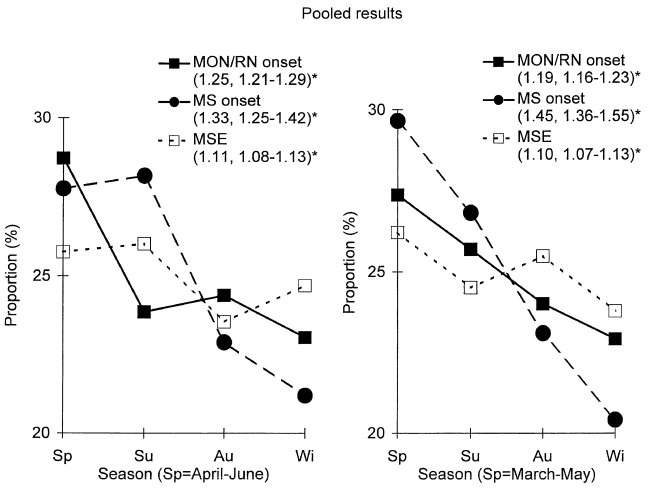

Fig. 3. Seasonal proportion in pooled MON/RN, MS onsets and MSE. Sp = Spring; Su = Summer; Au = Autumn; Wi = Winter. *HL ratio and 95% CI.

on MSE in Holstebro, Denmark — failed to overlap with that for the largest study ($n = 313$), based in N. Dakota, USA. Heterogeneity of seasonal variation between studies, as measured by differences in HL ratio in the specific outcome, failed to prove statistically significant. The results of the heterogeneity test yielded the following *P*-values: 0.080 for MON/RN, 0.267 for MS and 0.136 for MSE.

To sum up, the presence of: (1) a systematic funnel display; (2) a similar HL structure for HL ratios significantly different from unity; (3) only one outlier vis-à-vis magnitude of seasonal variation, namely, the Danish study on MSE; and (4) the lack of statistically significant heterogeneity, all point to the presence of an essentially similar seasonal process underlying each of the studied dimensions, where seasonal heterogeneity was tested.

Data for studies within each outcome group, except for the MSE data from Holstebro, Denmark, were pooled using the weighted approach. The pooled results for the two seasonal definitions of spring considered in our sensitivity analysis are depicted in Fig. 3. A predominant pattern with highest proportion in spring or summer and lowest in winter or autumn was observed for all three outcomes. Furthermore, when spring onset was defined as March–May, the trend corresponding to an HL spring/winter ratio proved more clearly discernible in MS onsets or MON/RN, and lower in MSE. All the pooled HL ratios were higher than one, and statistically significant, especially for MON/RN and MS onsets. The influence analysis, which involved dropping any one of the primary studies (data not shown), had little impact, thus suggesting that the general trend described here was not unduly influenced by any particular study. Fail-safe *N* calculations showed that 122, 80 and 125 unpublished or unretrieved studies for the three outcomes, or 160, 59 and 67 when spring was defined as March–May, were needed to nullify the reported seasonal patterns. These numbers exceeded the recommended resistance number of 55 ($5\times9+10$), 45 ($5\times7+10$) and 55 ($5\times9+10$), respectively. All such results therefore point to a similar and robust seasonal pattern for MON/RN, MS onsets and MSE.

Seven of nine, three of seven and nine of ten selected studies for MON/RN, MS onsets and MS respectively, signaled with ''*m*'' in Table 1, furnished monthly data. For MS onset, the data were limited to two geographical areas in NE Ohio, USA and the UK. The shape of the curves for proportion of pooled monthly events is shown in Fig. 4. The presence of two components with a different contribution to the seasonal pattern for each outcome, was suggested: (1) a peak in spring, defined as March–May, being most pronounced for MON/RN and MS onsets; (2) a peak in late summer–early autumn, being observed solely for MS onsets; and (3) no such element being in evidence in the systematic profile for MSE.

4. Discussion

The results of this meta-review suggest that MON/RN, MS onset and MSE tended to present at variable frequencies, ranging from a high in spring to a low in winter, a variation that was only modest for MSE. Errors in our

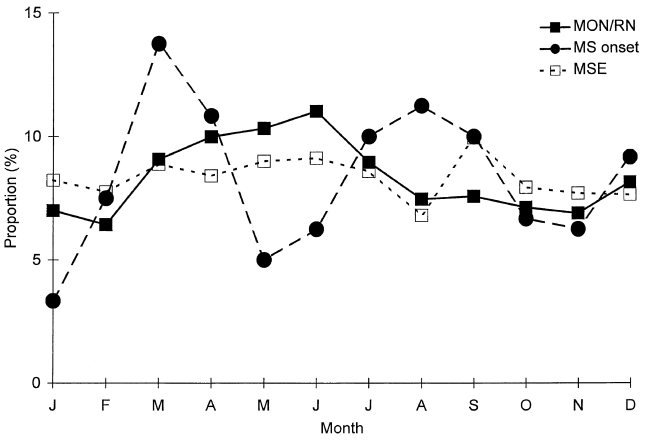

Fig. 4. Monthly proportion in pooled MON/RN, MS onsets and MSE.

estimates may have been introduced by multiple sources embodied in the original results and/or our data-handling, and other aspects of the evaluation procedure. In addition, some authors have cast doubts on the appropriateness of meta-analysis in the field of descriptive epidemiology.

Seasonally differential misclassification for outcome is, potentially, a major source of bias in our results. Several studies suggest that in MS only 10–15% of the changes recorded by magnetic resonance imaging (MRI) as white-matter lesions are clinically manifested [66–69]. Even where clinically expressed, some of the manifestations may nonetheless remain undiagnosed; this would apply particularly to MS onsets and MSE as markers of disease activity in MS. In contrast, it is generally accepted that MS-related lesions of the optic nerve are less likely to remain subclinical or undiagnosed than those in other white-matter regions, due to the alarm caused by the acute decrease in visual acuity. Since MON accounts for a minority of MS onsets [2,7], and symptoms of MS onset are more carefully scrutinized than those of MSE due to their relevance in MS diagnosis, it is possible that the accuracy of MS-onset identification, its value as a disease marker and its underdiagnosis reach medium values as against those for MON and MSE. A further difficulty affecting our study, linked to misclassification for outcome, is that no standard definition was adopted for MSE and that specific diagnostic criteria for MON/RN or MS onset were not always used. However, since such problems ought to be seasonally non-differential, the results should not be affected.

Seasonally differential case-finding or underdiagnosis of MON/RN, MS onsets or MSE might be related to access to neurological expertise or to referral bias in general. This might be expected to occur particularly in summer and late autumn due to summer holidays, and again over the Christmas period. If such lower referral had indeed been present, it should be reflected by shifts in the seasonal pattern towards spring/summer, spring/autumn, winter/summer or winter/autumn. The fact that a different predominant HL ratio, i.e., spring/winter, was observed in the pooled results, despite six such ratios (spring/summer and spring/autumn in particular) being found among the 13 statistically significant HL ratios, would suggest that such bias: (1) was present in some studies; (2) was not the cause of the most frequently identified pattern, namely, spring/winter; and (3) may have diluted the latter's magnitude.

In our study, another potential factor capable of generating seasonally differential misclassification lies in the possibility of the outcomes representing less well-defined categories: some MS onsets might correspond to MON/RN, and both MON/RN and MS onsets may have been included in MSE counts. For example, the frequency of ON as the initial manifestation of MS ranged from 8% to 35% in Western countries [2,7] and the reported frequency of ON occurring at any stage of MS ranged from 27% [9] to 66% [2]. Recall bias too may be another source of error in identifying calendar time of onset of symptoms, particularly for MSE that are not so well-defined, i.e., events less important for the diagnosis of MS or its clinical management than MON/RN or MS onsets. Since MON/RN and MS onsets would have accounted for only a small proportion of MS onsets and MSE respectively [2,7,16,52], and differential misclassification for season would require considerable error in identifying month of onset (an error unlikely to be present here), we therefore conclude that the pattern of seasonal variation for the three outcomes — MON/RN, MS onsets and MSE — is similar, i.e., spring/winter, albeit somewhat less evident in the case of MSE. The large number of negative and nonsignificant unpublished studies needed in all the three outcomes to overturn our results provided additional support to such conclusion.

There is a dearth of information on seasonally varying events that precede, are concurrent with or immediately follow onset of MON or MS. In the case of MS onsets this may be explained by difficulty experienced in recalling remote events. Paradoxically, the bulk of information available for such events corresponds to MSE, where seasonality is less evident. The infections documented as being highly correlated with MSE were common viral infections, most often upper respiratory tract infections (URTI) and sinusitis [29,30,41,49,70,71]. Influenza vaccination showed a considerable protective effect for MSE in an observational study [72]. Since a rational hypothesis is that MS is induced in genetically susceptible individuals by (1) a sensitization process occurring before puberty, and (2) common virus infections mediating a secondary autoimmune response against self-myelin [56,73], viral infections peaking in late winter or summer might be agents potentially implicated in onset and early progression of MS, acting at different time points via different immunomodulating mechanisms. To conclude, MON/RN, MS onsets and MSE present with a similar seasonal variation with highest frequency in spring and lowest in winter, that is somewhat less evident in the case of MSE.

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