Time- and Region-Specific Season of Birth Effects in Multiple Sclerosis in the United Kingdom

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IMPORTANCE The reports of seasonal variation in the births of people who later develop multiple sclerosis (MS) have been challenged and attributed to the background pattern in the general population, resulting in a false association.

OBJECTIVE To study the seasonality of MS births after adjusting for temporal and regional confounding factors.

DESIGN, SETTING, AND PARTICIPANTS A study was conducted using case-control data from 8 MS-specialized centers from the United Kingdom, MS cases from a population-based study in the Lothian and Border regions of Scotland, and death records from the UK Registrar General. Participants included 21 138 patients with MS and control data from the UK Office of National Statistics and the UK government office regions. The seasonality of MS births was evaluated using the Walter and Elwood test, after adjusting for the temporal and regional variations in the live births of the UK population. The study was conducted from January 16, 2014, to September 2, 2015.

MAIN OUTCOMES AND MEASURES Diagnosis of multiple sclerosis.

RESULTS Analysis of the general population indicated that seasonal differences are present across time and region in the United Kingdom, with both factors contributing to the monthly distribution of live births. We were able to demonstrate that, when adjusting for the temporal and regional variations in the live births of the UK population, there was a significant season of birth effect in patients with MS, with an increased risk of disease in the peak month (April) compared with the trough month (November) (odds ratio, 1.24; 95% CI, 1.10-1.41) and 15.68% fewer people who developed MS being born in November (observed to expected birth ratio, 0.840; 95% CI, 0.76-0.92).

CONCLUSIONS AND RELEVANCE Season of birth is a risk factor for MS in the United Kingdom and cannot be attributed to the background pattern in the general population. The reasons for the variations in birth rates in the general population are unclear, but not taking them into consideration could lead to false-positive associations.
The cause of multiple sclerosis (MS) remains elusive, but environmental factors are thought to be important. Environmental exposures might contribute to MS susceptibility acting at different periods. Seasonal variation in the births of people who later develop MS has been reported in different populations with a spring peak and autumn nadir. If this effect is real, early environmental influences may be acting before the disease is clinically evident, and further interrogation of this observation may give clues as to the cause of MS. The same seasonal pattern has also been reported in childhood-onset type 1 diabetes, and vitamin D and UV radiation have been observed to modify the risk of disease in both diabetes and MS. However, although the seasonality effect of births in childhood-onset type 1 diabetes is well accepted following appropriately controlled studies, the validity in MS has been challenged and attributed to the background pattern in the general population. Adjusting for temporal and geographical variations indicated that the apparent seasonal patterns for month of birth suggested to be specific for MS are expected by chance alone; therefore, previous claims for an association of MS with month of birth were probably false-positives. Thus, it is unclear whether a seasonal birth effect exists in MS, and adequately controlled comparisons using the background general population birth rate patterns for the same time and place are required.

In both MS and childhood-onset type 1 diabetes, the largest seasonal effects on birth patterns have been observed in the United Kingdom, particularly in Scotland. However, previous studies on MS have been underpowered or lacked appropriate controls to reliably quantify regional and latitudinal effects within the United Kingdom. We therefore studied more than 20,000 UK patients with MS, with the primary objective of determining the month of birth effect with appropriate adjustments for general population time of birth patterns by region.

Methods

MS Data
Month and year of birth of 31,806 UK individuals with a diagnosis of MS were derived from 5 main sources (Table). Most of the data were supplied by 8 specialist regional MS centers (Oxford University Hospitals National Health Service Trust, University of Nottingham, Cardiff University, Plymouth University, Imperial College London, The Walton Centre Liverpool, Barts and The London School of Medicine and Dentistry, and Northern Ireland Neurology Service) had a local research ethics agreement for database storage and analysis of deidentified patient data. The other sources included data on individuals collected as part of the UK Risk Sharing Scheme provided by the Multiple Sclerosis Trust, which was established by the Department of Health in 2002 to monitor a cohort of patients with MS to ensure cost-effective provision of interferon beta and glatiramer acetate. Eligibility included all UK patients with MS who met the Association of British Neurologist criteria for use of these drugs. In addition, population-based MS incidence and prevalence studies in the Lothian and Border regions of Scotland were included. The control data were obtained from the UK Office of National Statistics and were composed of 3 data sets (Table). Two population data sets covered England and Wales (1941-2000) and Scotland (1941-2000), including monthly annual live births for each region. The third source included regional data from the UK government office regions (1965-1999), which was made up of monthly annual live births for each region. Regional birth data were not collected before 1965 in the United Kingdom. The latter data were obtained to compare with an MS cohort from the same period matched on birth location.

Normalization of Control Data
We adjusted for the seasonality of live births in the general population by calculating the normalized birth rate per month for each year (r). This adjustment was done by constructing pseudocohorts of births adjusted for the different number of days per month, including leap years, assuming no seasonal variation (eMethods in the Supplement). The deviance (excess or deficit) in the normalized birth rate per...
month was calculated as $D = 100 \times (r - 1)$ and represents the percentage difference of the monthly annual live births compared with the pseudocohorts previously described (eMethods in the Supplement).

**Examination for Potential Temporal Effect**

We examined temporal changes in the seasonality of births in the general population by using the UK (England, Wales, and Scotland) monthly annual live births data sets from the period 1938-2000. Deviances in the monthly rates over time were plotted together with their respective trend lines.

**Examination for Potential Regional Effect**

First, we compared the monthly distribution of live births for England and Wales in 1938-2000 with the distribution in Scotland using the Walter and Elwood test.25 This test was specifically designed to investigate the seasonality of events with a variable population at risk. The strength of this test is that it does not assume any specific expected seasonal pattern, such as the sinusoidal pattern, that is the basis of other tests of seasonality. Rather, the Walter and Elwood test evaluates whether the center of gravity (centroid) of the “clock face” of monthly births differs significantly between 2 groups (eFigure 1 in the Supplement). The test only assumes that any seasonal trend will be asymmetrical: any excess of observed births will tend to cluster in adjacent months and with a roughly annual periodicity, resulting in a difference between case and control populations in their centers of gravity on the clock face, the significance of which can then be calculated using a single $\chi^2$ test. Therefore, this test avoids the issue of multiple comparisons by not using month-specific $\chi^2$ tests of association for individual months.

Second, we performed a regional analysis by using the monthly annual live-births figures available from different UK government office regions in 1965-1999. We looked for regional differences in the seasonality of births by comparing the monthly annual live births of Scotland (ie, the region with the most extreme latitude) with all other UK regions (Walter and Elwood test) and by plotting the mean normalized monthly birth rates of the regions against latitude.

**Comparison of the MS and Control Cohorts**

**Assessing Seasonality After Adjusting for Temporal Effect**

We calculated the MS-expected births for each month after adjusting the live births in the control population to the relative frequency of MS births per year (1938-1980) and for country of origin. The expected numbers were compared with those observed using the Walter and Elwood test. The peak-trough month ratio was calculated as an approximate measure of the amplitude of seasonality and is given as an odds ratio (95% CI).

**Assessing Seasonality After Adjusting for Temporal and Regional Effect**

We calculated the MS-expected births for each month after adjusting the live births from the UK government office regions to the relative frequency of MS births per region (and per year to allow for a temporal effect). The Walter and Elwood test was used to compare the expected numbers with the observed numbers. The peak-trough month ratio was calculated as an approximate measure of the amplitude of seasonality. Because the regional control data set covered live births during 1965-1999 and the regional MS data (obtained from the specialist MS centers and the Multiple Sclerosis Trust) covered births during 1989-1980, we selected data from 1965-1999.

**Statistical Analysis**

Data were originally registered in a database (Microsoft Excel 2010; Microsoft Corp). Statistical analysis was performed using SPSS, version 19 (IBM). The Walter and Elwood test was performed according to the authors’ instructions.25 $P < .05$ was used as evidence for a statistically significant difference.

**Results**

**Temporal and Regional Effects In Control Data**

Examination of a regional effect on control birth rates showed seasonal differences in the births of the general population between England and Wales compared with Scotland during most individual years (eFigure 2A in the Supplement) and decades (eFigure 2B in the Supplement) in 1938-2000. The regional

### Table. Multiple Sclerosis and Population Control Data Sets

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>Period</th>
<th>Patients</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1</td>
<td>England, Wales, and Northern Ireland</td>
<td>1899-1980</td>
<td>12,567</td>
<td>Specialist MS center databases</td>
</tr>
<tr>
<td>MS2</td>
<td>England, Wales, Northern Ireland, and Scotland</td>
<td>1941-1980</td>
<td>5,864</td>
<td>MS Trust</td>
</tr>
<tr>
<td>MS3</td>
<td>Scotland (Lothian region)</td>
<td>1900-1978</td>
<td>2,279</td>
<td>Lothian data set</td>
</tr>
<tr>
<td>MS4</td>
<td>Scotland</td>
<td>1890-1972</td>
<td>2,356</td>
<td>Death certificates from Scotland</td>
</tr>
<tr>
<td>MS5</td>
<td>England, Wales</td>
<td>1893-1975</td>
<td>8,740</td>
<td>Death certificates from England and Wales</td>
</tr>
<tr>
<td>C2</td>
<td>UK Office of National Statistics</td>
<td>1938-2000</td>
<td>5,123,010</td>
<td>Scotland</td>
</tr>
<tr>
<td>C3</td>
<td>Government office regions</td>
<td>1965-1999</td>
<td>12,522,051</td>
<td>UK GORs (Wales, North East, North West, Yorkshire, East Midlands, West Midlands, East Anglia, South East, South West, Scotland, and Northern Ireland)</td>
</tr>
</tbody>
</table>

Abbreviations: C, control; GORs, government office regions; MS, multiple sclerosis.
analysis using the mean data available within 1965-1999 demonstrated significant differences between Scotland and several southern regions of England and Wales; for example, there was a 5.3% excess in births in the South West region in May compared with Scotland (Figure 1). These differences were greater in regions with milder latitudes (eFigure 3 in the Supplement).

Examination of the temporal effect in the UK general population showed a correlation between the deviance in the normalized birth rates and the year of birth except for January, June, and December, when the tendency reached a plateau (eFigure 4 in the Supplement). Therefore, seasonal differences in case-control studies might change depending on the time-frame population used as controls (eFigure 5 in the Supplement).

Control vs MS Monthly Birth Rates
UK MS Cohort (1938-1980)
A seasonal effect was found in the UK MS group (n = 21138) compared with the UK general population from the same period after adjusting for the relative frequency of MS births per year and for country of origin (P < .001), with a peak-trough amplitude of 1.17 (95% CI, 1.09-1.25) compared with controls. The peak-trough months were April (observed to expected birth ratio, 1.07; 95% CI, 1.02-1.11), with 6.77% more MS births, and November (observed to expected birth ratio, 0.91; 95% CI, 0.87-0.95), with 9.01% fewer MS births than expected (Figure 2A). When grouping the data into quartiles, the seasonal effect persisted (eFigure 6 in the Supplement).

Regional MS Cohort (1965-1980)
There remained a seasonal effect in the regional MS group (n = 6372) compared with the regional controls after adjusting for the relative frequency of MS births per year and region (P < .001), with a peak-trough amplitude of 1.24 (95% CI, 1.10-1.41) compared with controls. This effect was particularly marked in November (observed to expected birth ratio, 0.840; 95% CI, 0.76-0.92), with 15.68% fewer MS births than expected (Figure 2B). When the data were grouped into quartiles, the seasonal effect persisted (eFigure 7 in the Supplement).
Discussion

The findings of this study appear to confirm that, after making the appropriate corrections for regional origin and year of birth, the month of birth effect in development of MS in the United Kingdom remains significant. We have shown that seasonal differences in population birth rates are present across time and regions in the United Kingdom, with both factors contributing to the monthly distribution of births in the general population. Therefore, these confounders should be considered when studying the seasonality of diseases.

In most populations, birth rates vary by season, although not in an identical manner. The causes of these seasonal variations are not fully understood, although cultural, environmental, and socioeconomic factors could have an important effect. It is also not clear what drives the temporal and regional trends in the seasonality of births in the general population. It is interesting that the seasonality in the control population appears to have declined over time (eFigure 1 in the Supplement), although control data from the past decade suggest that the seasonal effect has reversed (eFigure 8 in the Supplement). These findings highlight the need to use reliable controls in association studies that are matched on time and region of birth and regional origin. The size of the regions chosen should also be considered since the use of smaller regions can be useful in detecting regional MS risk microvariations. However, the use of small regions is often limited by the availability of data.

The validity of the season of birth effect in MS has been questioned on the basis that some previous studies used unreliable controls unmatched for time and region of birth. The other problem with previous studies has been a lack of statistical power to reliably quantify modest seasonality of birth. To avoid both of these pitfalls, we used the largest UK MS cohort to date and adjusted the control data sets according to the relative frequency of MS births per time and region of birth. The power of the Walter and Elwood test to detect a seasonal variation of 5% amplitude or more for a given size of approximately 25,000 MS cases would be as high as 99% (P < .05). However, the power of this test will, in general, be higher than that of the usual x² test for heterogeneity of rates between the number of time periods.

We found a consistent seasonal pattern in a large MS cohort weighted by country of birth and year of birth. This pattern was also confirmed in a cohort of patients with MS weighted by regional origin (regional effect) and year of birth (temporal effect). These results support the findings of previous smaller studies in Australia (1524 patients with MS) and the Italian region of Sardinia (810 patients with MS) that used adequate controls.

The seasonal pattern of MS is shared by other immune-mediated diseases, especially type 1 (insulin-dependent) diabetes. In the United Kingdom, type 1 diabetes has a similarity of season of birth with MS in relation to the same peak trough months, latitude trends in seasonality, and overall epidemiology. This similarity supports the idea of a common factor responsible for the environmental effects seen in both conditions. One of the main candidates is sunlight exposure since UV radiation is the main determinant of vitamin D concentration, and numerous studies have pointed out that poor vitamin D status is associated with an increased risk of MS. In addition, the vitamin D hypothesis in type 1 diabetes is closer to being established and widely accepted. However, there are other possible environmental factors that could act in the perinatal period, including viral infections during pregnancy and dietary differences related to season. Environmental exposures could also have an effect during childhood and adulthood.

The limitations of our study include the lack of information on socioeconomic class, race, culture, and other factors, which could be biases; the differences in data acquisition; and the controls not matched for sex, although there seem to be no appreciable sex differences in population birth rates. Other limitations are the accuracy of death certificates for MS because 100% specificity cannot be guaranteed and the possibility of a low number of duplicate individuals in the data sets owing to the deidentified data. We were not able to exclude patients with MS who were not born in the United Kingdom because this information was not systematically collected. However, data from the UK MS register and migration studies suggest that such persons represent a very small proportion of the sample. In addition, we have not allowed for individuals with MS who move from their birth regions, although internal migration studies in the United Kingdom suggest a small effect. The fact that patients with MS are identified only after diagnosis could also represent a bias for those born in the 1970s (especially males, who tend to develop the disease later and have not lived through their entire disease risk period), increasing the proportion of females with relapsing-remitting MS and an earlier age of onset. This limitation does not apply to individuals born earlier, and therefore will not have an effect throughout the entire MS cohort. However, these factors are unlikely to produce a systematic bias that would cause a seasonal effect once time and region are controlled for. Some of the limitations may have introduced noise into the analysis and thus could have diluted our findings.

Conclusions

The findings of our study demonstrate that the month of birth effect is a risk factor for MS in the UK population, with a pattern similar to that reported for type 1 diabetes. This study provides data consistent with the hypothesis that very early environmental influences contribute to the risk of developing MS. Regional origin and year of birth influence the seasonality of population birth rates and therefore should be considered when studying the seasonality of births in disease groups. Further studies are required to determine the cause of the month of birth effect in MS in the United Kingdom. The symmetrical deviations could imply a natural cycle; therefore, studying factors such as the variation in sunlight hours across regions of the United Kingdom would be of great interest.
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Author Contributions: Dr Palace had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Rodríguez Cruz, Matthews, Oppenheimer, Rothwell. Administrative, technical, or material support: Boggild, Cavey, Evangelou, Hawkins, Nicholas, Robertson, Zajicek, Palace. Study supervision: Boggild, Hawkins, Zajicek, Palace.

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