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BRIEF COMMUNICATION

Month of birth and risk of multiple sclerosis: confounding and adjustments

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Abstract

A month of birth effect on multiple sclerosis (MS) risk has been reported from different countries. Recent critics have suggested that this finding is caused by confounding and that adequately adjusting for year and place of birth would markedly reduce this effect. All inhabitants in Norway are registered in the Norwegian Population Registry (Statistics Norway), making this an ideal area for performing adjusted analyses. Using the entire Norwegian population born between 1930 and 1979 (n = 2,899,260), we calculated the excess between observed and expected number of births for each month for 6649 Norwegian MS patients, 5711 mothers, 5247 fathers, and 8956 unaffected siblings. The analyses were adjusted for year of birth and place of birth according to the 19 counties in Norway. An unadjusted analysis revealed 13% fewer MS births than expected in February ($P = 0.0015$; Bonferroni corrected $P = 0.018$), 10% more in April ($P = 0.0083$; Bonferroni corrected $P = 0.0996$) and 15% more in December ($P = 0.00058$; Bonferroni corrected $P = 0.007$). Adjustments for both year and place of birth significantly altered our results for February and December, but even after these adjustments there were still 10% more MS births than expected in April ($P = 0.00796$; Bonferroni corrected $P = 0.096$). MS patients had a higher incidence of April births than their siblings (Fisher-exact test; $P = 0.011$), mothers (Fisher-exact test; $P = 0.004$), and fathers (Fisher-exact test; $P = 0.011$) without MS. Adjustments for confounding significantly affected our results. However, even after adjustments, there appears to be a persistent higher than expected frequency of April births in the MS population.

Introduction

The month of birth effect on multiple sclerosis (MS) risk reported by numerous groups,[1–3] has been interpreted as evidence of environmental exposures during the prenatal period influencing the future risk of MS. A recent publication by Fiddes et al.[4] suggests that these results rather reflect the failure of adjusting for confounding factors that likely varied according to the areas and cohorts included in these studies. The authors pointed out that no earlier studies had adequately controlled for confounding factors, and they presented analyses showing that adequately adjusting for year and place of birth would reduce confounding and most likely eliminate the month of birth effect.[4] We have previously reported a month of birth effect for MS in Norway.[3] The results were adjusted for year, but not place of birth. In Norway, a unique national identification number allows identification of individual citizens and permits record linkage with the Norwegian Population Registry (Statistics Norway), making this an ideal area for performing these kinds of adjusted analyses. In this study, we have obtained year, month and county of birth for all available MS patients in Norway born during 1930–1979, as well as in (1) their siblings without MS, (2) mothers, (3) fathers, and (4) the background population. We have performed both unadjusted analyses and analyses adjusted for year and place of birth to determine to which degree confounding underlies our previous results.

Methods

The retrieval of data is described in detail in Data S1. A total of 6649 MS patients were included in the analysis. All patients were born in Norway between 1930 and 1979 (inclusive) and diagnosed with MS according to the diagnostic criteria of Poser et al.[5] or McDonald et al.[6] Date of birth and place of birth were available for the patients, as well as 5711 mothers, 5247 fathers, and 8956 unaffected siblings born within 5 years of the patients' birth. Siblings identified as MS patients were excluded. Information on month of birth, year of birth, and county of birth for the controls was obtained for the entire Norwegian population born between 1930 and 1979 (n = 2,899,260). All data from the controls were retrieved from the Norwegian Population Registry (Statistics Norway). We obtained data on month of birth from each county in Norway for this period (n = 19; Fig. S1) and also the month of birth distribution for each year. For unadjusted analysis, the month of birth distribution in the MS population was compared to the month of birth distribution in 1979 by Chi-square test. For yearly adjusted analysis (presented in our previous study), the distribution of month of birth in the MS population was compared with the distribution of month of birth in the corresponding Norwegian population (birth years 1930–1979). Further adjustments for both year of birth and place of birth, as suggested by Fiddes et al.,[4] were performed by comparing the distribution in the MS population in each county with the distribution of month of birth in the corresponding county for each year of birth (birth years 1930–1979). This adjustment was accomplished by applying a standardizing for each year, making the contribution of each year similar in the MS and control population. Each month was analyzed separately and compared with the other 11 months using a 2×2 table for the Chi-square test. Unadjusted P-values were corrected for 12 comparisons. Birth rates in April were compared between MS patients, siblings, mothers, and fathers using Fishers exact test. All 95% confidence intervals were calculated based on Poisson distributions for describing the variation in number of events during a period of time. Data were analyzed using IBM SPSS statistics 20 (IBM Corporation, Armonk, NY).

Results

We found 13% fewer MS births than expected in February (P = 0.0015; Bonferroni corrected P = 0.018), 10% more MS births than expected in April (P = 0.0083; Bonferroni corrected P = 0.0996) and 15% more MS births than expected in December (P = 0.00058; Bonferroni corrected P = 0.007), after performing analysis of month of birth in MS patients (n = 6649) without any adjustments, using births in 1979 in Norway as controls (Table S1, Fig. S2). When year of birth adjustment was applied for the whole population (as reported in our previous publication [3]) (Table S2, Fig. S3), the MS risk was 11% higher for those born in April compared to the other months (P = 0.0038; Bonferroni corrected P = 0.046). There were still 12% fewer MS births than expected in February (P = 0.0044; Bonferroni corrected P = 0.053), but the increase in MS births in December dropped to 4% and was no longer significant (P = 0.32). When analysis was performed with adjustments for both year of birth and county of birth, there were still 10% more MS births in April than expected (P = 0.00796; Bonferroni corrected P = 0.096). The reported decrease in MS births in February, however, fell to 9% and was no longer significant (P = 0.051) (Fig. 1, Table S3, Fig. S4). Siblings without MS, fathers, and mothers of MS patients, all had a month of birth distribution similar to that of their age-adjusted controls (Tables S4–S6; Figs. S5–S7). When month of birth of all MS patients was compared to their siblings, mothers or fathers without MS, the incidence of MS births was significantly higher in April (Fisher-exact test; P = 0.011) than the three other groups, while there were no significant differences in April births between siblings, mothers or fathers without MS or between these groups and the corresponding population. MS patients were consistently more frequently born in April than their siblings (Fisher-exact test; P = 0.011), mothers (Fisher-exact test; P = 0.004) and fathers (Fisher-exact test; P = 0.011) (Fig. 2).

Discussion

As suggested by Fiddes et al.,[4] our results were affected by adjustments for both year and place of birth. In the

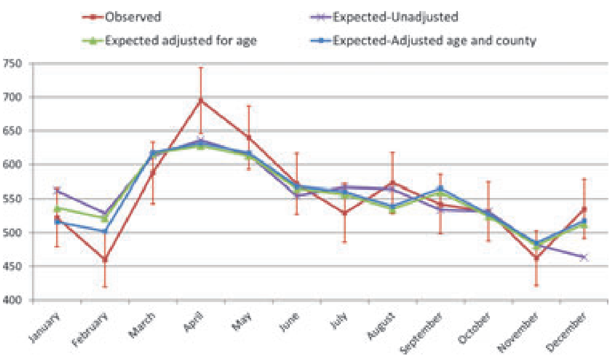

Figure 1. Seasonality of MS births in Norway, with 95% confidence intervals. Adjustments for age and county significantly altered the results. After adjustments for year of birth and county, there was no longer any significant decrease in MS births during any winter months. There was, however, still a 10% higher frequency of MS births in April ($P = 0.00796$) than would be expected.

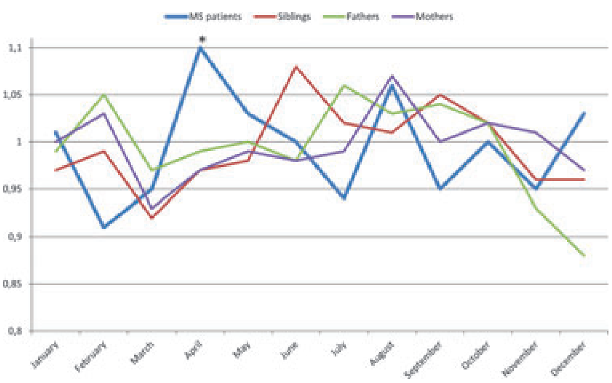

Figure 2. Observed/expected births in each month in Norway for MS patients, siblings without MS, mothers without MS, and fathers without MS. *MS patients were born significantly more often in April than their siblings ($P = 0.011$), mothers ($P = 0.004$) and fathers ($P = 0.011$).

unadjusted data, we found 13% fewer MS births than expected in February, 10% more than expected in April, and 15% more MS births than expected in December. Interestingly, the disproportionate findings in February and December were significant even after Bonferroni corrections, thus confirming that not adequately adjusting for confounders can lead to highly significant false positive results. After adjustment for year of birth, there was no longer any increase in MS births in December, while the increase in MS births in April became even stronger. When adjusting for both year and place of birth, we were no longer able to detect any significantly decreased risk of MS births in any winter months. Including place of birth also adjusted our expected curve, indicating that the decrease in February MS births previously reported by our group[3] may have been caused by confounding. However, even after these adjustments, the MS patients had a significantly higher birth rate in April than expected by chance. The result was, however, not significant after Bonferroni correction. Most groups have used Bonferroni corrections to adjust for multiple testing in month of birth studies.[1–3] This method gives a proper adjustment when analyzing uncorrelated data, but in a situation of correlated data, which we have for month of birth, Bonferroni corrections could yield an overly conservative estimate of the *P*-value.[7] The effect size of April births was, however, significant with Bonferroni corrections before adjusting for place of birth, and was almost unchanged after all adjustments were performed (10% more April births among the MS patients), suggesting a consistent result.

Both siblings without MS, and fathers and mothers of MS patients, had significantly lower birth rates in April than the MS patients, corroborating that the pattern of increased birth rate in April was unique for the MS group. Obviously, we cannot rule out that additional confounders not captured by place and year of birth, such as educational level, could have influenced our finding of a disproportionally high frequency of MS births in April. It is also possible that there exist variations in birth frequency within each county that would selectively affect MS births. An even more specific place of birth adjustment would, however, be difficult, as it would result in very small numbers of MS patients in each region.

To our knowledge, this is the first study on month of birth which performs both unadjusted and adjusted analysis on confounders in an actual dataset. Our analysis demonstrates that adjustment for confounders significantly alters the month of birth effects in MS and confirms the concerns expressed by Fiddes et al.[4] However, even after adjustments, MS patients in Norway appear to be born disproportionally more often in April than would be expected by chance, thus indicating that there may be a real month of birth effect in MS.

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Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Data retrieval.
Figure S1. Counties in Norway.
Figure S2. Observed and expected MS births in Norway, unadjusted analysis based on the 1979 birth cohort in Norway, with 95% confidence interval (n = 6649).
Figure S3. Observed and expected MS births in Norway 1930–1979, adjusted for year of birth, with 95% confidence interval (n = 6649).
Figure S4. Observed and expected MS births in Norway, adjusted for year of birth and county of birth with 95% confidence interval (n = 6649).
Figure S5. Observed and expected births for each month among siblings of MS patients in Norway with 95% confidence interval (n = 8956).
Figure S6. Observed and expected births among mothers of MS patients in Norway with 95% confidence interval (n = 5711).
Figure S7. Observed and expected births for each month among fathers of MS patients in Norway with 95% confidence interval (n = 5247).
Table S1. Observed and expected MS births in Norway, unadjusted analysis based on 1979 births in Norway (n = 6649).
Table S2. Observed and expected MS births in Norway, adjusted for year of birth (n = 6649).
Table S3. Observed and expected MS births in Norway, adjusted for year of birth and county of birth (n = 6649).
Table S4. Observed and expected numbers of monthly births in siblings of persons with MS compared to the general population (n = 8956).
Table S5. Observed and expected numbers of monthly births in fathers of people with MS (n = 5247).
Table S6. Observed and expected numbers of monthly births in mothers of people with MS (n = 5711).