THE AUTHORS REPLY

We appreciate the letters of Berlanga-Taylor et al. (1) and Ha (2), suggesting that vitamin D exposure, smoking, and medical contacts may confound the association we observed between antibiotic use and multiple sclerosis risk (3). Berlanga-Taylor et al. (1) note the pleiotropic effects of vitamin D and the hypothesized importance of adequate vitamin D levels during
central nervous system development. Although our data set lacks vitamin D measurement, we know that production of sun-induced vitamin D peaks when the ultraviolet index is above 3. This occurs during approximately half of the year in temperate areas such as Denmark. Previous studies have demonstrated the seasonality of births, with an excess of individuals born in spring and fewer in winter (4, 5).

In our cohort of 3,259 multiple sclerosis patients, we found modest variation in birth month, with the highest number of births in March–May and a peak-to-low ratio of 1.14 (95% confidence interval: CI: 1.03, 1.25). Among controls, who were matched on birth date confidence interval (CI): 1.03, 1.25). Among controls, who were born in March–May and a peak-to-low ratio of 1.14 (95% CI: 1.12, 1.19). The birth month distribution of multiple sclerosis patients in our data set was similar to that of the general population.

We found no evidence of seasonality in the date of multiple sclerosis diagnosis, with a peak-to-low ratio = 1.02 (95% CI: 1.00, 1.13), consistent with previous Danish studies (6). Still, seasonality of the multiple sclerosis diagnosis date may differ substantially from the seasonality of the first symptom date, which was not captured in our data set. A Scottish study found seasonal variation in hospitalizations for multiple sclerosis, with an excess of admissions in April and June and a decrease in March and October (7). This pattern may suggest that vitamin D affects multiple sclerosis activity, but other explanations are possible.

To address Ha’s concern that cigarette smoking may have confounded our results, we conducted a probabilistic bias analysis following published methods (8). We assigned a trapezoidal density distribution to the association between ever exposure to tobacco smoke and multiple sclerosis incidence, with a minimum odds ratio of 1.0, lower mode odds ratio of 1.3 (9), upper mode odds ratio of 1.5 (10), and maximum odds ratio of 2.0. On the basis of smoking prevalence among multiple sclerosis cases and controls provided by Ha, we assigned trapezoidal density distributions of (0.40, 0.43, 0.47, 0.50) to cases and (0.35, 0.38, 0.42, 0.45) to controls. With adjustment for confounding by smoking under these assumptions, our results for the association between ever penicillin use and multiple sclerosis risk changed from 1.21 (95% CI: 1.10, 1.27) (3) to 1.19 (95% simulation interval: 1.10, 1.28). Assuming a valid bias model, adjustment for confounding by smoking therefore would have had little impact on our results.

Ha also notes that unusual symptoms occurring before the first-reported multiple sclerosis symptom may hasten contact with the health-care system and increase the likelihood of antibiotic prescriptions. She therefore suggests adjusting for the number of total prescriptions as a proxy for extent of medical care. We are reluctant to do this, because a true association may be masked if multiple sclerosis cases require more medical attention because of infections.

Finally, Ha questions whether increased multiple sclerosis risk following antibiotic use could be explained by underlying mononucleosis initially treated by antibiotics. However, mononucleosis is not likely misdiagnosed as a urinary tract infection. Because our estimates were similar for urinary tract infection-specific antibiotics, such as pivmecillinam and other antibiotics, we conclude that underlying mononucleosis cannot solely explain our findings.

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REFERENCES