

## REPLY TO LETTER

**Reply to comment: Month of birth and risk of multiple sclerosis: confounding and adjustments**

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Dear Editor,

We thank Fiddes et al.<sup>1</sup> for their interest and comments to our manuscript.<sup>2</sup> Our main finding was an empirical demonstration of how inadequate adjustments for year and place of birth can generate false positive associations, even after Bonferroni corrections, thus supporting the results reported by Fiddes et al.<sup>3</sup> However, in our paper,<sup>2</sup> we also reported that although corrections for year and place of birth significantly altered the results, the effect size for April births was virtually unchanged. Fiddes et al.<sup>1</sup> raise concerns regarding our interpretation of this finding. First, we agree that we cannot rule out that even more rigorous place of birth adjustments could have influenced our results. As stated in our article,<sup>2</sup> there could be variations in birth frequency within each county that could selectively affect MS births. A more rigorous place of birth adjustment would, however, yield small cells with too few cases, as there are 428 municipalities in Norway, with a median number of inhabitants of less than 4500 people (<http://www.kartverket.no/Kunnskap/Fakta-om-Norge/Fylker-og-kommuner/Tabell/>). Second, Fiddes et al.<sup>1</sup> are also right that although the effect size of April births remained unchanged, the higher than expected frequency of April births was no longer significant with Bonferroni corrections after adjustments for year and place of birth. However, we disagree that Bonferroni corrections do not give a conservative estimate; if you are born in March, you cannot be born in any other month. Since almost all previous studies in the northern

hemisphere have found an increased risk in April/May,<sup>4</sup> our study could also be argued to represent a test of a hypothesis based on these observations; thus, there would be no need for correction for multiple comparisons all together. Furthermore, we also included three more groups for comparisons; siblings, mothers, and fathers without MS. As reported in our article,<sup>2</sup> we found a significantly higher than expected number of April births compared to all three groups, as well as compared to the unadjusted and adjusted background population. Thus, if the finding of excess of April births among MS patients is caused by confounding, there must be a systematic bias in ascertainment of controls working in the same direction in siblings, mothers, fathers, and the general population. Nevertheless, based on the possibility of residual confounding due to imperfect adjustment, our findings should not be interpreted as a proof of the existence of a month of birth effect in MS. Still, our persistent finding of a higher than expected number of MS births in April after adjustments leaves open the question of a possible genuine month of birth effect.

### Conflict of Interest

None declared.

### References

1. Fiddes B, Wason J, Sawcer S. Comment on: Month of birth and risk of multiple sclerosis: confounding and adjustments. *Ann Clin Transl Neurol* 2014;1:375.

2. Torkildsen Ø, Aarseth J, Benjaminsen E, et al. Month of birth and risk of multiple sclerosis: confounding and adjustments. *Ann Clin Transl Neurol* 2014;1:141–144.
3. Fiddes B, Wason J, Kemppinen A, et al. Confounding underlies the apparent month of birth effect in multiple sclerosis. *Ann Neurol* 2013;73:714–720.
4. Torkildsen Ø, Grytten Torkildsen N, Aarseth J, et al. Month of birth as a risk factor for multiple sclerosis: an update. *Acta Neurol Scand Suppl* 2012;195:58–62.