

Vitamin D intake and incidence of multiple sclerosis

To the Editor: We read with interest the article by Munger et al.¹ A protective effect of sunlight on multiple sclerosis (MS) risk was first suggested by Acheson et al.² Vitamin D is a potential mediator of this relationship. We are sympathetic to the hypothesis being tested³ by Munger et al. but have the following concerns.

1) NHS studied women age >30, but more than half of female patients with MS have onset below this age. Of those accrued, some 50,000 were excluded from analysis.¹ Was this done before testing the vitamin D hypothesis? What were the characteristics, when known, of exclusions for calculated vitamin D estimates compared to those retained? Perhaps MS risk can be altered after age 30, but earlier ages are implicated from migration studies.

2) 61 and then 130 questions were asked in the NHS and NHS II questionnaires. Was correction made for multiple analyses? Could the authors explain the assumptions and approach used to calculate the “*p* trend” statistic that forms the basis of this report?

3) The apparent association of low MS risk with intake of <400 units of vitamin D from supplements per day seems at odds with the recent report that those intakes of supplements have minimal effects on 25(OH)D levels. Furthermore, young women who took multivitamins were more likely to exercise outdoors. Multivitamin use correlated better with summer 25(OH)D levels than winter.⁵ Vitamin D production in the skin requires UVB that is not intense enough at latitudes >30 for at least 1 month each winter.

4) The association of MS with latitude seems unambiguous from Kurtzke’s US Veterans’ studies and from Australia.⁶ The lack of interaction with latitude in this study⁴ is surprising if vitamin D intake in adulthood is causally related to MS risk, since D levels and putative functional effects are dependent on latitude related UVB.

5) We note that the NHSII cohort had more MS “cases/person-yr” ($97/7.5 \times 10^5$) compared to the NHS cohort ($76/1.5 \times 10^6$). These data are difficult to compare. As age specific incidences seem less in NHSII, is there evidence for a decreasing incidence or prevalence in the areas surveyed?

6) How does the nurses’ D intake relate to that in the general population? Vitamin intake could vary by ethnicity. Did the definition of “white” include ethnic groups known to be resistant to MS? Recall bias has been reported within weeks of illness-associated events. Has the accuracy of four yearly reports been validated for the measures in this article?

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Reply from the Authors: We thank Ebers et al. for their interest in our study. We excluded women with an incomplete baseline food frequency questionnaire. This exclusion was made a priori following the same rules used in all previous dietary analyses in these cohorts. Adjustment for multiple analyses in our study was not necessary as only two measures of vitamin D intake were considered: the combined amount of vitamin D intake from food and from supplements. The *p* for trend was calculated using a

proportional hazards regression model using the median intake values for each category of vitamin D from food or supplements as a continuous variable. This method tests the overall null hypothesis that vitamin D intake is unrelated to risk of MS without any specific assumptions.

In contrast with the results of Vieth et al.⁵ quoted by Ebers et al., in a substudy among 323 healthy women from the NHS cohort, we found that vitamin D intake at levels below 400 IU does increase 25(OH)D levels. Average winter plasma levels of 25(OH)D were positively correlated with levels of vitamin D intake: 40 nmol/L in the lowest quintile of intake (median = 108 IU), 55 nmol/L in the third quintile (median = 301 IU), and 70 nmol/L in the highest quintile (median = 703 IU). Further, in our cohorts, the association between vitamin D intake from supplements and risk of MS was not materially altered by adjustment for physical activity (unpublished data).

The women in the NHS cohort are older than those in the NHSII cohort and because of modest overlap between the two cohorts, age-specific incidence rates are difficult to compare. However, age-specific incidence rates are slightly higher, not lower, in NHS II (unpublished data). Further, the increasing use of MRI may reduce the time between onset of MS and diagnosis, possibly causing spurious changes in incidence rates.

The nurses’ intake of vitamin D is similar to that of women in other US cohort studies.⁷ Race was self-reported and “White” did not include ethnic groups with low risk of MS.

The lack of significant interaction between latitude and vitamin D in our study may be explained by the insufficient power to detect such an interaction.

As this was a prospective study, recall bias was not of concern as none of the women had MS or MS symptoms when completing the food frequency questionnaires.

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