Vitamin D deficiency is an etiological factor for MS – Commentary

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In the present issue’s ‘Controversies in Multiple Sclerosis’, the authors argue the merits of vitamin D’s role in multiple sclerosis (MS). Manousaki and Richards (the ‘Yes’ camp), on one hand, argue that there is significant evidence for vitamin D’s role in MS, both directly in the form of cohort studies assessing contemporaneous and historical vitamin D levels with subsequent MS risk, and indirectly via the Mendelian randomisation models. Langer-Gould and Lucas (the ‘No’ camp), on the other hand, argue that vitamin D does not satisfy the criteria of causality very well on a number of points. While we have our biases and beliefs, we shall endeavour to provide a fair commentary on the two articles in this controversy.

The ‘No’ camp is stating that ‘If vitamin D deficiency causes MS, as smoking causes lung cancer, then we would expect this to be true across all racial/ethnic groups’. This inferences that they view vitamin D as being necessary in order to cause MS. However, a more appropriate model for a complex disease as MS is one where causal factors are neither necessary nor sufficient. The causal pie model, proposed by Rothman et al., conceives of the risk structure leading to a health outcome as being composed of different ’pieces’, each adding up to the minimum threshold for disease. This model implies that different people have different pie pieces, and moreover, the pieces can influence each other (biologic basis for interaction). This model explains neatly that vitamin D deficiency can be a causal factor in MS despite this association being absent in American Blacks and Hispanics.
case of vitamin D in MS satisfies the criteria. In terms of consistency, vitamin D and sun exposure have been remarkably consistent, both directly – in the form of numerous incident case-control and cohort studies – and indirectly via the well-described latitudinal gradient.

Specificity is an issue which Langer-Gould and Lucas point out, given that vitamin D has been implicated in a number of conditions. Bradford Hill and contemporaries regarded risk factors to be more convincing if they were ‘associated with one, or at most a few diseases’. This construction of specificity, however, has changed dramatically to reflect the fact that agents can impact upon multiple systems across the body. Vitamin D, like tobacco, is a multifunctional agent with a diversity of effects, well beyond its initial remit in bone health to having a role in adaptive and innate immunity, as well as potentially impacting on gene expression via vitamin D response elements. The more modern interpretation of specificity, then, is not that an exposure is specific to only one condition, but rather that its effects are specific in terms of what is affected, the nature of the association and what is expected, and that impact is evident only in those at risk. In these respects, then, the specificity of vitamin D is manifest.

Two additional elements of the Bradford-Hill criteria are dose-dependency and biological plausibility. In both of these respects, vitamin D is well supported by the data. A number of studies have demonstrated beautiful dose-dependency, as reviewed previously. Similarly, for biological plausibility, vitamin D has several possible modes of action. At a minimum, vitamin D acts on both the adaptive and the innate immune responses. Beyond this, the increasing number of cell types with vitamin D receptors, and genes with vitamin D response elements, suggests that vitamin D has a potent role in a variety of cell processes, including some yet to be identified. Coherence with laboratory models is also supportive, including in vitro evidence for the immunomodulatory effects of vitamin D, as well as results showing the impacts of vitamin D supplementation on the prevention/reversal of disease in the animal model of MS – experimental autoimmune encephalomyelitis.

Mendelian randomisation was discussed as alternative evidence for causation by both authors. This approach makes use of genes which are strongly related to the exposure of interest – in this case, the genes involved in vitamin D synthesis and catabolism serve well for the purpose – and associating these with the outcome. Since the genes are randomised during conception, the potential confounding effects that would be an issue for sun exposure and vitamin D intake of the patient, or even those of the mother while the patient was in utero, are removed, leading to an unbiased association of the exposure with the outcome. Despite vitamin D-related genes predicting a low percentage of the variance, the evidence from Mendelian randomisation studies of vitamin D in MS thus far have indicated that genotypes leading to higher vitamin D are protective against MS, while those leading to lower vitamin D are associated with greater MS risk.

As the reader would be aware, we are in favour of a role for vitamin D in MS, though we are not so biased in this viewpoint as the tobacco companies were in their support of tobacco. We believe that, taken together, there is a wealth of evidence indicating that vitamin D is a causal factor of MS. It is by no means a necessary component of the disease, but even smoking is not a necessary component of lung cancer. The literature would indicate that vitamin D, in genetically susceptible individuals, alongside other elements of their causal pies, is a risk factor for MS.

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