Vitamin D deficiency is an etiological factor for MS – Yes

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Epidemiological studies indicate that the prevalence of multiple sclerosis (MS) increases at higher latitudes, where sunlight exposure is lower. Since circulating levels of vitamin D, as measured by 25-hydroxyvitamin D (25(OH)D) levels, are partially derived from sunlight exposure, one proposed risk factor for MS is low vitamin D levels. If low vitamin D levels did cause MS, this would have important public health implications, since vitamin D insufficiency, as defined as 25(OH)D levels <50 nmol/L, is common, affecting up to 40% of the population in developed countries, and vitamin D supplementation is relatively safe and inexpensive.

However, epidemiological associations do not allow for inferences of causality. One of the main reasons precluding a causal interpretation of such evidence is that vitamin D levels are highly confounded. Low vitamin D levels have been associated in observational epidemiology studies with ethnicity, socioeconomic status, smoking, body mass index, several psychiatric diseases, metabolic disease, allergic disease, cancer, immune diseases, and of course bone disease. While it may be possible that low vitamin D levels influence all of these outcomes, it also remains possible that vitamin D is a marker for confounding factors, or poor health in general. Furthermore, such associations can be influenced by reverse causation, where the disease leads to less time outdoors, less sunlight exposure, and lower vitamin D levels. Given these concerns, some skepticism is required when assessing evidence from vitamin D epidemiology.

Nevertheless, large, well-conducted observational epidemiology studies have consistently demonstrated a relationship between low vitamin D levels and increased risk of MS. This includes evidence from the Nurses’ Health Study, which reported that the risk of developing MS was significantly reduced in women taking ≥400 international units/day of vitamin D (relative risk (RR) 0.59, 95% confidence interval (CI) 0.38–0.91). A large, prospective case–control study involving more than seven million US military recruits of European ancestry, with 25(OH)D levels <50 nmol/L, found an almost twofold increased risk for later development of MS. The most recent epidemiological evidence in support of the involvement of vitamin D in MS etiology comes from two nested case–control studies. In the first study, which was based on two Swedish population–based biobanks with 291,500 samples from 164,000 persons, the authors investigated the association between 25(OH)D levels and the risk of MS using blood samples collected prospectively and during gestation. They identified prospectively collected samples from 192 MS cases and gestational samples from 37 pregnant mothers where the offspring had subsequently developed MS. Levels of 25(OH)D ≥75 nmol/L in prospectively collected samples were associated with a decreased risk of MS (odds ratio (OR) 0.39, 95% CI 0.16–0.98), but no discernible effect on MS risk was found in the offspring exposed to gestational 25(OH)D levels ≥75 nmol/L (OR 1.8, 95% CI 0.53–5.8). In a more recent nested case–control study using the Finnish Maternity Cohort, the authors compared 25(OH)D levels in serum samples from 1092 women diagnosed later with MS to those of 2123 women without MS who gave birth around the same time and in the same geographic region. They reported that each 50 nmol/L increase in 25(OH)D levels was associated with a 39% reduced risk of MS (RR 0.61, 95% CI 0.44–0.85). Women with vitamin D deficiency, defined as 25(OH)D levels <30 nmol/L, had a 43% higher MS risk (RR 1.43, 95% CI 1.02–1.99), compared to women with adequate 25(OH)D levels (≥50 nmol/L) and 27% higher risk (RR 1.27, 95% CI 1.07–1.50), compared to women with insufficient 25(OH)D levels (30–50 nmol/L). An additional line of evidence for a temporal effect of vitamin D on MS comes from a nested case–control study using the Danish Neonatal Screening Biobank, which showed that the future risk of MS in neonates decreased by 26% for each 25 nmol/L increase in 25(OH)D. Combining the results of the three above adult studies, the risk for future MS appears to be greatest in the vitamin D deficient group.
D–deficient individuals, although there is evidence for a protective effect of 25(OH)D levels greater than those typically considered sufficient (>99 nmol/L).\(^5\) The above observation provides relatively consistent evidence that vitamin D may influence MS risk.\(^9,10\)

The next logical step to test a causal relationship between vitamin D and MS would be a disease prevention randomized controlled trial. Such a trial is unlikely to ever be accomplished. This is because the sample size required to test such an effect would be extremely large, given that MS is uncommon. Furthermore, it would likely need to be started in childhood (or in utero) with follow-up lasting decades. Since vitamin D is not patentable, such a trial would be reliant on the limited means of the public purse.

One way to provide evidence supporting or contradicting causality of a modifiable risk factor is through Mendelian randomization. Mendelian randomization uses genetic determinants of modifiable risk factors, such as vitamin D, as unbiased proxies for the risk factor to help determine the causal relationship between the exposure and disease. This provides two main advantages. First, since alleles are randomly assigned at conception (Mendel’s second law), this breaks potential association with confounding factors, much like randomization achieves in a randomized controlled trial. Second, since alleles are inherited at birth, they provide an estimate of lifelong exposure to the risk factors and cannot be influenced by reverse causation, where the disease would influence the risk factor. Nonetheless, Mendelian randomization studies can be biased by pleiotropy, wherein the alleles influence the disease, independent of the exposure.

Three recent Mendelian randomization studies have provided evidence that lowered vitamin D levels increase the risk of MS. First, Mokry et al.\(^11\) demonstrated that genetically lowered 25(OH)D levels by 1 standard deviation doubled the risk of MS (OR 1.0, 95% CI 1.7–2.5) in ~15,000 MS cases and 24,000 controls. A separate Mendelian randomization\(^12\) study in a different population again demonstrated that lowered vitamin D levels increased risk of MS. Finally, a Mendelian randomization meta-analysis of pediatric-onset MS found that lowered 25(OH)D levels increase the risk of MS.\(^13\) These three studies greatly decrease the probability that the relationship between 25(OH)D levels and MS is confounded. In contrast, nearly all other Mendelian randomizations testing a causal effect of vitamin D on disease have generated null results.

In all areas of medicine, it is helpful to take a triangulation approach to inferences of causality. This approach relies upon using different study designs to assess causal relationships. If all study designs have their own potential sources of bias, yet these sources of bias are orthogonal, and the different study designs yield the same result, it increases the validity of the findings. In the case of vitamin D and MS, observational epidemiology may be biased by confounding, yet results from Mendelian randomization greatly reduce this possibility.

Taken together, the above evidence supports the statement that vitamin D deficiency is an etiologic factor for MS. Ideally, a large, long-term randomized controlled trial would be completed to provide additional evidence, but such a trial is unlikely to be completed. Given the severity of MS, we therefore suggest that clinical guidelines should aim to ensure vitamin D sufficiency for individuals at elevated risk of MS, such as offspring and siblings of affected individuals. Doing so might prevent a serious disease.

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Vitamin D deficiency is an etiological factor for MS – No

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If vitamin D deficiency causes multiple sclerosis (MS), as smoking causes lung cancer, then we would expect this to be true across all racial/ethnic groups, and we would expect populations with high prevalence of vitamin D deficiency to have high incidence of MS. Neither is true; indeed, the evidence is quite the contrary.

The guidelines of the US Surgeon General, developed to evaluate smoking as a cause of lung cancer, are widely used to make public health decisions, particularly when large-scale randomized controlled trials are unethical or infeasible. There are 5 criteria: (1) consistency, (2) strength, (3) specificity, (4) temporal relationship and (5) coherence of the association. Most, if not all, criteria should be met. For instance, smoking causes lung cancer and other diseases, just as vitamin D deficiency purportedly causes several diseases, and thus neither would meet the criterion for specificity. However, smoking as a cause of lung cancer satisfies the other four criteria, while vitamin D deficiency as a cause of MS does not clearly satisfy any.

The first criterion, consistency, requires that findings are consistent across different study types, in different locations and across different populations, for example, race/ethnicity. This is not evident for the association between vitamin D deficiency and MS.

The starkest example is in Asian populations. In China, the prevalence of MS is very low, yet vitamin D deficiency (25OHD < 50 nmol/L) and insufficiency (<75 nmol/L) are common at 69% and 94%, respectively. Similarly, the prevalence of vitamin D deficiency in the United States is 65%, 44% and 14% in blacks, Hispanics and whites, respectively; this does not correspond to the incidence of MS. Compared to whites, the incidence of MS is less than half in Hispanics, over 80% lower in Asians and slightly higher in blacks residing in Southern California.

In the only multi-racial population-based study of 25OHD levels and incident MS, there was a significant association in whites, but not in blacks or Hispanics, despite good sample size in all racial/ethnic groups. In a prospective cohort study using samples from the US Army serum repository, 25OHD levels were inversely associated with MS risk in whites, but not in blacks.

These inconsistencies are in stark contrast to smoking and lung cancer, where the associations are consistent.