Sunlight exposure exerts immunomodulatory effects to reduce multiple sclerosis severity

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Multiple sclerosis (MS) disease risk is associated with reduced sun-exposure. This study assessed the relationship between measures of sun exposure (vitamin D [vitD], latitude) and MS severity in the setting of two multicenter cohort studies ($n_{NationMS}$ = 946, n_{BIONAT} = 990). Additionally, effect-modification by medication and photosensitivity-associated *MC1R* variants was assessed. High serum vitD was associated with a reduced MS severity score (MSSS), reduced risk for relapses, and lower disability accumulation over time. Low latitude was associated with higher vitD, lower MSSS, fewer gadolinium-enhancing lesions, and lower disability accumulation. The association of latitude with disability was lacking in IFN-β–treated patients. In carriers of *MC1R*:rs1805008(T), who reported increased sensitivity toward sunlight, lower latitude was associated with higher MRI activity, whereas for noncarriers there was less MRI activity at lower latitudes. In a further exploratory approach, the effect of ultraviolet (UV)-phototherapy on the transcriptome of immune cells of MS patients was assessed using samples from an earlier study. Phototherapy induced a vitD and type I IFN signature that was most apparent in monocytes but that could also be detected in B and T cells. In summary, our study suggests beneficial effects of sun exposure on established MS, as demonstrated by a correlative network between the three factors: Latitude, vitD, and disease severity. However, sun exposure might be detrimental for photosensitive patients. Furthermore, a direct induction of type I IFNs through sun exposure could be another mechanism of UV-mediated immune-modulation in MS.

sunlight | multiple sclerosis | vitamin D | latitude | melanocortin 1 receptor

Multiple sclerosis (MS), characterized by demyelinating lesions, is the most common neuroinflammatory disease of the central nervous system and presumably of autoimmune origin (1). In most cases, the disease is diagnosed at a young age, predominantly occurs in women, and follows a relapsing-remitting course, which can be superseded by a secondary, progressive stage (2). Etiologically, environmental factors have been shown to play an important role (3) and insufficient sunlight exposure has been suspected to be critical for the initial development of MS (4). The best characterized mediator of ultraviolet radiation (UVR)-dependent effects is vitamin D (vitD), which is generated from its precursor 7-dehydrocholesterole (7-DHC) in the skin, further metabolized in the liver and kidney, and that exerts its function in its active form 1-α,25-dihydroxyvitamin D_3 [$1\alpha,25(OH)_2D_3$], also known as calcitriol (5). Precursors of active vitD can also be found in food in the form of ergocalciferol (or vitamin D_2), which is, however, of little relevance for total serum vitD levels (6). For MS, low vitD levels have been shown to be associated with disease risk (7, 8) and Mendelian randomization studies hint toward a causal role for vitD (9, 10). However, it is possible that alternative UVR-dependent pathways play a role as well (11). A study by Langer-Gould et al. (12) suggested that serum vitD is only a risk factor for MS in Whites, but not in people of color, although lifetime UVR-exposure was associated

Significance

Low sunlight exposure and low vitamin D (vitD) levels are risk factors for the development of multiple sclerosis. However, there is still an ongoing debate, whether sunlight and vitD also modulate disease severity and worsening. Observational studies suggested vitD-dependent effects, but prospective supplementation studies have so far been inconclusive and reverse causality cannot be excluded as a source of bias. By using the sun-exposure measures vitD and latitude, we show correlations between vitD/latitude, vitD/disease severity, and latitude/disease severity in two multicentric cohorts. Although vitD cannot be proven as the causal factor, we provide evidence for clinically relevant effects of sunlight exposure. Furthermore, this study suggests sunlight-triggered pathways other than vitD could play additional and modulatory roles, as well.

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