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Using a Mendelian randomization approach to explore a causal relationship between vitamin D and nonmelanoma skin cancer

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In this issue of the BJD, Winsløw *et al*.[1] examine the causal association between 25-hydroxyvitamin D [25(OH)D] levels and nonmelanoma skin cancer (NMSC) using a Mendelian randomization (MR) approach. MR is a method that uses genetic variation known to be associated with a modifiable exposure (in this case, serum vitamin D levels) to examine the causal effect of that exposure on a disease (in this case, NMSC). Given that genetic variants are presumed to be assigned randomly by nature, the association is analysed as if it were a randomized trial. Thus, MR can overcome the innate limitations of observational studies, such as residual confounding, and provide causal inferences between exposure and outcome.[2]

MR is a potentially powerful tool to assess the causality of serum 25(OH)D levels on NMSC risk using single-nucleotide polymorphisms (SNPs) associated with serum 25(OH)D levels as a surrogate for serum 25(OH)D. Winsløw *et al*. used data from two Danish cohorts, and genotyped subjects for four SNPs identified from prior genome-wide association studies associated with serum 25(OH)D levels, and found that genetically determined high serum 25(OH)D levels did not appear to protect against NMSC.

Although MR is a powerful tool, it makes certain assumptions, the violation of which impact the interpretation of results. MR assumes that: (1) the genetic variant is associated with the exposure; (2) the genetic variant influences the outcome only through the exposure; and (3) the genetic variant is independent of confounders. However, these assumptions are not always carefully assessed, and they may not hold.[2] For example, if a genetic variant independently influences both the exposure of interest and another factor – a phenomenon called pleiotropy – then assumption (2) would be violated. Similarly, if a second variant associated with a confounding factor is located nearby and is in linkage disequilibrium with the first, exposure-related variant, then assumption (2) would again be violated. Winsløw *et*

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Conflicts of interest

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al. note these potential concerns and performed several analyses to rule out putative pleiotropic or colocalization effects. In addition, population stratification (the nonrandom distribution of alleles in the population) could violate assumption (3), although Winsløw *et al.*'s relatively homogeneous study population reduces the risk and magnitude of such bias. Aside from bias, many MR studies can have low power, due to the low correlation between many genetic instruments and exposure. In this case, even though the F statistic is quite large, indicating that the authors' genetic instrument is valid (i.e. it is certainly associated with circulating 25(OH)D levels), the genetic instrument explains only 1% of variability in 25(OH)D levels. Still, given the large number of genotyped NMSC cases and controls, the MR estimates of the effect of circulating 25(OH)D on risk of NMSC are precise enough to rule out the large effects seen using measured 25(OH)D.

Defining a causal relationship with an exposure can help optimize prevention and management of NMSCs. Winsløw *et al.* provide an important piece of evidence that vitamin D may not be protective against NMSC development, and the association between vitamin D and NMSC risk is confounded by ultraviolet radiation (UVR). UVR is a major risk factor for NMSC,[3] and is needed for vitamin D synthesis in keratinocytes. While observational studies have reported that higher vitamin D levels are associated with NMSC risks, evidence from animal and in vitro studies supports antiproliferative and proapoptotic effects of vitamin D on keratinocytes, which may protect against NMSC.[4,5] Winsløw *et al.*'s findings, showing no causal association between genetically defined 25(OH)D levels and NMSCs, are consistent with previous reports that higher prediagnostic serum 25(OH)D levels are associated with NMSC risk.[6] The clinical implication of their work is that higher serum vitamin D levels may not play a role in primary NMSC prevention.

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