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Author's reply

Giovannucci enquires whether intervention studies were long enough to allow full expression of health benefits associated with high serum 25-hydroxyvitamin D (25[OH]D) concentrations. Recent meta-analyses that compared top to bottom quantiles of 25(OH)D found summary relative risks of 0·67 (95% CI: 0·59–0·75) in 16 studies of type 2 diabetes[1] and of 0·66 (0·54–0·81) in eight studies of colorectal cancer.[2] We plotted relative risks of diabetes and colorectal cancer occurrence reported by prospective studies against follow-up duration (figure). For diabetes, despite follow-up ranging from 1–22 years, the protective effect of high 25(OH)D remained constant over time. For colorectal cancer, follow-up of 6–19 years suggest that, with time, high 25(OH)D has a steadily lower ability to protect against this cancer. Therefore prospective studies do not support the duration hypothesis.

Giovannucci mixes up causal inference for disease risk factors and for drugs. The carcinogenicity of tobacco, asbestos, and HPV has never been tested in randomised trials, but few would doubt that causal relationships exist between chronic exposure to these agents and cancer. Indeed, establishment of causal associations between many agents and diseases is challenging. To this end, scientific institutions (eg, the European Food Safety Agency, and the US Institute of Medicine) have developed batteries of methods for critical appraisal of scientific data. Also, natural experiments show that reduction of exposure to truly noxious agents leads to reductions in the burden of diseases due to these agents. Such results have been reported for artificial UV tanning devices.[3] For drugs (note that vitamin D is a drug), randomised trials represent the gold standard for verification of causal relationships, and claims for health benefit must be supported by intervention studies. For instance, some prospective studies recorded reduced risk of cardiovascular disease with use of hormone replacement therapy.[4] If the Women's Health Initiative trial[5] had been done before granting marketing authorisation, many women would probably not have incurred cardiovascular side-effects associated with long-term use of these hormone preparations. Giovannucci contends that one should not consider results of intervention studies that were not purposely designed to test relevant biological hypotheses. If this statement were followed, then results of randomised trials not associated with the relevant biological hypothesis being assessed should be ignored, such as adverse events not explicable by the hypothesis.

Holick and Grant question the applicability of the medical model of evidence to natural compounds, but many drugs are natural, such as insulin, and their efficacy is tested in randomised trials. Of the nine articles we cited documenting 25(OH)D reductions associated with acute inflammatory episodes, and of all our discussion of the inflammation-vitamin D hypothesis, Holick and Garland picked up one sentence related to two articles on critically ill patients, which they misread.[6,7] The sentence concerned does not allege that in these two studies authors suggested a causal link between low 25(OH)D and inflammation, but that data reported in these articles support our hypothesis of an association between inflammation and low 25(OH)D in critically ill patients. In the trial by Van den Berghe et al,[6] compared with healthy controls matched for age, sex, and BMI, 22 critically ill patients had much higher serum concentrations of inflammatory cytokines and their 25(OH)D was half of the concentration of those with low or healthy inflammatory cytokines. For both articles, Holick and Grant missed the crucial point that, despite the low 25(OH)D concentrations of these patients, vitamin D supplementation could not appreciably increase 25(OH)D, most likely because of deregulation of the vitamin D metabolism associated with inflammation.[7] Holick and Grant also missed that the serum tumour necrosis factor and interleukin 1 concentrations were unaltered in the Van den Berghe trial.[6] They asserted that the decrease in CRP and interleukin 6 recorded in the trial was dose-related, which is impossible to assess because there were only two randomisation groups. A dose-related response could have been assessed by a recently published randomised trial that assigned 328 African Americans in four groups of escalating doses of vitamin D supplementation (placebo,

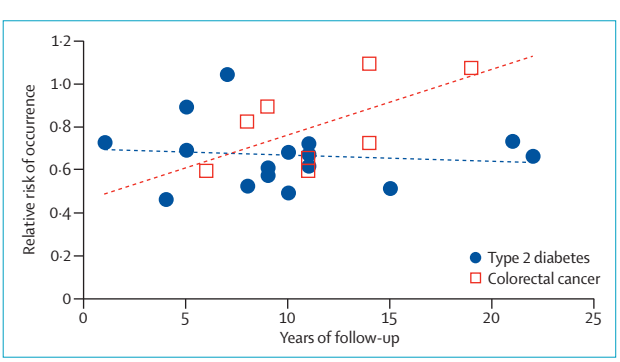

Figure: **Relative risk of type 2 diabetes and colorectal cancer in prospective cohort studies according to duration of follow-up**

25, 50, and 100 μg/day), but the trial found no change in circulating inflammatory markers.[9]

Naughton and Petroczi argue that we have probably not yet found the vitamin D form that would cause health benefits. We are sceptical about this possibility because during the past 50 years basic science experiments and animal studies have produced many mechanistic hypotheses supporting the putative positive health effects of many vitamins, antioxidants, and their diverse forms. By contrast, results of intervention studies have invariably shown that long-term intake of these compounds brings no health benefit, and can even reduce life expectancy.[10]

We declare that we have no competing interests.

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