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Vitamin D Level, Respiratory Tract Infections, and Controlled Trials

Proponents of evidence-based medicine argue that conclusions of treatment effects should be based on controlled trials and not on observational studies. Nevertheless, based on the correlation between serum vitamin D level and infections, Ginde et al¹ proposed that vitamin D supplementation may reduce the incidence of upper respiratory tract infections.

Nutrition is associated with a wide range of lifestyle variables, and there is a great risk of residual confounding caused by inadequate adjustments for complex social and environmental exposures acting over a person's life.² Residual confounding may explain, for example, the divergent findings in observational studies and controlled trials on vitamin E.² Therefore, great caution should be exercised when interpreting correlations between serum vitamin D levels and health outcomes.

Furthermore, certain randomized controlled trials on multivitamin supplements are relevant when considering the effect of vitamin D supplementation on respiratory tract infections. If a multivitamin supplement has no effect on infections, it seems justified to conclude that there is a lack of effect by each constituent of the supplement. In contrast, if a multivitamin supplement does have an effect, we cannot draw any specific conclusions because the effect can be caused by any single substance or the combination of several of them together. In this respect, the implications are quite different when the result of a multivitamin trial is positive or negative. Two multivitamin trials with 748 and 652 elderly participants included 160 and 200 IU/d of vitamin D in their supplements.^{3,4} The supplements had no effect on the incidence of upper or lower respiratory tract infections.^{3,4} Thus, following this logic, these trials indicate that increasing vitamin D intake has no effect on the incidence of respiratory tract infections in the elderly people studied.

Finally, the comment by Ginde et al¹ on vitamin C is somewhat inaccurate. Although regular vitamin C (ascorbic acid) supplementation has not reduced the incidence of the common cold in ordinary people, it has con-

sistently reduced the duration of colds that occurred during the supplementation period. In adults, the reduction in common cold duration was 8% and in children it was 13%.⁵ Therefore, we concluded in our Cochrane review that the therapeutic effects of vitamin C should be further studied, in particular in children because no therapeutic trials with children have been carried out, although the effect of regular vitamin C has been greater in them.⁵

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In reply

We thank Dr Hemilä for this correspondence. The Cochrane review by Douglas et al¹ supported our statement that vitamin C has a limited role in prevention and treatment of colds and concluded that the prophylactic or therapeutic use of vitamin C does not reduce the incidence or severity of colds. There was a modest reduction (approximately 12 hours) in duration of colds with prophylactic but not therapeutic use of vitamin C, but as those authors conclude, "there seems no justification for routine mega-dose vitamin C supplementation in the normal population" and "therapeutic supplementation has not been shown to be beneficial."¹

We agree that observational data have limitations, particularly in nutrition research. As demonstrated by the vitamin E experience,² randomized controlled trials may provide different conclusions than suggested by preceding observational studies, often because of incompletely controlled confounding. In addition, as we discussed,³ vitamin D has a particular risk for reverse causation—that is, individuals with lung disease or respiratory tract infections are more likely to remain indoors and consequently have lower vitamin D synthesis. However, data from the 2 trials cited by Dr Hemilä,^{4,5} which did not find a reduction of respiratory tract infection with a vitamin D dose of 200 IU/d or lower, are notably limited by the low vitamin D dose contained in these supplements.

Conversely, a randomized controlled trial of bone loss in postmenopausal black women found that 7.7% of women randomized to vitamin D supplementation, 800 to 2000 IU/d, reported respiratory symptoms over the 3-year follow-up, compared with 25.0% in controls.⁶ Another substudy of a randomized controlled trial for fracture prevention found

a non-statistically significant reduction in wintertime infection in participants randomized to vitamin D supplementation, 800 IU/d (adjusted odds ratio, 0.90; 95% confidence interval, 0.76-1.07)).⁷ Although promising, these studies were post hoc analyses of adverse events reported in skeletal health trials. Since serum 25-hydroxyvitamin D levels in the US population are relatively low,⁸ vitamin D supplementation of at least 1000 to 2000 IU/d would be needed to raise levels above 30 to 40 ng/mL (to convert to nanomoles per liter, multiply by 2.496), which we believe is necessary for improved immune function and reduction of respiratory tract infection. A recently published pilot randomized controlled trial of 2000-IU/d vitamin D did not find a reduction of respiratory tract infections, but it was significantly limited by small sample size, delayed enrollment, incomplete recruitment, and high baseline serum 25-hydroxyvitamin D levels.⁹ We are planning larger randomized controlled trials in high-risk populations to understand whether the observed association between vitamin D and respiratory tract infection is causal and reversible.

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Fluconazole Use as an Important Risk Factor in the Emergence of Fluconazole-Resistant *Candida glabrata* Fungemia

We read with interest the article by Lee et al,¹ who conducted a case-case-control study to evaluate risk factors for fungemia caused by fluconazole-resistant *Candida glabrata*. The authors identified previous fluconazole use (and linezolid use)

as a significant risk factor for fluconazole-resistant *C glabrata* fungemia, whereas cefepime and metronidazole use were independent risk factors for fluconazole-susceptible *C glabrata* fungemia.

Although with a smaller number of patients, a similar investigation with the same study design was previously carried out by our group.² In accordance with Lee et al,¹ our study had identified prior fluconazole exposure as the most important predisposing factor for subsequent *C glabrata* fungemia due to a less-susceptible isolate. We found that diabetes mellitus and central venous catheters were other independent risk factors for fungemia caused by a fluconazole-less-susceptible isolate, whereas previous surgery and central venous catheterization were independent risk factors for fungemia due to a susceptible isolate; unfortunately, these variables do not appear to have been analyzed by Lee et al.¹ With regard to the antibiotic use, we did not find a significant association between fluconazole-resistant *C glabrata* fungemia and the use of any antibiotics; it was not possible to assess the impact of linezolid use because this drug was not largely used in Italy during the first years of our study. We found that cephalosporin (and glycopeptide or aminoglycoside) use was significantly associated with fluconazole-susceptible *C glabrata* fungemia, but in univariate analysis only.

We agree with the authors' hypothesis that previous fluconazole use may promote de novo resistance through the CgPDR1-dependent³ upregulation of drug efflux pump-encoding genes CgCDR1 and CgCDR2 and also CgSNQ2.⁴ In fact, in our study,² expression of these genes was upregulated in both the fluconazole-resistant and fluconazole-susceptible-dose-dependent isolates, but not in the fluconazole-susceptible isolates, making it likely that their reduced fluconazole susceptibility was acquired or induced following drug exposure. Our recent findings⁵ showed that CgPDR1 hyperactive alleles not only conferred a selective growth advantage compared with the wildtype allele in the murine model of systemic candidiasis in the absence of fluconazole, but also contributed to fluconazole treatment failure in the mouse model.

Finally, in our study,² we observed that 6 of 7 patients receiving inadequate initial antifungal treatment died, and 5 of these patients were infected by a fluconazole-resistant isolate and empirically treated with fluconazole, supporting the conclusion that reduced susceptibility of *C glabrata* to fluconazole contributes to a poor outcome after invasive infection, especially in conjunction with inadequate empirical antifungal treatment. When considering the larger population size studied by Lee et al,¹ it would have been interesting if they had extended their analysis to this important issue.

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