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Statistical problems in the vitamin D and respiratory infection meta-analysis

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The meta-analysis on vitamin D and respiratory infections by Martineau et al. [1] has two major problems: 1) the use of the odds ratio (OR) as the effect measure and 2) not exploring potential causes for the highly significant heterogeneity between the trials.

Altman et al. pointed out that “The odds ratio should not be interpreted as an approximate relative risk [RR] unless the events are rare in both groups (say, less than 20-30%)”[2]. Acute respiratory infections are not rare. In Figure 2 of the Martineau et al. meta-analysis, only 2 of the 24 trials had event rates less than 20% in both groups [1]. I reproduced their Figure 2 using the random effects Mantel-Haenszel approach and calculated OR=0.82 (95% CI 0.72 to 0.95) for the 24 trials. The minor discrepancy with their published OR is explained by adjustments [1]. The Figure 2 data gives RR=0.92 (95% CI 0.87 to 0.98). Thus, the OR suggests that the incidence of respiratory infections might be reduced by 18%, but the RR shows that 8% reduction is the valid estimate. Thus, OR exaggerates the effect of vitamin D by over two times.

When there is highly significant heterogeneity, researchers should explore causes for the heterogeneity. Of the included studies, Camargo et al. [3] and Manaseki et al. [4] found significant effect of vitamin D on the risk of respiratory infections. However, the former was carried out with Mongolian schoolchildren and the latter with 1-36 months old children in Afghanistan. If those two trials are removed from the meta-analysis in a sensitivity analysis, the evidence of heterogeneity decreases substantially (from P=0.001 to P=0.04) and the evidence of benefit from vitamin D vanishes to RR=0.95 (95% CI 0.90 to 1.00; P = 0.07; based on 4157 infections among 10202 participants in the remaining 22 trials).

Thus, the positive overall finding in the meta-analysis of all the 24 trials depends on the inclusion of the two trials carried out in Mongolia and in Afghanistan, with very special participants [3,4]. Panagiotou et al. showed that for many treatments, the efficacy was substantially greater in less developed compared with more developed countries [5]. It is possible that the effects in the two trials were genuine [3,4], but their findings should not be extrapolated to populations of more developed countries, neither to adults and not even to children.
References

[1] http://www.bmj.com/content/356/bmj.i6583
[2] http://www.bmj.com/content/317/7168/1318.1