Irish Medical Journal
Established 1867

*Issue: Ir Med J; Vol 113; No. 7; P146*

# *Authors of Article* **'Optimisation of Vitamin D Status for Enhanced Immuno-Protection against Covid-19'** by McCartney et al (Ir Med J; Vol 113; No. 4; P58) *comment on response letter* **'Incorrect and Misleading Claims Regarding Vitamin D'** by Bolland et al (Ir Med J; Vol 113; No. 7; P145)

D.M. McCartney[1], D.G. Byrne[2,3]

1. School of Biological and Health Sciences, College of Sciences & Health, Technological University Dublin - City Campus, Kevin Street, Dublin D08 NF82, Ireland.
2. Department of Internal Medicine, St. James's Hospital, James's Street, Dublin 8, Ireland.
3. Dept. of Clinical Medicine, School of Medicine, Trinity College Dublin, Dublin 2, Ireland.

Dear Editor,

In response to Bolland and Avenell's comments on our recent response letter in the *IMJ*, we are very happy to clarify our reference to *relative* risk rather than absolute risk reduction. We view relative risk to be a meaningful representation of risk reduction which significantly augments that shown by absolute risk reduction alone, particularly in interventions with a binary outcome (respiratory infection versus no respiratory infection in this case). For example, in a study of 200 individuals where the treatment group's risk of an adverse outcome was 17% (i.e. 34/200) versus 20% in the control population (i.e. 40/200), it would be helpful to report this difference between the two groups as a 15% reduction in relative risk (i.e. 1-(34/40) x 100) rather than just reporting a 3% absolute risk reduction in isolation, as the latter may appear inconsequential and be overlooked in clinical decision making. In other words, the use of relative risk takes account of the background incidence of the adverse outcome, as well as the reduction in incidence associated with the intervention. In the same way, a 7% reduction in relative risk of respiratory infection amongst a treatment group will augment the interpretation of a 2% absolute risk reduction presented in isolation[1]. This has significant implications for healthcare utilisation projections and resource planning where the prospective value of initiating any treatment regimen needs to be clearly understood. So while we are happy to clarify our point from a methodological perspective, we would suggest that the best approach is to report both the relative risk and absolute risk reduction in evaluating studies of this nature. It is notable that Bolland & Avenell do report this relative risk in their subsequent *BMJ* rapid response[2], but that this larger relative risk reduction figure was not cited by Rabbitte & Slattery[3].

We are also happy to clarify the 70% reduction in the *odds* of respiratory infection rather than relative risk in the sub-group analysis of those with baseline 25(OH)D levels below 25nmol/l in Martineau et al[4]. The key finding from this meta-analysis however, is that there is a very substantial reduction (~48%) in relative risk for those with low baseline serum 25(OH)D receiving vitamin D supplementation. In their disaggregation of the <25nmol/l sub-group analysis, Bolland & Avenell have opined that the analyses in Camargo et al. were *post hoc* – this is not the case; as stated directly in the publication: "This comparison was determined *a priori."* Also in the study by Camargo et al., the reason why the comparison between group 1 and group 6 was reported was because the goal of the study was to compare daily vitamin D vs. placebo. Arms 2-5 of this study comprised different regimens (with the same overall vitamin D dose), but only group 6 facilitated a direct comparison where the vehicle (Mongolian milk), and the dosing regimen (daily) were exactly the same as that used in the vitamin D intervention group.

It is also noteworthy that in Martineau et al.[4], the data used to estimate relative risk reduction in those with baseline serum 25(OH)D <25nmol/l were also derived from five other studies where bolus supplementation was not used, albeit with lower participant numbers than the Camargo study.

Age was not identified as a covariate influencing this relative risk reduction in the overall fourteen studies with baseline 25(OH)D <25nmol/l, although dosing regimen and baseline 25(OH)D were, suggesting that the applicability of these findings to other age groups should not be discounted.

There is biological plausibility[5] as well as meta-analysis data to suggest an association between vitamin D status and risk of respiratory tract infection. These data have recently been augmented by experimental data which specifically demonstrate a direct suppressive effect of calcitriol (the active metabolite of vitamin D), on Covid-19 viral replication in cultured human nasal epithelial cells *in vitro*[6]. Further RCTs and meta-analyses will be required to fully articulate the effects of vitamin D supplementation on Covid-19 risk and severity. Until such data are available for measured consideration, we are self-evidently reliant on the existing peer-reviewed data in this area and we are compelled, in a manner redolent of Tennyson's Ulysses, 'To follow knowledge like a sinking star, Beyond the utmost bound of human thought.'[7]

Yours sincerely,

Dr. D.M. McCartney, Dr. D.G. Byrne

**Corresponding Author:**
Dr Daniel McCartney,
School of Biological and Health Sciences,
Technological University of Dublin - City Campus,
Kevin Street,
Dublin D08 NF82,
Ireland.
Email: Daniel.McCartney@TUDublin.ie

**References:**

1. Bolland MJ, Avenell A. Do vitamin D supplements help prevent respiratory tract infections? BMJ. 2017 Feb 15;356:j456. doi: 10.1136/bmj.j456.
2. Rabbitt L, Slattery E. Vitamin D and Covid-19: A Note of Caution. Ir Med J; Vol 113; No. 5; P92.
3. Bolland MJ, Avenell A. The editorialists respond to the authors. BMJ. 2017: http://www.bmj.com/content/356/bmj.j456/rr-2. doi: https://doi.org/10.1136/bmj.j456.
4. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017; 356:i6583. doi: 10.1136/bmj.i6583.
5. Greiller CL, Suri R, Jolliffe DA, Kebadze T, Hirsman AG, Griffiths CJ, Johnston SL, Martineau AR. Vitamin D attenuates rhinovirus-induced expression of intercellular adhesion molecule-1 (ICAM-1) and platelet-activating factor receptor (PAFR) in respiratory epithelial cells. J Steroid Biochem Mol Biol. 2019; 187:152-159. doi: 10.1016/j.jsbmb.2018.11.013.
6. Mok CK, Ng YL, Ahidjo BA, Lee RCH, Choy Loe MW, Liu J, Tan KS, Kaur P, Chng WJ, Eu-Li Wong J, Wang DY, Hao E, Hou X, Tan YW, Mak TM, Lin C, Lin R, Tambyah P, Deng JG, Hann Chu JJ. Calcitriol, the active form of vitamin D, is a promising candidate for COVID-19 prophylaxis. BioRxiv preprint: doi.org/10.1101/2020.06.21.162396. Available at: https://www.biorxiv.org/content/10.1101/2020.06.21.162396v1. Accessed 4th July 2020.
7. Tennyson, Lord Alfred. Ulysses in POEMS. Volume 2. Edward Moxon Dover Street, London. 1842.