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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 report* **'Covid-19, Cocooning and Vitamin D Requirements'** by McKenna et al (Ir Med J; Vol 113; No. 5; P89)

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,

Many thanks for forwarding these comments from Prof. McKenna and Prof. Flynn on our recent paper; we expect and welcome all scrutiny of our paper, both before and after publication, as valuable academic discourse in relation to this important issue, particularly at this time of crisis.

We will preface our response with two important points. Firstly, we would like to fully acknowledge the role of the Food Safety Authority of Ireland and the Department of Health in developing and prescribing policy in this area; and we are entirely accepting of this fact. Indeed given the immediacy and gravity of the escalating Covid-19 crisis, an early draft of the paper was submitted to the Department of Health in mid-March, along with all of its supporting and referenced documentation, with the explicit intention that this work could inform clinical and public health considerations through the appropriate channels at the appropriate time. Secondly, we would like to emphasise that our paper is not a "report" as referred to by Prof. McKenna in his communication; it has been published in a peer-reviewed medical journal, the intended audience of which are medical and other healthcare professionals; *not* the public. The paper was submitted as an occasional article to provide new information to clinicians managing this pandemic at the coal-face, with the expectation that these practitioners could assimilate the presented evidence and findings and exercise their own professional clinical judgement as to how they might use, or not use, that information in relation to their patients or themselves. Equally, the recommendations in relation to vulnerable population groups constitute a considered professional opinion based on the peer-reviewed evidence cited in the paper, but it is entirely for the statutory regulatory agencies which are charged with policy development in this area to determine what credence (if any) they give these observations and recommendations with regard to public health policy formulation. A further related point which we would finally like to make is that the endorsement of this article by third-party learned or expert professional bodies, and its reporting in the print and broadcast media, are not within the control of the authors.

From a technical perspective, we note that Prof. McKenna references the TILDA Report *Vitamin D deficiency in Ireland – implications for Covid-19 - Results from the Irish Longitudinal Study on Ageing (TILDA)*[1] in his own letter, highlighting the strong evidence base underpinning its recommendations. We are fundamentally in agreement with Prof. McKenna and TILDA on the need for vitamin D supplementation in older adults, and it is salient that these

recommendations from TILDA intersect with those in our own paper at their upper guideline of 20-25 micrograms per day in adults aged over 70 years.

The main difference is that while the TILDA recommendations refer principally to "frail housebound elderly" (15-20 µg of supplemental vitamin D daily), and "healthy late-middle aged to elderly" (10 µg of supplemental vitamin D daily in winter); our recommendations are primarily targeted at even more vulnerable older adults (nursing home residents) and hospital inpatients. Neither of these groups are represented in the TILDA study, and both have demonstrably poorer vitamin D status than that reported for the TILDA cohort (51% and 45% with 25(OH)D <30nmol/l respectively[2]). It is also salient that nursing home residents are the population group who have experienced the highest mortality from Covid-19 in Ireland (~50% of case fatalities to date).

In relation to Prof. McKenna's report itself, the assertion that our findings are other than evidence-based is incongruent with the extensive peer-reviewed references which we have provided to support our position, several of which are also cited in the TILDA report. It is also at variance with the fact that our paper has already been cited twice in the British Medical Journal (Brown R, 7th April, 2020[3]; Brown et al., 24th April 2020[4]), where it presumably has been subjected to the full rigour and scrutiny of their editorial process; and also by Molloy et al.[5] in the same issue of the *Irish Medical Journal*. While we are in agreement with Prof. McKenna's concerns about high dose vitamin D supplementation in children, these issues are outside the scope of the current discussion; we have explicitly and exclusively referred only to vulnerable adults in our findings and recommendations, and at no point have we offered any opinion or view on whether children should supplement with vitamin D.

Prof. McKenna states that "high dose vitamin D studies, where the primary endpoint was prevention of fracture or prevention of falls, have shown harm: more fractures[8] and more falls[9-11]." We do not agree with Prof. McKenna's interpretation of these selected studies, and we furthermore feel that the implicit identification of our paper's recommendations with the adverse findings from these "high dose vitamin D studies" is a false equivalence. In Cummings et al. (2016)[6] (McKenna Report Reference 9), falls risk was *reduced* at supplemental doses of 24,000iu (averaging at 20 micrograms per day); falls risk was only increased in the group receiving the very high dose bolus supplementation of 2 x 60,000iu per month (equivalent to 100 micrograms per day; twice the maximum upper limit of what we have suggested). In Bischoff Ferrari et al. (2016)[7] (McKenna Report Reference 10), falls risk was *lowest* in the group receiving 24,000iu per month (equivalent to 20 micrograms per day), and was increased only in the group receiving 60,000iu per month *as a bolus* (equivalent to 50 micrograms per day). In Smith et al. (2017)[8] (McKenna Report Reference 11) falls risk was *minimised* in the groups taking "medium doses" of vitamin D (40 micrograms, 60 micrograms and 80 micrograms per day); falls risk was only increased in the groups receiving the high dose 100 microgram and 120 microgram per day supplementation as a bolus (again, more than twice the upper possible supplemental dose that we have suggested).

So in reality, two of the three studies cited by Prof. McKenna indicate that falls risk is *lowest* at the supplemental dosage range we have suggested, while the third suggests an increased risk of falls only at a *bolus intake* of 1,500micrograms per month, and only amongst those who already have baseline levels of vitamin D >50nmol/l, and only after 12 months of such supplementation. Furthermore, the findings of the more recent VIDA study (also cited by Prof. McKenna), have demonstrated no increased risk of falls in older adults supplemented with the equivalent of 83 micrograms per day over three and a half years[9], a finding which is conspicuously absent in the report, but which would appear to contradict the earlier findings of Sanders et al. (2010)[10] (McKenna Report Reference 8). It is also noteworthy that Prof. McKenna has himself produced research highlighting the safety and efficacy of daily dosing with 20 micrograms of vitamin D per day for up to 16 months, a regimen which has been described in these publications as "low dose" supplementation[11,12]. For clarity, we have not recommended any bolus dosing, and the dosage levels we have suggested for short-term risk mitigation against this virus are less than half of the European Food Safety Authority's and US Institute of Medicine's 100 microgram per day tolerable upper limit for vitamin D for adults of all ages (and including pregnancy)[13,14] (i.e. less than half of "the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans"[15]).

In relation to adequacy, Prof. McKenna states that "this concern about the elderly could be safely met by supplemental vitamin D intake of 10 µg to 20 µg daily. The vitamin D needs of all other adults can be met through dietary intake of vitamin D fortified foods and natural food sources (such as oily fish)… For those consumers who

need to take a supplement, they should be advised to choose one that provides between 5 µg to 10 µg vitamin D daily." While these intakes may achieve the minimum serum 25(OH)D levels for bone health (25-30nmol/l), they demonstrably will not achieve the minimum 25(OH)D threshold of 50nmol/l required for protection against viral respiratory infection. In this regard, a large recent Irish study (n>24,000) showed that 42% of nursing home residents and 37% of hospital inpatients respectively had serum 25(OH)D levels <25nmol/l (51% and 45% <30nmol/l respectively)[2], and deficiency has similarly been shown to occur with high frequency in the other vulnerable constituencies we have highlighted[16], including front-line healthcare professionals[17]; and in the general Irish adult population[18]. Kinetic studies have shown that on average, serum 25(OH)D levels rise by ~0.6-0.7nmol/l for each additional microgram per day of oral intake[19], and that this incremental rise in 25(OH)D *takes several weeks to occur*[20]. Therefore, given the prevalence and depth of vitamin D deficiency in these vulnerable groups, the typical dose-response effects of vitamin D supplementation, and the immediate and grave risks posed by Covid-19; it is clear that the addition of 5-10 microgram per day supplemental doses of vitamin D to existing population dietary intakes of ~3-5 micrograms per day (which include the contribution from fortified foods amongst the 62% who actually consume these products)[21] will not achieve the serum thresholds required for potential reduction of respiratory infection risk, and particularly not in the context of ongoing cocooning and social isolation.

There is still far more unknown than is known about this novel virus and how the current pandemic can be best managed. What is clear however, is that there is a considerable excess of preventable deaths, and that these fatalities are proportionately more dominant in the frail and vulnerable. In the context of this ongoing crisis, and as we await a viable vaccine or effective drug treatment to manage it, we have presented what we believe to be useful, objective information which can be referred to or not, at the discretion of others, to inform practice and policy development at this time of national and international emergency.

We consider the evidence-based proposals which we have made in our paper to be safe and potentially beneficial, and indeed clinical research work is ongoing here in Ireland and elsewhere (including Italy, Spain, France and the US), to more clearly articulate the value of vitamin D supplementation in ameliorating Covid-19 risk. While the outcome of these supplementation trials is awaited, it is noteworthy that recent observational data linking population vitamin D status with Covid-19 incidence and mortality have emerged[22], and are now being augmented by international data which demonstrate a clear association between vitamin D status and clinical outcome in Covid-19 patients. Specifically, these studies have shown that the odds of a mild rather than a critical clinical outcome in Covid-19 were 19.61 times greater for each standard deviation rise in 25(OH)D[23], and that after adjustment for age, sex and comorbidity, the risk of mortality in Covid-19 patients was 10.12 times higher amongst those with serum 25(OH)D <50nmol/l versus those with levels >75nmol/l[24]. Further emerging clinical evidence has also highlighted the association between lower vitamin D status and ICU admission in Covid-19 patients[25]. Finally, it is notable that a recent publication from one of the world's foremost authorities on nutritional immunology has explicitly recommended a daily vitamin D intake of 50 micrograms per day for optimal immune function against viral infection, citing the unambiguous safety profile of intakes at this level[26].

However, we fully acknowledge the primacy of the FSAI and the Department of Health in the formulation of policy in this area.

Yours sincerely,

Dr Daniel McCartney, Dr Declan 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

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