

### Question submitted to RapidInfo4U

Is there sufficient evidence to warrant a change in the established position (i.e. NICE guidelines of June 2020) regarding vitamin D for the prevention or treatment of COVID-19?

### Answer

There is insufficient evidence to warrant a change in the established position (i.e. NICE guidelines of June 2020) regarding vitamin D for the prevention or treatment of COVID-19. Best practice remains maintaining recommended levels of Vitamin D, which may include supplementation of vitamin D in groups at high-risk of deficiency.

## Vitamin D and COVID-19

### Vitamin D and COVID-19: Current position

Vitamin D is a micronutrient that is essential to help maintain bone and musculoskeletal health and is also involved in the inflammatory response to viral infection [1, 2]. The Oxford COVID-19 Evidence Service Team performed a rapid review of the evidence for Vitamin D and the treatment or prevention of COVID-19 [3]. They concluded, based on evidence generated before April 4th (the date of their search) that there was no clinical evidence for Vitamin D for the treatment or prevention of COVID-19 [3]. The National Institute for Healthcare Excellence also reviewed the available evidence up to June 18th, and reached the same conclusion: no clinical evidence for Vitamin D for the treatment or prevention of COVID-19 [4]. The National Institutes of Health, in their comprehensive COVID-19 treatment guidelines, state that as of July 17th there is insufficient evidence to make recommendations regarding Vitamin D and COVID-19 [5]. On the World Health Organisation FAQ pages it responds to the question “can micronutrient (vitamin and mineral) supplements prevent COVID-19 in healthy individuals or cure it in those with COVID-19 disease” with the following:

*No. There is currently no guidance on micronutrient supplementation for the prevention of COVID-19 in healthy individuals or for the treatment of COVID-19. Micronutrients are critical for a well-functioning immune system and play a vital role in promoting health and nutritional well-being. Wherever possible, micronutrient intakes should come from a nutritionally balanced and diverse diet, including from fruits, vegetables and animal source foods [6].*

This WHO FAQ webpage was last updated on August 14<sup>th</sup> but it is not clear when the evidence for each individual FAQ was revised [6]. They have no other guidance on Vitamin D intake and COVID-19.

There are several studies published throughout July, August and September, after the publication of the above reviews, which suggest that Vitamin D deficiency is associated with increased COVID-19 risk or severity. These studies however provide low level evidence due to their methodological design: retrospective cohort studies [e.g. 7, 8], correlational analyses [e.g. 1, 9], and pilot trials [e.g. 10]. These study designs cannot control for the many potential confounds to the effects of Vitamin D on COVID-19, consequently only randomised, controlled trials can provide appropriate level evidence [11, 12]. A UK observational study examined the data for 341,484 UK Biobank participants collected between 2006 and 2010; its results highlight the complexity of the association between Vitamin D and COVID-19 [9]. Participants were aged 37–73 years, 656 had inpatient confirmed COVID-19 and 203 died of COVID-19 infection [9]. Vitamin D was associated with COVID-19 infection and mortality when examined *independently*, but not after adjustment for confounders such as sex, ethnicity and socioeconomic deprivation. When examining all participant characteristics together, in a multivariate analysis, the research found that the variables significantly associated with risk of COVID-19 mortality were: age (HR1.12; 95% CI 1.10–1.15;  $p < 0.001$  per year), male sex (HR2.12; 95% CI 1.56–2.89;  $p < 0.001$ ), black ethnicity (HR8.13; 95% CI 4.56–14.50;  $p < 0.001$ ), obesity (HR1.68; 95% CI 1.11–2.56;  $p = 0.015$  compared with normal weight), socioeconomic deprivation (highest Townsend deprivation quintile compared with lowest HR1.96; 95% CI 1.24–3.09;  $p = 0.004$ ), and diabetes (HR1.96; 95% CI 1.34–2.86;  $p = 0.001$ ) [9]. This study also found that ethnicity, obesity, and lower socioeconomic status were associated with lower

Vitamin D concentration [9]. It is important to note that the baseline data used in this study was collected more than 10 years ago and therefore may no longer be representative. The researchers identified this limitation however, which is evident in all retrospective studies. To help address this issue, they examined the concordance rates of Vitamin D deficiency in a subsample of 15,473 participants who had measurements taken both at baseline and at a follow-up visit (on average 4.3 years later). In this subsample, 84% had the same Vitamin D concentration at both visits [9]. Thus, these findings do not support a link between Vitamin D and COVID-19 and highlight the many potential confounds in this association. There are also methodological issues in conducting research on Vitamin D. Formal set cut-off points which denote deficiency vary across countries, as do methods of measurement which can result in over or underestimation of concentrations [1, 13]. Well-designed and controlled trials are therefore required to determine the effects of Vitamin D on COVID-19.

There is a lot of research activity in this area. A search of [CINAHL](#) databases for papers published between June – Oct 2020 found 99 papers, a [PubMed](#) search for the same dates found 81 papers. There are no new reviews of the literature and no published RCT data. [ClinicalTrials.gov](#), a US database of privately and publicly funded clinical studies conducted around the world, have 46 studies registered examining Vitamin D as an intervention for COVID-19. Of these, 36 are clinical trials and the remainder are observational. All of the clinical trials are ongoing and just two of the observational studies are completed but they are yet to present findings. The [EU Clinical Trials Register](#), which contains interventional clinical trials that are conducted in the EU and the European Economic Area, has seven ongoing clinical trials registered. In the coming months we will see a huge influx of data on the topic of Vitamin D and COVID-19 but until then recommendations must remain unchanged.

### [Recommendations for Vitamin D intake](#)

Best practice for Vitamin D intake in the context of COVID-19 is to follow international guidelines for recommended daily intake. Following a request from the European Commission, the European Food Safety Authority (EFSA) published a report on dietary Vitamin D in 2016 [14]. In the context of low sun exposure, EFSA define adequate dietary intake levels of Vitamin

D as 15 ug/day for all groups [14]. For those individuals in at-risk groups for Vitamin D deficiency a supplement is recommended to reach adequate intake levels [15]. Risk groups include young children, adolescents, pregnant women, older people (especially the institutionalized) and non-Western immigrants [16]. Greater than 100 ug/day (4000 IU) may be harmful and should be avoided unless under personal medical/clinical advice by a qualified health professional [15, 17]. The UK Government is recommending that the general population take a 10 ug/day supplement during the COVID-19 pandemic to compensate for lost sun exposure due to indoor confinement [4]. In March 2020 the Food Safety Authority of Ireland announced that current Vitamin D intake guidelines for Ireland are being revised but this is yet to be released. They comment that low vitamin D status and vitamin D deficiency are widespread in the population of Ireland but do not give advice on dietary supplementation [18].

### The Irish context

A report on Vitamin D deficiency from the Irish Longitudinal Study on Ageing (TILDA) found that 21% of people aged 55+, 27% of people aged 70+ and 47% of people aged 85+ are deficient in Vitamin D in the winter [7]. Only 9.4% of the 55+ cohort and 11.5% of the 70+ cohort reported taking Vitamin D supplements [7]. The TILDA Vitamin D report notes that 1 in 12 people aged 55+ years in Rep. of Ireland are Vitamin D deficient during the summer and highlighted that because of COVID-19 related cocooning this figure may now be higher [7]. The TILDA findings are in keeping with international data. Vitamin D deficiency occurs in <20% of the population in Northern Europe, in 30–60% in Western, Southern and Eastern Europe and up to 80% in Middle East countries [16]. Griffin et al. [19] conducted a cross-sectional study on Vitamin D status of adults in the community, in outpatient clinics, in hospital, and in nursing homes in the West of Ireland. They examined data on 24,302 patients who had their Vitamin D measured in Galway University Hospitals between January 2011 and December 2015. They found that Vitamin D deficiency was more common in nursing home residents (n=273) than inpatients (n=2,339), or outpatients (n=6,371) or those sampled in the community (n=15,319; 42% vs 37% vs 17% vs 13%;  $p < .001$ ) [19]. The findings from TILDA [7] and Griffin et al. [19]

highlight that those groups that are most vulnerable to COVID-19 in our society are those at greatest risk of Vitamin D deficiency. The TILDA Vitamin D Deficiency Report recommend that housebound individuals should take a Vitamin D supplement of 15-20 ug/day and those aged 70+ years should take 20-25 ug/day [7].

## Conclusion

There is insufficient evidence to warrant a change in the established position (i.e. NICE guidelines of June 2020) regarding vitamin D for the prevention or treatment of COVID-19. Best practice remains maintaining recommended levels of Vitamin D which may include supplementation of vitamin D in groups at high-risk of deficiency [11].

### *Disclaimer*

This document has not been peer-reviewed; it should not replace individual clinical judgement. The views expressed in this document are not a substitute for professional medical advice. The content of this document is correct as of 17/9/2020.

### ***Rapid Evidence Search & Summary (RESS)***

Our team of multidisciplinary researchers and clinicians in conjunction with the University of Limerick Library and Information Services have developed a detailed protocol for conducting a Rapid Evidence Search & Summary (RESS) to answer questions submitted to RapidInfo4U. Our RESS protocol uses PICO or PEO methods to refine your question and follows a detailed search procedure capturing guidance documents from governments, institutions and professional bodies; searching clinical and COVID specific repositories; and identifying the most recent reviews and RCTs in the scientific literature using established databases.

## References

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