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The Role of Vitamin D Status in SARS-CoV-2 Infection and COVID-19 Disease Severity

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Introduction

Initial reports linking low vitamin D levels with increased risk and severity of COVID-19 began to emerge in April 2020[1,2,3], and were largely based on the finding that the population groups who experienced a higher incidence of severe disease and death from SARS-CoV-2 infection were the same groups who were more likely to be vitamin D deficient[4]. Previous research had also clearly demonstrated that acute respiratory infection[5] and community acquired pneumonia[6] were more common in those who were vitamin D deficient, and that these risks were significantly reduced in those taking vitamin D supplements, especially if they had low vitamin D levels at baseline[7]. These latter findings have since been corroborated by a further recent meta-analysis which showed a ~25% reduction in risk of acute respiratory infection in those supplementing with vitamin D on a daily basis[8].

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As the pandemic progressed, ecological data began to emerge which specifically showed both an increased incidence of SARS-CoV-2 infection and increased mortality from COVID-19 in populations with confirmed low vitamin D levels[9], and at latitudes where vitamin D deficiency was more likely to occur due to low sunlight exposure[10]. Again, these associations between higher risk and low sunlight exposure were confirmed by later work which demonstrated a coincident surge in SARS-CoV-2 infection rates as UVB irradiation from sunlight declined over Winter months[11].

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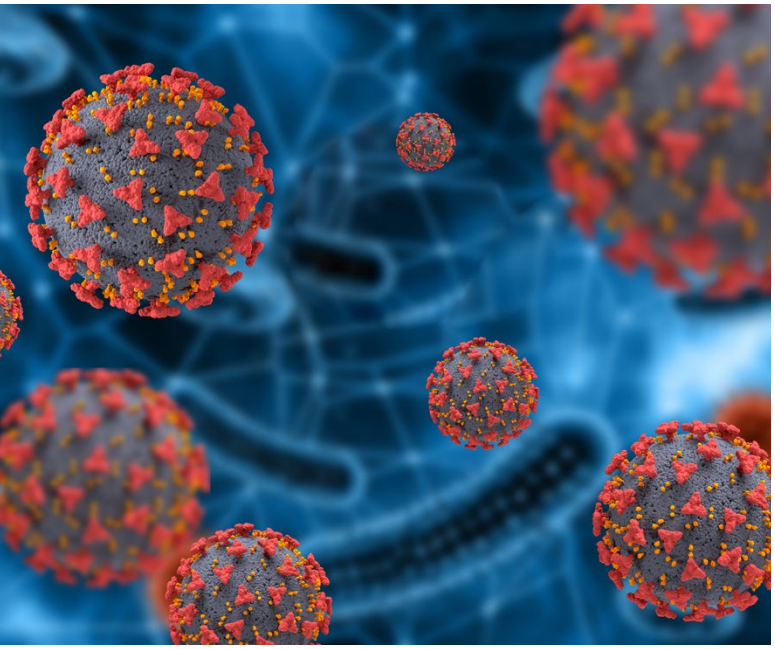
SARS-COV-2 INCIDENCE – OBSERVATIONAL DATA

Data explicitly describing the association between low vitamin D status and SARS-CoV-2 infection risk have been mainly observational to date, given the challenges of establishing patients' vitamin D status prior to infection. Notable findings include those from the UK where a study of 105 patients aged over 65 years presenting with symptoms consistent with SARS-CoV-2 infection revealed a significantly lower median 25(OH)D level in those who



subsequently tested positive for SARS-CoV-2 than in those who tested negative (27nmol/l vs. 52nmol/l; p=0.0008)[12]. In Chicago, another study examined data from nearly 500 suspected SARS-CoV-2 cases with available vitamin D data, of whom 71 patients ultimately tested positive. This study showed a 77% increased risk of SARS-CoV-2 positivity amongst those with confirmed or likely low vitamin D status (25(OH) D <50nmol/l) over the preceding year (p=0.02)[13]. A further large US study of 191,779 individuals from across all 50 US States also found an association between 25(OH)D levels from the preceding year and SARS-CoV-2 infection. SARS-CoV-2 positivity was 12.5% in those with serum 25(OH)D <50nmol/l, falling to 8.1% in those with 25(OH)D levels of 75-85nmol/l, and to 5.9% in those with 25(OH)D levels >137nmol/l. These differences in SARS-CoV-2 positivity according to serum 25(OH)D were preserved after adjustment for ethnicity, age, gender and geographic location, with a 6.4% decrement in risk associated with each 10nmol/l increase in circulating 25(OH)D level[14].

Two large Israeli studies have also examined SARS-CoV-2 positivity in relation to vitamin D status. One amongst 7,807 individuals (782 positive cases) revealed a 45% increased risk of SARS-CoV-2 infection amongst those with serum 25(OH)D levels <75nmol/l (p < 0.001)[15]. While a much larger study among 52,405 SARS-CoV-2 positive cases and 524,050 SARS-CoV-2 negative controls showed an 82% increased risk of SARS-CoV-2 positivity (p<0.001) amongst those with serum 25(OH)D <30nmol/l, a 37% increased risk in those with 25(OH) D of 30-50nmol/l (p<0.001) and a 10% increased risk in those with 25(OH)D of 50-75nmol/l (p<0.001) when compared against those achieving a serum 25(OH) D level >75nmol/l; differences which persisted even after adjustment for ethnicity[16].

Two meta-analyses in this area have also reported in recent months. The first examined data from 10 studies including 361,934 participants. It confirmed the presence of lower vitamin D levels in SARS-CoV-2 positive patients, with a 43% increased risk of SARS-CoV-2 infection in those with 25(OH)D levels less than 72.5nmol/l[17]. The second systematic review and meta-analysis evaluated data from 39 individual studies, citing a 77%

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increased riskof SARS-CoV-2 positivity in the adjusted studies examined and a 75% increased risk in the studies which were unadjusted for confounders, amongst the vitamin D deficiency groups[18].

COVID-19 SEVERITY AND MORTALITY - OBSERVATIONAL DATA

From May 2020 onwards, explicit clinical data linking low vitamin D status to increased COVID-19 severity and mortality also began to emerge. For example, Prof. John Faul's work in Connolly Hospital Blanchardstown showed not only very low serum 25(OH)D levels in patients admitted with COVID-19, but also a gradient in these blood levels between non-critical patients admitted with pneumonia (median 41nmol/l) and those with more severe Acute Respiratory Distress Syndrome (ARDS) (median 27nmol/l). This study also identified a *3.2-fold* increased risk of intubation in COVID-19 patients with serum 25(OH)D levels <30nmol/l[19].

These Irish data were soon augmented by those from international studies which also showed an association between low vitamin D status and severe COVID-19 disease (e.g. ICU admission, invasive mechanical ventilation)[12,20] and COVID-19 mortality[20,21], even after adjustment for potential confounders. One of these studies showed a 14.7 times increased risk of death in COVID-19 patients with 25(OH) D levels <30nmol/l after adjustment for age, gender and underlying disease[20].

Many studies have concurred with these findings over recent months, with systematic reviews and meta-analyses now appearing in the literature. One of these examined data from fifteen studies evaluating the association between vitamin D deficiency and composite COVID-19 disease severity. In the studies which adjusted for confounders, severe COVID-19 disease was *more than two-and-a-half times* more likely in those who were vitamin D deficient. While in the non-adjusted studies, risk of severe COVID-19 disease increased more than *10-fold* in those who were vitamin D deficient[18].
In relation to mortality, the same meta-analysis showed that in unadjusted studies COVID-19 patients who were vitamin D deficient were *2.6 times* more likely to die from their infection than those who were vitamin D replete. Even after adjustment for confounders, these vitamin D deficient COVID-19 patients remained *2.35 times* more likely to die than patients with adequate vitamin D levels. This meta-analysis concluded that there was a significant inverse association between vitamin D status and mortality from COVID-19[18].

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ESTABLISHING CAUSALITY

In establishing whether these observed associations between low vitamin D status and increased risk and severity of SARS-CoV-2 infection are causal in nature, we are afforded clues from studies which highlight the biological plausibility of such associations. Also from intervention studies which demonstrate a reduced risk of severe COVID-19 disease and mortality in those receiving vitamin D supplementation.

BIOLOGICAL PLAUSIBILITY

The proposed mechanisms by which low vitamin D status contributes to increased risk of acute respiratory infection[22] and SARS-CoV-2 infection specifically[23,24] have been comprehensively described. In brief, vitamin D is known to potentiate important elements of the innate immune system including cathelicidin and Beta-defensin expression, and also macrophage chemotaxis and phagocytosis which enhance viral clearance. Regarding the adaptive immune system, Vitamin D repletion is associated with promotion of the benign Th2 immuno-phenotype, rather than the aggressive Th1 response which characterises the 'cytokine storm' often observed in severe COVID-19 disease. Vitamin D is also known to have a direct suppressive effect on some of the inflammatory cytokines implicated in this catastrophic inflammatory cascade including IL-6 and TNF-α. Furthermore, low vitamin D status is associated with inappropriate over-activation of the Renin Angiotensin System (RAS) with consequent pro-inflammatory and pro-thrombotic effects. Finally, vitamin D deficiency is associated with higher circulating levels of free vitamin D binding protein (VDB), enabling its attachment to globular actin proteins liberated during tissue damage to create pro-inflammatory complexes which drive further tissue damage. For all of these reasons, it is not just eminently plausible, but highly probable, that low vitamin D status is causally linked to both increased risk of SARS-CoV-2 infection, and to increased severity of COVID-19 disease where such infection does occur.

INTERVENTION STUDIES

Since the initial intervention study which reported an odds ratio of 0.03 (i.e. a ~30-fold reduced risk) of ICU admission in COVID-19 patients administered activated vitamin D (calcifediol or 25(OH)D) early in their admission[25], several other studies have indicated a similar protective effect. For example, one French study cited an odds ratio for mortality of 0.11 in nursing home residents receiving large bolus doses of vitamin D within a month of their COVID-19 admission compared with patients who were unsupplemented (44% mortality in the vitamin D group versus 83% mortality in the unsupplemented group at 5 weeks post-discharge)[26]. A much larger UK study comprising nearly 1,000 patients reported a *7-8 fold* reduced risk of death in COVID-19 patients receiving bolus vitamin D supplementation during their admission even after adjustment for potential confounders. In their follow-up validation study which adjusted for an even more extensive list of potential confounders, risk of death remained *two-and-a-half times* lower in patients receiving this vitamin D 'booster' therapy[27].

While meta-analyses have yet to appear in this area, the published studies to date strongly support a protective effect of vitamin D supplementation against severe COVID-19 disease. Prospective data from intervention trials examining the association between vitamin D supplementation and reduced risk of SARS-CoV-2 infection are awaited.

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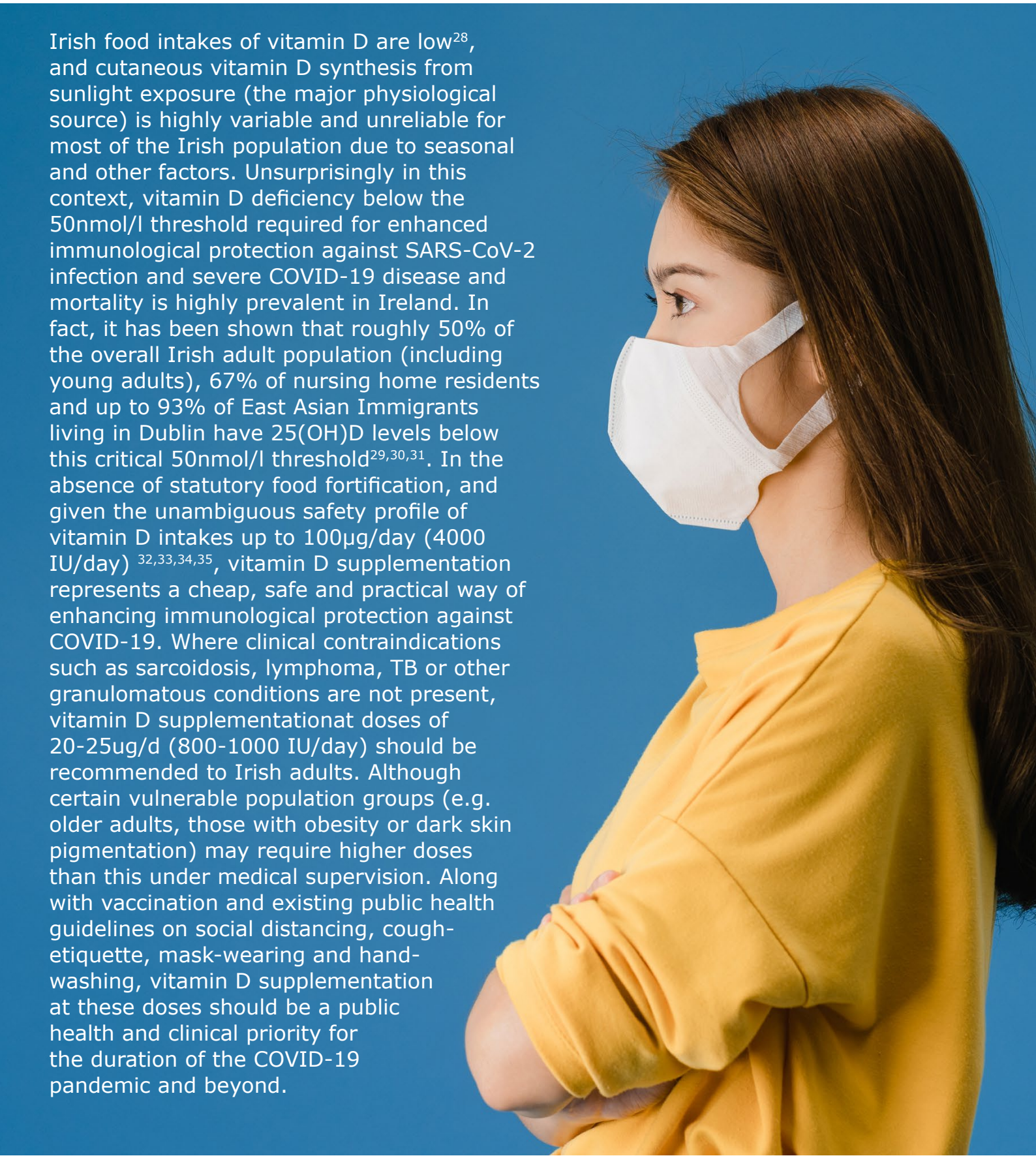
CONCLUSION AND RECOMMENDATIONS

Irish food intakes of vitamin D are low[28], and cutaneous vitamin D synthesis from sunlight exposure (the major physiological source) is highly variable and unreliable for most of the Irish population due to seasonal and other factors. Unsurprisingly in this context, vitamin D deficiency below the 50nmol/l threshold required for enhanced immunological protection against SARS-CoV-2 infection and severe COVID-19 disease and mortality is highly prevalent in Ireland. In fact, it has been shown that roughly 50% of the overall Irish adult population (including young adults), 67% of nursing home residents and up to 93% of East Asian Immigrants living in Dublin have 25(OH)D levels below this critical 50nmol/l threshold[29,30,31]. In the absence of statutory food fortification, and given the unambiguous safety profile of vitamin D intakes up to 100µg/day (4000 IU/day) [32,33,34,35], vitamin D supplementation represents a cheap, safe and practical way of enhancing immunological protection against COVID-19. Where clinical contraindications such as sarcoidosis, lymphoma, TB or other granulomatous conditions are not present, vitamin D supplementationat doses of 20-25ug/d (800-1000 IU/day) should be recommended to Irish adults. Although certain vulnerable population groups (e.g. older adults, those with obesity or dark skin pigmentation) may require higher doses than this under medical supervision. Along with vaccination and existing public health guidelines on social distancing, cough-etiquette, mask-wearing and hand-washing, vitamin D supplementation at these doses should be a public health and clinical priority for the duration of the COVID-19 pandemic and beyond.



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