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The Causal Role of Vitamin D Deficiency in Worse Covid-19 Outcomes: Implications for Policy and Practice Development

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Introduction

Covid-19 continues to contribute to excess morbidity and mortality in Ireland. The associated hospitalisation and ICU admissions impose an unsustainable burden on the Irish public health system. In the last twenty-eight days alone, there have been a further 176 Covid-19 related deaths, with total mortality now standing in excess of 8,515 case fatalities[1]. Since early in the pandemic, emerging evidence has supported a role for insufficient vitamin D status as a contributor to both SARS-CoV-2 infection and severity of Covid-19 outcomes[2-5].

Evidence from Observational Clinical Studies

Whereas initially, these associations were premised on evidence describing the importance of vitamin D in immune response, particularly against viral respiratory infection[6-8], and on the observed preponderance of more severe Covid-19 outcomes in those most likely to be vitamin D deficient (e.g. older adults and those with obesity and darker skin pigmentation)[9], more recent and explicit international evidence has confirmed that vitamin D levels correlate inversely with the likelihood of symptomatic SARS-CoV-2 infection[10-13], and with the risk of more severe Covid-19 disease including hospitalisation, mechanical ventilation, ICU admission and mortality[14-18]. Amongst these studies, the meta-analysis of Borsche and colleagues[17] is particularly noteworthy in that it captures only studies where 25(OH)D levels were measured either prior to infection or on the first day of admission, essentially out-ruling the possibility of reverse causation.

Nationally, in addition to the seminal work of Faul *et al*. in early 2020[3], four further separate Irish studies have now articulated an increased risk of severe Covid-19 outcomes including mortality in patients with low vitamin D status[19-22]. The largest and most recent of these studies[22] describes substantially lower ICU admission rates in Covid-19 patients with serum 25(OH)D >50nmol/L on admission, and a 4.6 times increased risk of mortality in patients with 25(OH)D <30nmol/L versus those with levels above this 30nmol/L threshold after adjustment for major confounders including age, BMI, gender, pre-existing diabetes mellitus and ethnicity. This strongly suggests that the excess mortality risk observed in these vitamin D deficient patients is specifically and independently associated with their vitamin D deficiency, and that it is not explained by the presence of other established risk factors.

International Studies	**Outcome**	**Methodology**	***n***	**Clinical End-point**	**Effect Size**	**Source**
	SARS-CoV-2 Infection	Retrospective observational analysis of US SARS-CoV-2 positivity (US)	191,779	SARS-CoV-2 positivity	Positivity in 12.5% of patients with 25(OH)D<50nmol/L, 8.1% in 25(OH)D 75-85nmol/L, 5.9% in 25(OH)D ≥137nmol/L. OR for positivity 0.984 for each 2.5nmol/L increment in 25(OH)D.	Kaufman *et al*. 2020 (10)
		Meta-analysis	361,934 (10 studies)	SARS-CoV-2 positivity	OR of 1.43 for SARS-CoV-2 positivity with serum 25(OH)D <72.5nmol/l.	Liu *et al*. 2021 (11)
		Systematic Review and Meta-analysis	8,377 (3 adjusted studies); 4,758 (5 non-adjusted studies)	SARS-CoV-2 positivity	Adjusted OR of 1.77; non-adjusted OR of 1.75 for SARS-CoV-2 positivity in the vitamin D deficiency groups.	Kazemi *et al*. 2021 (12)
		Systematic Review and Meta-analysis	612,601 (43 studies)	SARS-CoV-2 positivity	OR of 1.26 for SARS-CoV-2 positivity in vitamin D deficiency.	Petrelli *et al*. 2021 (13)
	Covid-19 Disease Severity	Retrospective cohort study (Germany)	185 SARS-CoV-2 positive patients	Mechanical ventilation Mortality	Adjusted HR of 6.1 for mechanical ventilation; adjusted HR of 14.7 for mortality in patients with 25(OH)D<30nmol/L vs. those >30nmol/L.	Radujkovic *et al*. 2020 (14)
		Retrospective cohort study (US)	116,370 SARS-CoV-2 positive patients	Hospitalisation for Covid-19	Adjusted OR of 1.71 for hospitalisation in SARS-CoV-2	Tallon *et al*. 2022 (15)

					patients with 25(OH)D <75nmol/L in previous 90 days.	
			1,403,715 (54 studies)	SARS-CoV-2 positivity Hospitalisation ICU admission Mortality	SARS-CoV-2 positivity: OR of 1.68 for 25(OH)D<25nmol/L; 1.83 for 25(OH)D<50nmol/L; 1.49 for 25(OH)D<75nmol/L. Hospitalization: OR of 2.51 for 25(OH)D<25nmol/L; 2.38 for 25(OH)D<50nmol/L; 1.82 for 25(OH)D<75nmol/L. ICU admission: OR 2.63 for 25(OH)D<25nmol/L; 2.16 for 25(OH)D<50nmol/L; 2.83 for 25(OH)D<75nmol/L. Mortality: OR of 2.60 for 25(OH)D<25nmol/L; 1.84 for 25(OH)D<50nmol/L; 4.15 for 25(OH)D<75nmol/L.	Chiodini *et al*. 2021 (16)
		Systematic review and Meta-analysis (25(OH)D measured pre-infection or on day of admission)	1,601+ (8 studies)	Mortality	Negative Pearson correlation between 25(OH)D and mortality of -0.4154 and -0.3989 in two datasets of Covid-19 patients.	Borsche *et al*. 2021 (17)
		Systematic review and Meta-analysis of supplementation studies	205,565 (38 studies)	Severe Covid-19 Disease Mortality	Summary relative risk (SRR) in Covid-19 patients taking vitamin D supplements: Severe disease: 0.38 (6 studies) Mortality: 0.35 (8 studies).	d'Ecclesiis *et al*. 2022 (18)
Irish Studies	Covid-19 Disease Severity	Prospective cohort study (Connolly Hospital Blanchardstown)	33	Progression to ARDS Intubation	Lower 25(OH)D in Covid-19 patients progressing to ARDS (27nmol/L) than in patients who did not (41nmol/L) (p=0.03). HR of 3.2 for intubation in Covid-19 patients with 25(OH)D<30nmol/L vs patients with levels >30nmol/L (p=0.03).	Faul *et al*. 2020 (3)
		Retrospective cohort study (St. James's Hospital)	138	Mortality	Lower 25(OH)D in Covid-19 patients who died (22nmol/L) than in those who survived (38nmol/L) (p=0.054).	Breslin *et al*. 2021 (19)
		Prospective Cohort study (Connolly Hospital Blanchardstown)	114	Mortality	Adjusted OR for mortality of 10.37 in Covid-19 patients with 25(OH)D<30nmol/L vs. Covid-19 patients with 25(OH)D>30nmol/L (p=0.056).	Connolly *et al*. 2021 (20)
		Prospective Cohort study (Connolly Hospital Blanchardstown)	114	Mortality	Lower 25(OH)D in Covid-19 patients who died (25nmol/L) than in those who survived (42nmol/L) (p<0.001).	O'Shea *et al*. 2021 (21)
		Prospective Cohort study (Connolly Hospital Blanchardstown)	232	ICU admission Mortality	ICU admission: 25(OH)D<30nmol/L: 21.6%, 25(OH)D 30-50nmol/L: 28.3%, 25(OH)D>50nmol/L: 9.5% (p=0.013). Mortality: Adjusted OR of 4.6 for mortality in Covid-19 patients with 25(OH)D<30nmol/L vs Covid-19 patients with 25(OH)D>30nmol/L (p=0.006).	Barrett *et al*. 2022 (22)

Table 1. International and National Data describing the Association between Covid-19 Risk and Vitamin D Status

It is also notable that emerging data from Connolly Hospital Blanchardstown have indicated a very substantially increased risk of both ICU admission and mortality in unvaccinated Covid-19 patients with 25(OH)D levels less than 30nmol/L compared with unvaccinated patients with 25(OH)D levels above 50nmol/L, even after adjustment for these major confounders (*Personal Communication – Prof. JL Faul*).

Evidence from Interventional Clinical Studies

A number of studies, including at least six well-designed meta-analyses, have demonstrated reduced risk of SARS-CoV-2 infection[23,24], reduced Covid-19 disease severity (lower risk of mechanical ventilation, ICU admission, and mortality)[18,25-31], and enhanced recovery from Covid-19[32,33] in those taking vitamin D supplements. Of the individual studies cited, the findings of Ling et al.[25] are particularly compelling as they describe very considerable reductions in mortality (~two- to three-*fold*) with vitamin D supplementation in hospitalised Covid-19 patients after adjustment for an extensive range of confounders including age, sex, hospital of admission, non-Caucasian ethnicity, baseline respiratory status, baseline 25(OH)D, CRP and creatinine levels, and the presence of obesity, diabetes mellitus and ischaemic heart disease. Overall, the evidence from these intervention studies has strengthened considerably over the past year, with the most recent meta-analysis declaring 'definitive', 'conclusive' and 'indisputable' protective effects of vitamin D supplementation against ICU admission in Covid-19 patients[31].

Policy Context in Ireland

Traditionally[34,35], and more recently[36], the Food Safety Authority of Ireland have focused on bone health in their formulation of population guidelines for vitamin D supplementation. In this respect, they have cited target serum 25(OH)D thresholds for the avoidance of bone disease which are similar to those advocated by SACN in the UK[37], albeit substantially lower than those recommended by other European[38,39] and US advisory groups[40,41] as shown below.

Serum 25(OH)D (nmol/L)	Food Safety Authority of Ireland (FSAI) (35,36)	Scientific Advisory Committee on Nutrition (SACN, UK) (37)	European Calcified Tissue Society (ECTS) (38)	European Food Safety Authority (EFSA) (39)	Institute of Medicine (US) (40)	Endocrine Society (US) (41)
<25/30	Risk of deficiency	Deficient	Severely deficient	Deficient	Deficient	Deficient
25/30-50	Risk of inadequacy		Deficient	Deficient	Uncertain*	Deficient
50-75			Sufficient	Sufficient	Sufficient	Insufficient
>75						Sufficient

* FSAI consider serum 25(OH)D <30nmol/L to represent 'an increased risk of vitamin D deficiency, as it relates to bone health'[36]
** IoM in the US consider that serum 25(OH) of 30-50nmol/L can be either adequate or inadequate[40]

(*adapted from Lips et al., 2019[38]*)

Table 2. Targets for Serum 25(OH)D from National and International Advisory Agencies

Consequently, the recommended daily oral vitamin D intakes recommended by FSAI to achieve these SACN and FSAI serum 25(OH)D thresholds are lower than those advised by most international expert groups[42] as shown below.

	Adults	Older Adults	Pregnancy	Source
Ireland	15*	15**	15***	FSAI 2020 (35); FSAI 2023 (36)
UK	10	10	10	SACN, 2015 (37)
Netherlands	0-10	20	10	Weggemans et al. 2013 (43)
DACH	20	20	20	Spiro & Buttriss, 2014 (44)
Central Europe	20-50	20-50	20-50	Pludowski et al. 2013 (45)
EFSA	15	15	15	EFSA, 2016 (39)
IoM	15	20	15	IoM, 2011 (40)
Endocrine Society	37.5-50	37.5-50	37.5-50****	Holick et al. 2011 (41)

* Total daily intake: in Ireland, adults of fair-skinned ethnicity are advised to take a 15µg/day supplement from October to March each year; adults of dark-skinned ethnicity are advised to take a 15µg/day supplement all year round[36].

** Total daily intake: in Ireland healthy adults aged >65 years living independently who get sunlight exposure during Summer, are advised to take a 10 µg/day supplement from October to March each year; adults aged >65 years of darker-skinned ethnicity are advised to take a 10 µg/day supplement all year round. Housebound adults aged >65 years with limited/no sun exposure are advised to take a 15µg/day supplement all year round.

*** In Ireland, women who are pregnant are advised to take a 15µg/day supplement all year round[36].

**** Pregnant adolescents aged 14-18 years: 15-25µg/day[41].

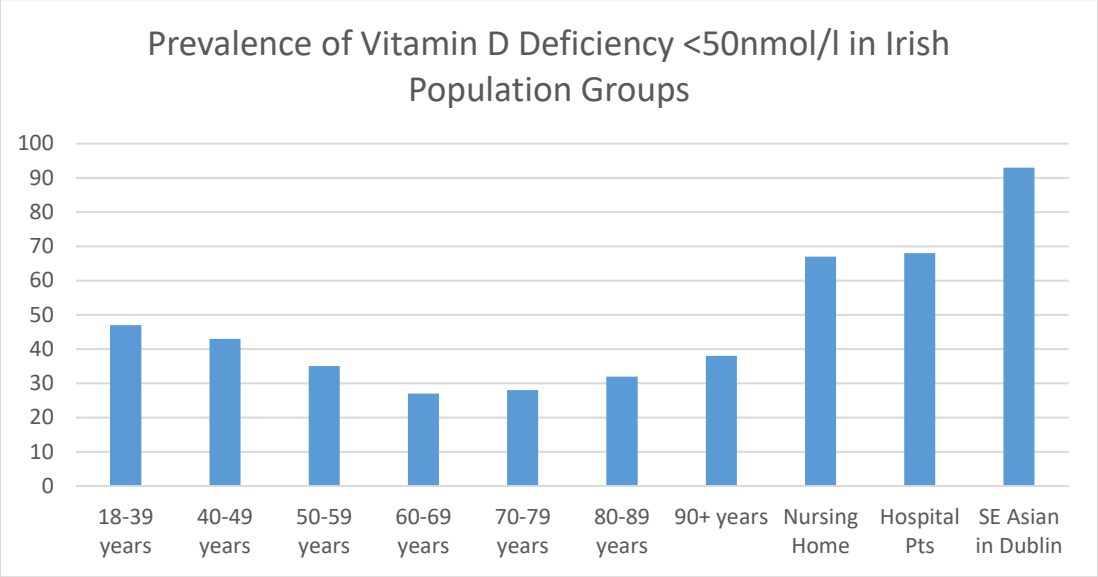
(*adapted from Lips et al., 2019[38]*)

Table 3. Recommended Daily Oral Intakes of Vitamin D (µg/day) from National and International Advisory Agencies

Implications for Policy and Practice Guideline Development in Ireland

The import of pandemic preparedness has been highlighted by the WHO[46]. Current evidence supports a causal protective role for vitamin D against severe Covid-19 outcomes particularly, with these immunological and biochemical mechanisms of protection now well described[47-50]. It is therefore important that new vitamin D guidelines are inclusive of not only bone health, but also of immunological health, a point further emphasised by the emergence of novel SARS-CoV-2 variants which may not be addressed by current vaccines.

Also of critical relevance in this regard is the high prevalence of poor vitamin D status recorded in recent Irish population studies, where 40% of adults have serum 25(OH)D <50nmol/L on a year-round basis, rising to 55% in Wintertime[51]. Indeed, even higher rates of deficiency and insufficiency are observed in some specifically vulnerable groups in the Irish adult population as shown in Figure 1, many of whom have experienced disproportionately severe Covid-19 outcomes.



(*adapted from Scully et al., 2020[52]; Griffin et al., 2020[53]; Laird et al., 2020[54]*)

Figure 1. Prevalence of Low Vitamin D Status amongst Irish Adult Population Groups

For enhanced immune protection, and particularly in relation to the ongoing Covid-19 pandemic and the acute care crisis which it has precipitated, population serum 25(OH)D levels of at least 50nmol/L, and preferably 75-125nmol/L are required. These higher target levels are supported by data describing lower risk of symptomatic SARS-CoV-2 infection[10], and reduced risk of hospitalization[15], severe Covid-19 disease[55] and Covid-19 mortality[17,56,57] amongst those with 25(OH)D concentrations in this range. These higher target levels also meet the recommended serum thresholds proposed by the major international advisory groups in relation to bone protection e.g. the US Endocrine Society[41].

Given the depth and prevalence of vitamin D deficiency in Ireland (e.g. 42% of nursing home residents and 37% of hospital inpatients respectively with serum 25(OH)D levels <25nmol/l, and 51% and 45% respectively with levels <30nmol/l in the West of Ireland)[53], as well as the prominent and increasing presence of further depletive factors such as obesity and advanced age[58], the vitamin D supplement dose required by Irish adults to achieve both bone health and enhanced immune coverage against Covid-19 and other respiratory pathogens is 20-50 micrograms/day (800-2000 IU/day).

In the absence of clinical contraindications such as sarcoidosis, tuberculosis, lupus, lymphoma or other granulomatous conditions, this implies a guideline supplementation dose of 20-25 micrograms per day (800-1000 IU/day) for the general adult population[42], rising to 25-50 micrograms per day (1000-2000 IU/day) for those with specific vulnerability to severe deficiency (e.g. older adults, nursing home residents, those with darker skin, those with obesity)[53,54,59]. These supplementation guidelines are predicated not just on the prevalence and degree of deficiency present in these population groups, but also on kinetic studies which 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[37,60], and that in overweight and obese patients, oral vitamin D3 doses need to increase by 1.5 times to 2-3 times respectively to achieve the same physiological response as that observed in individuals of ideal bodyweight[61].
The Institute of Medicine/National Academy of Medicine in the US[40], the European Food Safety Authority[62], the Scientific Advisory Committee on Nutrition in the UK[37] and the Food Safety Authority of Ireland[63] are all in

agreement that oral vitamin D intakes up to 100 micrograms/day (4000 IU/day) are safe for adults including pregnant women.

In this context, we strongly recommend that emerging population guidelines on vitamin D supplementation and overall vitamin D intake for the Irish adult population are now aligned to reflect the compelling evidence which supports the need for higher oral vitamin D consumption, and that these guidelines are published and promoted to the public expeditiously to ameliorate the ongoing Covid-19 pandemic.

Conflict of Interest Statement:
None declared.

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