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Rising trend in 250HD during COVID-19 pandemic in Ireland

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3 4	1	Rising trend in 250HD during COVID-19 pandemic in Ireland
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2 3	19	ABSTRACT
4 5	20	Objectives: Vitamin D status has improved substantially in Ireland over the past 40 years.
6 7	20	Objectives. Vitamin D status has improved substantiany in incland over the past 40 years.
8 9	21	Since the onset of the Covid-19 pandemic in 2020, there have been plausible suggestions
10 11	22	about the need to augment vitamin D intake by supplementation on a population basis in
12 13 14	23	order to prevent SARS-Co-V2 infection and reduce mortality. Some groups have advocated
15 16	24	supplementations for all adults, but governmental agencies have advocated targeted
17 18 19	25	supplementation. We sought to explore the effect of COVID-19 pandemic on vitamin D status
20 21	26	from April 2020 to March 2021 by comparison with prior trend analysis of vitamin D status
22 23 24	27	over the past 28 years.
25 26 27	28	Setting: University hospital, Dublin, Ireland.
28 29 30	29	Participants: Laboratory-based samples of circulating 25-hydroxyvitamin D (250HD).
31 32 33	30	Primary and secondary outcome measures: Primary outcome: comparing yearly average
34 35	31	250HD in the 12 months prior to the pandemic (April 2019 to March 2020) with the first 12
36 37 38	32	months (April 2020 to March 2021) of the pandemic. Secondary outcome: comparing
39 40 41	33	prevalence of vitamin D deficiency and vitamin D excess during the two time periods.
42 43	34	Results: Regarding the primary outcome in a large sample ($n = 100,505$), we noted the
44 45 46	35	average yearly 25OHD increased by 2.8 nmol/L (61.4, 95%CI 61.5 – 61.7 vs 58.6, 95% CI 58.4-
47 48	36	58.9, $p < .001$). This yearly increase is almost 3-fold higher than the yearly increase in
49 50 51	37	average 250HD based on two similar trend analyses that we conducted between 1993 and
52 53	38	2016. Regarding secondary outcome, we showed a lower prevalence of low 25OHD
54 55 56	39	indicating benefit, but we also showed a higher prevalence of high 250HD.
57 58 59	40	Conclusions: The pandemic has emphasised the need to correct vitamin D deficiency. Rather
60	41	than a blanket recommendation about vitamin D supplementation for all adults during the

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2 3 4	42	pandemic, we recommend a targeted approach of supplementation within current
5 6 7	43	governmental guidelines that augments vitamin D intake in at-risk groups.
8 9 10	44	
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13 14 15 16	46	Strengths and limitations
17 18 19	47	• This is a laboratory-based 250HD trend analysis that includes a large sample size.
20 21	48	• This trend analysis is compared to with two prior trend analyses dating back to 1993.
22 23 24	49	• This is not a population-based representative sample and is subject to selection bias.
25 26 27	50	• There is no clinical information about reason for 250HD testing or about vitamin D
28 29 30	51	supplementation.
31 32 33		supplementation.
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52 INTRODUCTION

Vitamin D is an essential micronutrient in all age groups for bone and muscle health¹⁻ ⁴. Vitamin D may have a role in extraskeletal health such as the immune response to acute respiratory illnesses⁵, which is pertinent during the COVID-19 pandemic⁶. Following the onset of the pandemic, some reports advocated blanket oral supplementation to entire populations with doses ranging from 20 µg to 50 µg daily⁷⁻¹⁰, which are in excess of vitamin D intake requirement as specified by governmental agencies in Europe and North America¹⁻⁴. By contrast, other groups have countered this blanket recommendation, favouring a targeted approach based on modelling of total vitamin D intakes^{11 12}.

These governmental reports, which have been issued over the past decade prior to the pandemic, are based on similar health outcomes such as musculoskeletal health, falls and total risk of mortality, but not on immune response to infection. Subsequently, governmental agencies from England and Ireland issued advice about vitamin D supplementation during the pandemic, targeting at-risk populations, including measures to facilitate supplementation¹³ ¹⁴(Table 1). Given the ongoing concerns about vitamin D inadequacy across Europe¹⁵, we suggest that these governmental measures at augmenting vitamin D status during the pandemic can be beneficial to at-risk groups but that blanket recommendations may predispose to unnecessary self-supplementation of vitamin D doses more than requirement in healthy persons.

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Region Year Vitamin D Intake **Population Reference Intake** µg/day (age group) USA & Canada¹ 2011 Total intake 15 (<70 y) 20 (≥70 y) Nordic Countries² 2014 Total intake 10 (<75 y) 20 (≥75 y) European Union³ 2016 Total intake 15 (≥18) United Kingdom⁴ 2016 Total intake 10 (all adults) COVID-19 vitamin D Supplemental 20-50 (all adults, all year) 2020 advocates7-10 intake Post COVID-19 United 2020 Supplemental 10 (October to March for healthy Kingdom¹³ intake adults) 10 (all year for those with limited sunlight exposure) Post COVID-19 Ireland¹⁴ 2020 Supplemental 10 (October to March >65 y) intake 15 (all year for housebound >65 y)

Total intake refers to vitamin D intake from all sources: skin production and oral intake (natural foods, fortified foods, supplements). Population reference intakes for governmental agencies refers to intake that meets the needs of 97.5% on the population; these intakes are based on health outcomes such as musculoskeletal health, falls and total risk of mortality,

Ensuring adequate vitamin D intake across all age groups is a challenging population 78 health task. Vitamin D intake requirements must be modelled to cover total intake because 79 vitamin D supply has various sources: skin production on exposure to ultra-violet light, natural 80 foods, fortified foods, and supplements. There is almost complete unanimity about total 81 vitamin D intake requirements across governmental agencies for North America and for 82 Europe¹⁻⁴. In circumstances of minimal or no sunlight exposure, the total oral intake 83 requirement approximates to between 10 μ g and 20 μ g daily (400 IU to 800 IU daily)¹⁻⁴. The 84 pre-eminent measure of vitamin D status is the measurement of the circulating vitamin D 85 86 metabolite, 25-hydroxyvitamin D (250HD).

72 **Table 1** Vitamin D intake recommendations

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We have been engaged in clinical research on 25OHD since the 1970s¹⁷. We have noted substantial improvement in vitamin D status over the past 45 years. In our early studies in Ireland, we noted the primacy of oral intake over sunlight exposure for both the prevention and correction of vitamin D deficiency¹⁸⁻²¹. Following the advent of voluntary milk fortification in Ireland in the 1980s at 1 μ g/100 ml (but more recently some milk products fortify at 2 μ g/100 ml) and the ready availability of low-dose vitamin D supplements, vitamin D status improved substantially²². In more recent years, we reported instances of hypervitaminosis D raising concerns about excessive oral intake of vitamin D²³.

We have published two trend analyses of laboratory-based 25OHD results: the first trend study reported 250HD from 1993 to 2013 that incorporated a time series analysis to predict 250HD trend from 2014 to 2016²⁴; the second trend study reported 250HD from 2014 to 2016 that confirmed the forecast analysis from the first study²⁵. Our analyses over the past 24 years in Ireland show yearly average 25OHD concentrations increased by about 1 nmol/L/year. As early as 2014, we recognized a dual concern about vitamin D status in Ireland: hypovitaminosis D in at risk groups; and hypervitaminosis D due to high supplemental intake, especially from over-the-counter preparations in individuals who already have adequate vitamin D status²⁶. One of the consequences of raising public awareness, whether it be from governmental agencies or from professional bodies, is the increased supply of vitamin D supplements, which are available for over-the-counter purchase.

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We sought to explore the effect of COVID-19 pandemic on vitamin D status from April
 We sought to explore the effect of COVID-19 pandemic on vitamin D status from April
 2020 to March 2021 given the conflicting advice: governmental agencies promoting vitamin
 D supplementation in at-risk groups, and groups advocating blanket recommendations for
 vitamin D supplementation to all adults.

110 METHODS111 Data mining

Our laboratory data system was mined to identify all 25OHD samples over a 24-month period from April 2019 to March 2021: pre-COVID-19 era being represented by 12 months from April 2019 to March 2020, and the COVID-19 era being represented by April 2020 to March 2021. In order to identify duplicate samples, the following identifiers were extracted: date of birth and medical record number. Additional data included age, sex, referral source (either hospital consultant or general practitioner), and date of 25OHD test.

The sample size for the 24 months from April 2019 to March 2021 was 137,963; after excluding those with more than one sample during the 2 years (n = 37,458) the final sample was trimmed to 100,505. Regarding those cases with more than one 250HD sample, the analysis was based on the 250HD being first sample, which hereafter is termed the first in sequence. A secondary analysis was performed, whereby the selected 25OHD of those cases with more than one sample was the final sample, which hereafter is termed the last in sequence.

- 41 125 **Research Ethics Approval**
 - 126 The Clinical Audit Committee, St Vincent's Healthcare Group, approved the extraction and
 - 127 audit of the data from our hospital laboratory system (Reference number: 3174).

- 52 129 Public and Patient Involvement
- 130 It was not appropriate or possible to involve patients or the public in the design, or conduct,
- 5758 131 or reporting, or dissemination plans of our research

32	Study	design

The primary analysis related to comparison of 25OHD in the pre-Covid-19 era, hereafter referred to as group 1, with 25OHD in the Covid-19 era, hereafter referred to as group 2. The prevalence estimates for categories of 25OHD in the two groups was calculated according to the following thresholds: <30 nmol/L; 30-50 nmol/L; 50.1-125 nmol/L; 125.1 to 175 nmol/L; >175 nmol/L. In addition, a composite analysis of the entire group over the 2 years was performed in order to assess vitamin D status according to age, sex, and different age groups.

140 Analytical Methods

Serum 25OHD concentrations were quantified using the Elecsys Vitamin D Total (Roche Diagnostics GmbH, Mannheim, Germany) automated competitive binding protein assay, which measures total vitamin D, including isomers in the form of the C3 epimer as well as 24,250HD metabolites. This is not specifically corrected for; rather, an assumption is made that there is a non-statistically significant difference in the percent concentration of vitamin D metabolites relative to the measured concentration in patient samples tested over the three-year period. The average inter-assay coefficients of variation (CV) for the 250HD assay determined over the period studied were as follows: 14.6% at a mean concentration of 37.7 nmol/L, 8.7% at a mean concentration of 74.6 nmol/L, and 7.6% at a mean concentration of 112.1 nmol/L. Functional sensitivity was verified at 15 nmol/L (%CV <20%). To ensure a high standard of analysis for serum 25OHD concentrations, the laboratory participates in an external quality assurance scheme: the Vitamin D External Quality Assessment Scheme (DEQAS)²⁷. During the 2-year period 2019 to 2021, our assay displayed a mean bias of 1.12 % from target values provided by the Centers for Disease Control and Prevention (Atlanta,

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Georgia, USA) using their isotope dilution LC-MS/MS Reference Measurement Procedure²⁸. Assay performance met DEQAS defined performance criteria set at ±25%. For samples with undetectable 25OHD (<15 nmol/L), the result was censored at 14.9 pmol/L. For samples with high 25OHD (>175 mol/L), the result was censored at 175.1 nmol/L.

159 Statistical analysis

Descriptive statistics are presented as number and percent for categorical variables and as mean (95% confidence intervals) for continuous variables. Differences in independent categorical variables were tested by chi-square. The distribution for 25OHD exhibited positive skewness and thus was log-transformed prior to parametric statistical tests. Differences between two means were tested by independent-samples *t* test using Levene's test for equality of variances. Statistics were considered significant if *p* value <.05. Analyses were performed using IBM SPSS Statistics version 25 (Armonk, NY, USA).

RESULTS

Group 1 and group 2 were similar with respect to age, sex, and source of referral (Table 1). Mean 25OHD was 2.8 nmol/L higher in group 2 compared to group 1 (61.4, 95%CI 61.5, 61.7 nmol/L vs 58.6, 95% CI 58.4, 58.9 nmol/L, p <.001) (Table 1). If the 25OHD duplicate result was selected as last in sequence, then mean 250HD was 5.1 nmol/L higher in group 2 compared to group 1 (63.3, 95%CI 63.2, 63.6 nmol/L vs 58.2, 95% CI 58.0, 58.5 nmol/L, p <.001). In group 2 compared to group 1, there was a lower percent (12.0% vs 13.4%) of low vitamin D status (250HD <30 nmol/L) but a higher percent (2.1% vs 1.7%) of high vitamin D status (250HD >125 nmol/L) (p < .001) (Table 1). The monthly 250HD trimmed values for both groups are plotted showing the seasonal variation (Figure 1). The average seasonal change in

1 2		
2 3 4	177	250HD from nadir to peak was almost identical for both at 20.2 nmol/L in group 1 and 20.1
5 6	178	nmol/L in group 2.
7 8		
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180 **Table 2**: Descriptive statistics

	Variable	Group 1	Group 2
		(<i>n</i> = 58,642)	(n = 41,863)
	Age, years	52.5 (52.3, 52.7)	52.3 (52.1, 52.5)
	Women : Men, %	66.4 : 33.6	64.3 : 35.7
	Hospital : Primary Care, %	30.0 : 70.0	25.5 : 74.5
	250HD status, %		
	<30 nmol/L	13.4	12.0
	30-50 nmol/L	28.4	25.1
	51-125 nmol/L	56.6	60.7
	125.1-175 nmol/L	1.4	1.8
	>175 nmol/L	0.3	0.3
	25OHD, nmol/L	58.6 (58.4-58.9)	61.4 (61.5 – 61.7)
181	Results are presented as % for categoric	cal variables and as mean	(95%CI) for continuous
182	variables		
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184	For the composite analysis, mean 250HD was higher in women compared to men		
185	(61.3, 95%CI 61.1 – 61.5 nmol/L vs 56.9, 95% CI 56.7-57.3 nmol/L, p <.001), and in those		
186	sourced from primary care compared to hospital care (60.7, 95%CI 60.5 – 60.9 nmol/L vs 57.4,		
187	95% CI 57.0-57.7 nmol/L, <i>p</i> <.001). Vitamin D status according to age categories showed that		
188	infants and toddlers had the lowest prevalence of 250HD <30 nmol/L and the highest		
189	prevalence for 250HD >125 nmol/L (Table 3). Regarding vitamin D status according to age		
190	categories and sex, adult females had	better vitamin D status t	han males, but in infants a
191	greater percent of females compared	d to males had both th	e lowest and the highest
192	prevalence of vitamin D status, but the	numbers were small (Tabl	e 3).
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197	Age Categories			Vita	min D Status	s, nmol/L	
			<30	30 -	50.1 -	125.1 -	>175
				50	125	175	
	Infants	Female (<i>n</i> =87)	8.0	6.9	67.8	10.3	6.9
		Male (<i>n</i> =128)	4.7	10.2	76.6	7.8	0.8
		Total (<i>n</i> =215)	6.0	8.8	73.0	8.8	3.3
	Toddlers	Female (<i>n</i> =250)	3.6	17.6	74.4	3.2	1.2
		Male (<i>n</i> =288)	6.3	15.6	73.3	4.5	0.3
		Total (<i>n</i> =538)	5.0	16.5	73.8	3.9	0.7
	Children &	Female (<i>n</i> =3,253)	16.5	33.4	49.5	0.6	0.1
	adolescents	Male (<i>n</i> =2,271)	13.7	30.8	54.3	1.0	0.2
		Total (<i>n</i> =5,524)	15.4	32.3	51.4	0.7	0.1
	Young adults	Female (<i>n</i> =42,757)	12.0	28.4	57.8	1.6	0.3
		Male (<i>n</i> =20,533)	15.9	31.0	51.7	1.1	0.3
		Total (<i>n</i> =63,290)	13.3	29.2	55.8	1.4	0.3
	Older adults	Female (<i>n</i> =19,493)	10.0	19.1	68.3	2.3	0.4
		Male (<i>n</i> =11,415)	14.1	26.5	57.7	1.4	0.2
		Total (<i>n</i> =30,908)	11.6	21.8	64.3	2.0	0.3
	Total	Female (<i>n</i> =65,840)	11.6	25.8	60.5	1.8	0.3
		Male (<i>n</i> =34,635)	15.1	29.3	54.1	1.3	0.2
		Total (<i>n</i> =100,475)	12.8	27.0	58.3	1.6	0.3
98 99	Results are prese	ented as %					
00	DISCUSSION						
)1	In a tren	d analysis of laborator	y-based	250HD sa	amples com	paring yearly	/ avera
202	250HD in the 12	months before onset o	f the Cov	vid-19 pan	demic (Apri	2019 to Ma	rch 202
203	with the first 12	months of the Covid-19	pandem	ic in Irela	nd (April 202	20 to March 2	2021), v
204	showed the aver	age yearly 250HD increa	ased by 2	.8 nmol/L	/year. This y	early trend w	vas nea
205	2 fold higher the	in the average yearly in			f 1		

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.95	Table 2. Crosstabulation of vitamin D status according to age categories and sex
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in two prior trend analyses of laboratory-based samples from 1993 to 2016^{24 25}. If the 25OHD

duplicate was selected as last in sequence for the trend analysis, then average 25OHD

increase during the pandemic was even higher at 5.1 nmol/L/year. We did observe benefit

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with respect to their being lower prevalence of 25OHD <30 nmol/L, but to a lesser extent
there was a higher prevalence of 25OHD >125 nmol/L.

The 25OHD threshold for diagnosis of vitamin D deficiency depends on the approach: whether is it viewed as being population-based^{1 4} or as being case-based^{29 30}. There are important differences. For instance, the Institute of Medicine (IOM) for the USA and Canada in 2011 used a statistical probability method to determine the prevalence of nutrient inadequacy³¹. The IOM set a 250HD threshold of 30 nmol/L. IOM referred to 250HD as a "biomarker of exposure" but not as a "biomarker of effect", which means that 250HD is the preeminent measure of total vitamin D intake, but it only estimates risk of disease. Thus, 25OHD below 30 nmol/L was defined by IOM as "risk of deficiency". Choosing a higher 25OHD threshold for defining vitamin D deficiency inflates the prevalence³¹. Similarly, the Scientific Advisory Committee on Nutrition (SACN) for the UK set a 250HD threshold of 25 nmol/L⁴. Another key difference is that governmental agencies set their specifications for vitamin D intake based on total vitamin D intake. Modelling intake from all sources estimates the shortfall in vitamin D intake that can be bridged by supplemental intake³².

Whereas, in a case-based approach, the 250HD threshold is agreed by expert clinical opinion on optimal vitamin D status in individuals, such as the European Calcified Tissue Society that set a 25OHD threshold at 50 nmol/L²⁹. The Endocrine Society, which set an even higher 250HD threshold at 75 nmol/L, specified vitamin D intakes as supplemental intake not total vitamin D intake up to 37µg to 50µg that were up to 5-fold higher than those specified by IOM³⁰. The higher 25OHD threshold and higher vitamin D intakes were critiqued as lacking evidence and as overestimating the 25OHD response to vitamin D supplementation^{33 34}. That critique has been validated by the findings of the subsequent VITAL trial using 50 µg vitamin

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D daily for 5 years with 25,871 participants that reported no benefit with respect to lowering
incidence of invasive cancer or cardiovascular events³⁵.

Governmental agencies have adopted a precautionary approach to vitamin D harm. The tolerable upper intake level (UL) for vitamin D is 100 μ g (4000 IU) daily, as set by governmental agencies ^{1 36}. The UL is 10-fold higher than the average total vitamin D intake requirement for healthy adults¹. The UL is not intended as a target intake; rather, the risk for harm begins to increase once vitamin D intake surpasses this level³⁷. In Ireland, over-the-counter vitamin D products are regulated by the Food Safety Authority of Ireland. The UL determines the maximum dose of a vitamin D product that can be marketed over-thecounter. Labelling requires that the dose not exceed the UL. There is no requirement to model total vitamin D intake, such that a healthy adult with vitamin D intake from other sources can self-medicate with a vitamin D supplement at the threshold of the UL.

Risk of harm from vitamin D supplementation is vaguely defined. Defining harm just in terms of hypercalcemia sets the vitamin D dose and the 250HD threshold at high levels³⁰. Some vitamin D studies, where the primary endpoint was prevention of fracture or prevention of falls or increase in bone mineral density, have suggested increased risk of the primary outcome: (1) two studies showed more fractures using vitamin D 12,500 µg yearly³⁸ or using 7,500 μ g yearly³⁹; (2) five studies showed more falls using vitamin D 12,500 μ g yearly³⁸, or using daily dose of 100 µg vitamin D daily ⁴⁰, or using 1500 µg vitamin D monthly⁴¹, or using μ g vitamin D monthly, or using a range of daily vitamin D doses from 50 μ g to 100 μ g⁴²; (3) and one study showed lower bone mineral density using 100 μ g or 250 μ g vitamin D daily⁴³. A recent meta-analysis of RCTs showed that vitamin D did not have a beneficial effect on muscle but may have adverse effects on muscle health⁴⁴. An RCT investigating distal radius

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fracture healing with vitamin D bolus doses (placebo, 750 μg, or 1875 μg twice 6 weeks apart)
showed no benefit of the lower dose compared to control dose but adverse effects of the
highest dose compared to controls⁴⁵. Most participants in these trials did not have 250HD
below 30 nmol/L; also, intermittent boluses have a different pharmacokinetic profile to daily
dosing, thus limiting dose comparisons²⁹.

During the Covid-19 pandemic, some groups have advocated the need for mass vitamin D supplementation in order to enhance immune response to SARS-Co-V2 infection ⁷ ^{9 10 46 47}. EFSA permits stating that benefit from vitamin D supplementation covers the normal functioning of the immune system without specifying a vitamin D intake for this benefit⁴⁸. The is some evidence of benefit from vitamin D randomised controlled trials (RCTs) that have been conducted during the pandemic but there is wide variation in vitamin D doses⁴⁹⁻⁵⁴. Further studies should provide clarity about benefit and optimal vitamin D schedules. These studies might provide cogent evidence for higher vitamin D intake requirements that could forming part of population-based or case-based recommendations. Meanwhile, the likely effect of advocating for mass supplementation is that individuals, who are best able to selfmedicate, are the ones who are least likely to need supplementation. Frail older adults, lower socioeconomic groups and minority ethnic groups are more likely to have lower 25OHD and are less likely to afford the means for supplementation^{55 56}. It is better to have a targeted approach to vitamin D supplementation such as the frail older adult¹³¹⁴. Mandatory fortification of foodstuffs with vitamin D, which has been shown to be effective in Finland⁵⁷, poses many challenges⁵⁸. Voluntary fortification, while less satisfactory than mandatory fortification, is effective at ameliorating seasonal decline in 25OHD as has been shown in Ireland²². Fortification with any nutrient (whether mandatory or voluntary) in addition to supplementation (whether mandatory or voluntary), can result in total nutrient intakes that

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are higher than requirement and may even exceed the UL, especially if nutrient intake targets
the RDA and not the average requirement⁵⁹.

Our trend analysis has many limitations. First and foremost, it is not a representative sample because samples are not collected as part of a population-based survey. We do not have information on the clinical indication for the test nor do we know whether patients were on vitamin D supplements or had an underlying condition that predisposed to vitamin D deficiency. We only had limited information on calcium status and parathyroid status (not shown). The 12-month trend analysis is too short to declare with any certainty that the pandemic has contributed to a shift upwards in the yearly average 250HD increase.

In conclusion, we report in Ireland a laboratory-based trend analysis of 25OHD showing that the yearly average 25OHD has increased about 3-fold during the first year of Covid-19 pandemic compared to prior trend analysis. This trend reflects benefit for those with low 25OHD. Public health efforts should be redoubled at maximising the provision of specified daily vitamin D supplements in at-risk groups and clinically vulnerable patients. There should be a precautionary approach to population-based blanket recommendations for vitamin D supplementation to healthy adults. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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- MMcK. Laboratory analysis: PT and MK. Statistical analysis and data interpretation: MMcK.

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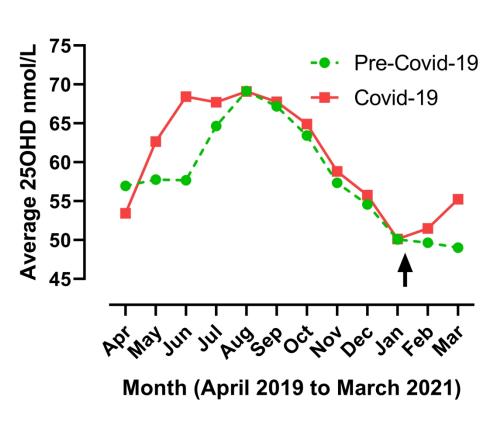
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Seasonal variation in monthly average 250HD over 1 year for both pre-Covid-19 group (green circles) and Covid-19 group (red squares). Yearly average 250HD was higher in Covid-19 group compared to pre-Covid-19 group (p <.001). The time of highest infection rate and admission rate to intensive care was in early January 2021 (black arrow).

98x80mm (600 x 600 DPI)

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STROBE Statement for bmjopen-2021-059477

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found. Done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported.
		Done
Objectives	3	State specific objectives, including any prespecified hypotheses. Done
Methods		
Study design	4	Present key elements of study design early in the paper Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,
		exposure, follow-up, and data collection Done
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
		selection of participants. Describe methods of follow-up Consecutive laboratory-
		based samples formed the cohort, as described
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of
		selection of participants
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed
		Case-control study—For matched studies, give matching criteria and the number of
		controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
		modifiers. Give diagnostic criteria, if applicable Done
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
		assessment (measurement). Describe comparability of assessment methods if there i
		more than one group Done
Bias	9	Describe any efforts to address potential sources of bias. Bias explained in
		Methods
Study size	10	Explain how the study size was arrived at Sample size was determined by number
5		of laboratory samples during the 2-year time period.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why. Done
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		Done
		(b) Describe any methods used to examine subgroups and interactions Done
		(c) Explain how missing data were addressed. Not pertinent
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Not
		pertinent
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was

eport numbers of individuals at each stage of study—eg numbers potentially eligible, ined for eligibility, confirmed eligible, included in the study, completing follow-up, at sed. Done ive reasons for non-participation at each stage Not pertinent onsider use of a flow diagram Not pertinent ive characteristics of study participants (eg demographic, clinical, social) and informat posures and potential confounders Done dicate number of participants with missing data for each variable of interest Not nent <i>ohort study</i> —Summarise follow-up time (eg, average and total amount) Not pertinent <i>rt study</i> —Report numbers of outcome events or summary measures over time Done <i>control study</i> —Report numbers in each exposure category, or summary measures of sure <i>sectional study</i> —Report numbers of outcome events or summary measures ive unadjusted estimates and, if applicable, confounder-adjusted estimates and their sion (eg, 95% confidence interval). Make clear which confounders were adjusted for a hey were included Not pertinent eport category boundaries when continuous variables were categorized Done
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The COVID-19 pandemic and vitamin D: rising trends in status and in daily amounts of vitamin D provided by supplements

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1 2				
2 3 4	22	ABSTRACT		
5 6	23	Objectives: Since the onset of the COVID-19 pandemic in 2020, there have been plausible		
7 8 9	24	suggestions about the need to augment vitamin D intake by supplementation in order to		
10 11	25	prevent SARS-Co-V2 infection and reduce mortality. Some groups have advocated		
12 13 14	26	supplementations for all adults, but governmental agencies have advocated targeted		
14 15 16	27	supplementation. We sought to explore the effect of COVID-19 pandemic on both vitamin D		
17 18	28	status and on the dose of new-to-market vitamin D supplements.		
19 20 21 22	29	Setting: University hospital, Dublin, Ireland.		
23 24 25	30	Participants: Laboratory-based samples of circulating 25-hydroxyvitamin D (250HD) (<i>n</i> =		
26 27	31	100,505)		
28 29 30	32	Primary and secondary outcome measures: Primary outcomes: comparing yearly average		
31 32 33	33	250HD prior to the pandemic (April 2019 to March 2020) with during the pandemic (April		
34 35	34	2020 to March 2021) and comparing the dose of new-to-market vitamin D supplements		
36 37 38	35	between 2017 and 2021. Secondary outcome: comparing prevalence of vitamin D deficiency		
39 40	36	and vitamin D excess during the two time periods.		
41 42 43	37	Results: The average yearly serum 250HD measurement increased by 2.8 nmol/L (61.4,		
44 45	38	95%Cl 61.5 – 61.7 vs 58.6, 95% Cl 58.4-58.9, <i>p</i> <.001), which was almost 3-fold higher than		
46 47 48	39	two similar trend analyses that we conducted between 1993 and 2016. There was a lower		
49 50	40	prevalence of low 250HD and a higher prevalence of high 250HD. The dose of new-to-		
51 52 53	41	market vitamin D supplements was higher in the years 2020-2021 compared to the years		
54 55 56	42	2017-2019 (<i>p</i> <.001).		
57 58	43	Conclusions: We showed significant increases in serum 25OHD and in the dose of new-to-		
60 44 market vitamin D supplements. The frequency of low vitamin D status reduced indicat				

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benefit, but the frequency of vitamin D excess increased indicating risk of harm. Rather than a blanket recommendation about vitamin D supplementation for all adults, we recommend a targeted approach of supplementation within current governmental guidelines to at-risk groups and cautioning consumers about adverse effects of high dose supplements on the market. Strengths and limitations This is a laboratory-based 250HD trend analysis that includes a large sample size. This trend analysis is compared to with two prior trend analyses dating back to 1993. This is not a population-based representative sample and is subject to selection bias. There is no clinical information about reason for 250HD testing or about vitamin D Liezoni supplementation.

57	INTRODUCTION
57	

Vitamin D is an essential micronutrient in all age groups for bone and muscle health[1-4]. Vitamin D may have a role in extraskeletal health such as the immune response to acute respiratory illnesses[5], which is pertinent during the COVID-19 pandemic[6]. Following the onset of the pandemic, some reports advocated blanket oral supplementation to entire populations with doses ranging from 20 µg to 50 µg daily[7-10], which are in excess of vitamin D intake requirement as specified by governmental agencies in Europe and North America [1-4]. By contrast, other groups have countered this blanket recommendation, favouring a targeted approach based on modelling of total vitamin D intakes[11, 12].

Governmental reports, which have been issued over the past decade prior to the
pandemic, are based on similar health outcomes such as musculoskeletal health, falls and
total risk of mortality, but not on immune response to infection[1, 3, 4]. Subsequently,
governmental agencies from England and Ireland issued advice about vitamin D
supplementation during the pandemic[13, 14]. This advice targeting at-risk populations
included measures to facilitate supplementation[13, 14](Table 1) given the ongoing
concerns about vitamin D inadequacy across Europe[15, 16].

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73 Table 1 Vitamin D intake recommendations

Region	Year	Vitamin D Intake	Population Reference Intake μg/day (age group)
USA & Canada[1]	2011	Total intake	15 (<70 у)
			20 (≥70 y)
Nordic Countries[2]	2014	Total intake	10 (<75 y)
			20 (≥75 y)
European Union[3]	2016	Total intake	15 (≥18)
United Kingdom[4]	2016	Total intake	10 (all adults)
COVID-19 vitamin D	2020	Supplemental	20-50 (all adults, all year)
advocates[7-10]		intake	
Post COVID-19 United	2020	Supplemental	10 (October to March for healthy
Kingdom[13]		intake	adults)
			10 (all year for those with limited
			sunlight exposure)
Post COVID-19	2020	Supplemental	10 (October to March >65 y)
Ireland[14]		intake	15 (all year for housebound >65 y)

Total intake refers to vitamin D intake from all sources: skin production and oral intake
(natural foods, fortified foods, supplements). Population reference intakes for governmental
agencies refers to intake that meets the needs of 97.5% on the population; these intakes are
based on health outcomes such as musculoskeletal health, falls and total risk of mortality,

79 Ensuring adequate vitamin D intake across all age groups is a challenging population health task. Vitamin D intake requirements must be modelled to cover total intake because 80 vitamin D supply has various sources: skin production on exposure to ultra-violet light, natural 81 foods, fortified foods, and supplements. There is almost complete unanimity about total 82 vitamin D intake population requirements across governmental agencies for North America 83 84 and for Europe[1-4]. In circumstances of minimal or no sunlight exposure, the total oral intake requirement varies between 10 µg and 20 µg daily (400 IU to 800 IU daily)[1-4]. The pre-85 eminent measure of vitamin D status is the measurement of the circulating vitamin D 86 metabolite, 25-hydroxyvitamin D (250HD). 87

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We have been engaged in clinical research on 250HD since the 1970s[17]. We have noted substantial improvement in vitamin D status over the past 5 decades. In our early studies in Ireland, we noted the primacy of oral intake over sunlight exposure for both the prevention and correction of vitamin D deficiency [18-21]. Following the advent of voluntary milk fortification in Ireland in the 1980s at 1 μ g/100 ml (but more recently some milk products fortify at 2 μ g/100 ml) and the ready availability of low-dose vitamin D supplements, vitamin D status has improved substantially[22]. In more recent years, we reported instances of hypervitaminosis D raising concerns about excessive oral intake of vitamin D[23].

We have published two trend analyses of laboratory-based 250HD results: the first trend study reported 250HD from 1993 to 2013 that incorporated a time series analysis to predict 250HD trend from 2014 to 2016[24]; the second trend study reported 250HD from 2014 to 2016 that confirmed the forecast analysis from the first study[25]. We reported that over 24 years in Ireland from 1993 to 2016 that the yearly average 25OHD concentration increased by about 1 nmol/L/year. As early as 2014, we recognized a dual concern about vitamin D status in Ireland: hypovitaminosis D in at-risk groups; and hypervitaminosis D due to high supplemental intake, especially from over-the-counter preparations in individuals who already have adequate vitamin D status[23]. One of the consequences of raising public awareness, whether it be from governmental agencies or from professional bodies, is the increased supply of vitamin D supplements, which are available for over-the-counter purchase.

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We sought to explore the effect of COVID-19 pandemic on vitamin D status from April 2020 to March 2021 given the conflicting advice: governmental agencies promoting vitamin D supplementation in at-risk groups, and groups advocating blanket

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recommendations for vitamin D supplementation to all adults. We examined vitamin D
status before and during the first year of the pandemic when public debate and temporary
emergency legislative measures (such as social distancing and mask wearing) were focused
on how people could protect themselves against COVID-19. We also assessed the Food
Safety Authority of Ireland (FSAI) notification database for new-to-market vitamin D
supplements notified between 2017 and 2021 ; all food supplements placed on the Irish
market must be notified to FSAI.[26]

118 METHODS

119 Data mining

Our laboratory data system was mined to identify all 250HD samples over a 24-month period from April 2019 to March 2021: pre-COVID-19 era being represented by 12 months from April 2019 to March 2020, and the COVID-19 era being represented by April 2020 to March 2021. In order to identify duplicate samples, the following identifiers were extracted: date of birth and medical record number. Additional data included age, sex, referral source (either hospital consultant or general practitioner), and date of 250HD test. The sample size for the 24 months from April 2019 to March 2021 was 137,963; after excluding those with more than one sample during the 2 years (n = 37,458) the final sample was trimmed to 100,505. Regarding those cases with more than one 250HD sample, the analysis was based on the 250HD being the first sample, which hereafter is termed the first in sequence. A secondary analysis was performed, whereby the selected 25OHD of those cases with more than one sample was the final sample, which hereafter is termed the last in sequence.

To enable closer monitoring of food supplements, Ireland took up the option within the
 To enable closer monitoring of food supplements, Ireland took up the option within the
 EU Directive regulating food supplements of mandating food businesses placing food
 supplements on the Irish market to notify all details on the products to the FSAI. We mined

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2 3 4	135	this FSAI notification database about new-to-market vitamin D supplements that were
5 6	136	notified between January 2017 and December 2021 ($n = 2688$).
7 8 9 10 11 12 13 14	137	Research Ethics Approval
	138	The Clinical Audit Committee, St Vincent's Healthcare Group, approved the extraction
	139	and audit of the data from our hospital laboratory system (reference number: 3174). Audits
15 16 17	140	reviewed and approved in Ireland by an institutional clinical audit committee are neither
18 19	141	subject to Research Ethics Committee approval nor require individual consent, as per Irish
20 21 22	142	Health Research Regulations 2018.
23 24	143	Public and Patient Involvement
25 26 27 28	144	It was not appropriate or possible to involve patients or the public in the design, or
29 30	145	conduct, or reporting, or dissemination plans of our research.
31 32 33	146	Study design
34 35 36	147	The primary analysis entailed a comparison of serum 250HD concentration in the pre-
37 38	148	COVID-19 era, hereafter referred to as group 1, with 250HD in the COVID-19 era, hereafter
39 40 41 42 43	149	referred to as group 2. The prevalence estimates for categories of 250HD in the two groups
	150	were calculated according to the following thresholds: <30 nmol/L; 30-50 nmol/L; 50.1-125
44 45 46	151	nmol/L; and >125 nmol/L. In addition, a composite analysis of the entire group over the 2
47 48	152	years was performed in order to assess vitamin D status according to age, sex, and different
49 50 51	153	age groups.
52 53 54	154	The list of vitamin D supplements that were notified to the FSAI between 2017 and
55 56	155	2020 was collated with respect to the total dose of vitamin D. Vitamin D supplements were
57 58 59 60	156	categorised as high dose according to two different standards: firstly, if they exceeded the

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tolerable upper intake level (UL) of 100 μg, which is defined as is the highest level of longterm daily intake of a nutrient, from all sources, judged to be unlikely to pose a risk of adverse
health effects to humans[27]; and secondly, if they exceeded the maximum safe level (MSL)
of 75 μg, which is defined as maximum amount of vitamin D that can safely be added to food
supplements targeting teenagers and adults in Ireland. The MSL is calculated using a risk
assessment approach: it is equal to the UL minus the estimated intake of vitamin D intake in
the highest consumers (95th percentile of intake from both base diet and fortified foods)[28].

164 Analytical Methods

Serum 250HD concentrations were quantified using the Elecsys Vitamin D Total (Roche Diagnostics GmbH, Mannheim, Germany) automated competitive binding protein assay, which measures total vitamin D, including isomers in the form of the C3 epimer as well as 24,250HD metabolites. This is not specifically corrected for; rather, an assumption is made that there is a non-statistically significant difference in the percent concentration of vitamin D metabolites relative to the measured concentration in patient samples tested over the three-year period. The average inter-assay coefficients of variation (CV) for the 25OHD assay determined over the period studied were as follows: 14.6% at a mean concentration of 37.7 nmol/L, 8.7% at a mean concentration of 74.6 nmol/L, and 7.6% at a mean concentration of 112.1 nmol/L. Functional sensitivity was verified at 15 nmol/L (%CV <20%). To ensure a high standard of analysis for serum 250HD concentrations, the laboratory participates in an external quality assurance scheme: the Vitamin D External Quality Assessment Scheme (DEQAS)[29]. During the 2-year period 2019 to 2021, our assay displayed a mean bias of 1.12 % from target values provided by the Centers for Disease Control and Prevention (Atlanta, Georgia, USA) using their isotope dilution LC-MS/MS Reference Measurement Procedure[30].

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Assay performance also met DEQAS defined quality assurance performance criteria. For samples with undetectable 25OHD (<15 nmol/L), the result was censored at 14.9 pmol/L. For samples with high 25OHD (>175 mol/L), the result was censored at 175.1 nmol/L.

183 Statistical analysis

Descriptive statistics are presented as number and percent for categorical variables 184 and as mean (95% confidence intervals) or median (interquartile range) for continuous 185 variables. Differences in independent categorical variables were tested by chi-square. 186 187 Differences between two means for 250HD (both yearly and monthly) were tested by 188 independent-samples t test using Levene's test for equality of variances. To account for 189 multiple testing of monthly mean 250HD, the Benjamini-Hochberg correction method was applied with a false discovery rate of 0.05; p values were converted to corresponding q values 190 for the determination of true significance. A one-way analysis of variance (ANOVA) was 191 conducted to explore the impact of year on dose of newly notified vitamin D supplements; 192 193 post-hoc comparisons were made using Tukey HSD test. Statistics were considered significant 194 if p value <.05. Analyses were performed using IBM SPSS Statistics version 25 (Armonk, NY, USA). 195

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196 RESULTS

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48197Group 1 and group 2 were similar with respect to age, sex, and source of referral (Table49
501981). Mean 25OHD was 2.8 nmol/L higher in group 2 compared to group 1 (61.4, 95%CI 61.5,52
5319961.7 nmol/L vs 58.6, 95% CI 58.4, 58.9 nmol/L, p < .001) (Table 1). If the 25OHD duplicate result53
54
55200was selected as last in sequence, then mean 25OHD was 5.1 nmol/L higher in group 256
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50201compared to group 1 (63.3, 95%CI 63.2, 63.6 nmol/L vs 58.2, 95% CI 58.0, 58.5 nmol/L, p59
60202<.001). In group 2 compared to group 1, there was a lower percent (12.0% vs 13.4%) of low</td>

1 2		
3 4	203	vitamin D status (250HD <30 nmol/L) but a higher percent (2.1% vs 1.7%) of high vitamin D
5 6	204	status (250HD >125 nmol/L) (p <.001) (Table 2).
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	Variable	Group 1	Group 2				
		(<i>n</i> = 58,642)	(<i>n</i> = 41,863)				
	Age, years	52.5 (52.3, 52.7)	52.3 (52.1, 52.5)				
	Women : Men, %	66.4 : 33.6	64.3 : 35.7				
	Hospital : Primary Care, %	30.0 : 70.0	25.5 : 74.5				
	25OHD status, %						
	<30 nmol/L	13.4	12.0				
	30-50 nmol/L	28.4	25.1				
	51-125 nmol/L	56.6	60.7				
	>125 nmol/L	1.7	2.1				
	25OHD, nmol/L	58.6 (58.4-58.9)	61.4 (61.5 – 61.7)				
206	Results are presented as % for cates	gorical variables and as mean	(95%CI) for continuous				
207	variables						
208	The monthly 250HD trimmed values for both groups are plotted showing the seasonal						
	·	a values for both groups are p	lotted showing the seas				
209	variation (Figure 1). The average se		-				
209 210	variation (Figure 1). The average se identical for both at 20.2 nmol/L in	easonal change in 250HD from	n nadir to peak was alr				
		easonal change in 25OHD fror group 1 and 20.1 nmol/L in gr	n nadir to peak was alr oup 2. Starting the mor				
210	identical for both at 20.2 nmol/L in	easonal change in 25OHD from group 1 and 20.1 nmol/L in gr y mean 25OHD in group 2 con	n nadir to peak was alr oup 2. Starting the mor npared to group 1 follor				
210 211	identical for both at 20.2 nmol/L in sequence in April 2020, the monthly	easonal change in 25OHD from group 1 and 20.1 nmol/L in gr y mean 25OHD in group 2 con r multiple comparisons was	n nadir to peak was alr oup 2. Starting the mor npared to group 1 follow significantly higher in				
210 211 212	identical for both at 20.2 nmol/L in sequence in April 2020, the monthly Benjamini-Hochberg correction for	easonal change in 25OHD from group 1 and 20.1 nmol/L in gr y mean 25OHD in group 2 con r multiple comparisons was one ($q < .001$), July ($q < .001$), Ou	n nadir to peak was alr oup 2. Starting the mor npared to group 1 follor significantly higher in ctober (q =.012), Nover				
210 211 212 213	identical for both at 20.2 nmol/L in sequence in April 2020, the monthly Benjamini-Hochberg correction for following months: May (q <.001), Ju	easonal change in 25OHD from group 1 and 20.1 nmol/L in gr y mean 25OHD in group 2 con r multiple comparisons was one ($q < .001$), July ($q < .001$), Ou	n nadir to peak was alr oup 2. Starting the mor npared to group 1 follor significantly higher in ctober (q =.012), Nover				

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> higher in May, June, July, October, November, December, February, and March (see results). For the composite analysis, mean 250HD was higher in women compared to men (61.3, 95%CI 61.1 – 61.5 nmol/L vs 56.9, 95% CI 56.7-57.3 nmol/L, p <.001), and in those sourced from primary care compared to hospital care (60.7, 95%CI 60.5 - 60.9 nmol/L vs 57.4, 95% CI 57.0-57.7 nmol/L, p <.001). Vitamin D status according to age categories showed that infants and toddlers had the lowest prevalence of 25OHD <30 nmol/L and the highest prevalence for 25OHD >125 nmol/L (Table 3). Regarding vitamin D status according to age categories and sex, adult females had better vitamin D status than males, but in infants a greater percent of females compared to males had both the lowest and the highest prevalence of vitamin D status, but the numbers were small (Table 3).

Table 3. Crosstabulation	n of vitamin D status a	according to age	categories and sex
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Age Categories	Vitamin D Status, nmol/L				
		<30	30 - 50	50.1 -125	>125
Infants	Female (<i>n</i> =87)	8.0	6.9	67.8	17.2
	Male (<i>n</i> =128)	4.7	10.2	76.6	8.6
	Total (<i>n</i> =215)	6.0	8.8	73.0	12.1
Toddlers	Female (<i>n</i> =250)	3.6	17.6	74.4	4.4
	Male (<i>n</i> =288)	6.3	15.6	73.3	4.8
	Total (<i>n</i> =538)	5.0	16.5	73.8	4.6
Children &	Female (<i>n</i> =3,253)	16.5	33.4	49.5	0.7
adolescents	Male (<i>n</i> =2,271)	13.7	30.8	54.3	1.2
	Total (<i>n</i> =5,524)	15.4	32.3	51.4	0.8
Young adults	Female (<i>n</i> =42,757)	12.0	28.4	57.8	1.9
	Male (<i>n</i> =20,533)	15.9	31.0	51.7	1.4
	Total (<i>n</i> =63,290)	13.3	29.2	55.8	1.7
Older adults	Female (<i>n</i> =19,493)	10.0	19.1	68.3	2.7
	Male (<i>n</i> =11,415)	14.1	26.5	57.7	1.6
	Total (<i>n</i> =30,908)	11.6	21.8	64.3	2.3
Total	Female (<i>n</i> =65,840)	11.6	25.8	60.5	2.1
	Male (<i>n</i> =34,635)	15.1	29.3	54.1	1.5
	Total (<i>n</i> =100,475)	12.8	27.0	58.3	1.9

227 Results are presented as %

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	228	Regarding the analysis of the FSAI notification database of new-to-market vitamin D
	229	supplements notified between 2017 and 2021, there was a significant difference in mean
	230	vitamin D doses over the 5 years ($p < .001$). Post-hoc comparisons showed no differences
)	231	between 2017, 2018, and 2019, but higher in 2020 compared to the 2017, 2108, and 2019
: ; ;	232	(respectively, $p = .002 p = .021 p = .001$) and higher in 2021 compared to 2020 ($p < .002$)
; ;	233	(Figure 2). Regarding the proportion of food supplement products notified that provide
, ;)	234	daily amounts of vitamin D exceeding the UL of 100 μ g (1%, n = 9) and the MSL of 75 μ g (3%,
)	235	n = 80), the majority were notified during the COVID-19 pandemic ($n = 3$ in 2017–2019 vs. $n =$
<u>}</u> }	236	6 in 2020–2021 above the UL; <i>n</i> = 18 in 2017–2019 <i>vs</i> . <i>n</i> = 62 in 2020–2021 above the MSL)
, , ,	237	(Table 4).
,		

238 Table 4

Year	Number of	Mean	SD	IQR	Median	25 th centile	75 th centile	Min.	Max.	Number	Number
	supplements	amount						amount	amount	above	above
	notified	of						of	of	UL (100	MSL (75
		vitamin						vitamin	vitamin	ug)	ug)
		D (ug)						D (ug)	D (ug)		
2017	491	10.6	14.3	5.0	5.0	5.0	10.0	0.08	100	0	4 (0.8%)
2018	383	11.3	16.5	5.7	5.0	4.3	10.0	0.002	200	1 (0.3%)	3 (0.8%)
2019	442	11.1	18.1	6.8	5.0	3.2	10.0	0.63	125	2 (0.5%)	11
											(2.5%)
2020	554	16.2	22.2	15.0	10.0	5.0	20.0	0.34	200	1 (0.2%)	17
											(3.1%)
2021	819	21.3	34.5	20.0	10.0	5.0	25.0	0.13	500	5 (0.6%)	45
											(5.5%)

239 UL = upper tolerable intake level: MSL = maximum safe level

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DISCUSSION

In a trend analysis of laboratory-based 25OHD samples comparing yearly average 250HD in the 12 months before onset of the COVID-19 pandemic (April 2019 to March 2020) with the first 12 months of the COVID-19 pandemic in Ireland (April 2020 to March 2021), we showed the average yearly 250HD increased by 2.8 nmol/L/year. This yearly trend was nearly 3-fold higher than the average yearly increase in 25OHD of 1 nmol/L/year that we recorded in two prior trend analyses of laboratory-based samples from 1993 to 2016[24, 25]. If the 25OHD duplicate was selected as last in sequence for the trend analysis, then average 25OHD increase during the pandemic was even higher at 5.1 nmol/L/year. We observed benefit with respect to their being lower prevalence of 25OHD <30 nmol/L, but to a lesser extent there was a higher prevalence of 250HD >125 nmol/L. Higher average monthly 250HD was noted in nearly all months except at the end of summer, suggesting an increase in the prevalence of vitamin D supplementation. The dose of new-to-market vitamin D supplements increased significantly during the pandemic with an increase in the frequency of supplements exceeding the UL and MSL.

The 250HD threshold for diagnosis of vitamin D deficiency depends on the approach: whether is it viewed as being population-based[1, 4] or as being case-based[31]. For a population-based approach, the Institute of Medicine (IOM) for the USA and Canada in 2011 used a statistical probability method to determine the prevalence of nutrient inadequacy[32]. The IOM set a 250HD threshold of 30 nmol/L. IOM referred to 250HD as a "biomarker of exposure" but not as a "biomarker of effect", which means that 250HD is the preeminent measure of total vitamin D intake, but it only estimates risk of disease. Thus, 250HD below 30 nmol/L was defined by IOM as "risk of deficiency". Similarly, the Scientific Advisory

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Committee on Nutrition (SACN) for the UK set a 25OH reshold of 25 nmol/L[4]. Governmental agencies set their specifications for vitamin D e based on total vitamin D intake. Modelling intake from all sources estimates the short n vitamin D intake that can be bridged by supplemental intake[33]. Whereas, a case-ba pproach, which is guiding clinicians about the need for supplemental vitamin D on a dividual basis, sets higher 25OHD thresholds – for example the European Calcified Tissue iety set a 250HD threshold at 50 nmol/L[31]. Case-based approaches tend to give guidant oout 250HD monitoring.

Governmental agencies have adopted a precautionar proach to vitamin D harm. The tolerable upper intake level (UL) from all oral sources of vit n D (natural foods, fortified foods, and supplement) in those with minimal sunlight is 100 (4000 IU) daily [1, 34]. The UL is 10-fold higher than the average total vitamin D intake rec ment for healthy adults[1]. The UL is not intended as a target intake; rather, the risk for m begins to increase once vitamin D intake surpasses this level[35]. In Ireland, over-theter vitamin D products are regulated by the FSAI. The UL determines the maximum dose vitamin D product that can be marketed. Labelling requires that the dose not exceed the

In addition to the UL, in Ireland the FSAI has also publis guidance for food business operators regarding the MSL of vitamin D that can be a to food supplements in Ireland[28]. Since the UL encompasses daily oral vitamin D int rom all sources (base diet, fortified foods, and food supplements), then the maximu afe dose of a vitamin D supplement should be less than the UL. Following risk assessm pproach, the FSAI deemed that the MSL for vitamin D in food supplements is 75 µg per da r teenagers and adults[28]. In our analysis of new-to-market vitamin D supplements, we noted that the frequency of supplements exceeding the MSL had increased from 0.8% to 6.1% between 2017 and 2021.

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> During the COVID-19 pandemic, some groups have advocated the need for mass vitamin D supplementation in order to enhance immune response to SARS-Co-V2 infection [7, 9, 10, 36, 37]. The European Food Safety Authority permits stating that benefit from vitamin D supplementation covers the normal functioning of the immune system without specifying a vitamin D intake for this benefit[38]. There is some evidence of benefit from vitamin D in randomised controlled trials (RCTs) that have been conducted during the pandemic but there is wide variation in vitamin D doses[39-44]. A Mendelian randomization study did not support an association between 250HD and COVID-19 susceptibility, severity[45], or hospitalization; similar findings have been reported in a UK biobank study [46]. Further studies should provide clarity about benefit and optimal vitamin D schedules. These studies might provide cogent evidence for higher vitamin D intake requirements that could form part of population-based or case-based recommendations. Meanwhile, the likely effect of advocating for mass supplementation is that individuals, who are best able to self-medicate, are the ones who are least likely to need supplementation. Frail older adults, lower socioeconomic groups and minority ethnic groups are more likely to have lower 250HD and are less likely to afford the means for supplementation[47, 48]. It is better to have a targeted approach to vitamin D supplementation such as the frail older adult[13, 14].

Mandatory fortification of foodstuffs with vitamin D, which has been shown to be
 Mandatory fortification of foodstuffs with vitamin D, which has been shown to be
 effective in Finland[49], poses many challenges[50], but has the major advantage of reaching
 lower socio-economic groups excluded from the benefits of foods voluntarily fortified with
 vitamin D due to the significantly higher prices of such foods. Voluntary fortification, while
 less satisfactory than mandatory fortification, is effective at ameliorating seasonal decline in
 250HD, as has been shown in Ireland[22]. Fortification with any nutrient (whether mandatory
 or voluntary) in addition to supplementation (whether mandatory or voluntary), can result in

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total nutrient intakes that are higher than requirement and may even exceed the UL, especially if nutrient intake targets the RDA and not the average requirement[51].

Our trend analysis has many limitations. First and foremost, it is not a representative sample because samples are not collected as part of a population-based survey. We do not have information on the clinical indication for the test nor do we know whether patients were on vitamin D supplements or had an underlying condition that predisposed to vitamin D deficiency. The plot of the seasonal variation of 250HD is open to many interpretations, such as: more outdoor activity during the first lockdown accounting for the increased in 25OHD early in the pandemic from May 2020 to July 2020, coupled with higher supplemental intake during the winter months accounting for higher 25OHD from October 2020 to March 2021 (excepting January 2021). The 12-month trend analysis is too short to declare with any certainty that the COVID-19 pandemic has contributed to a shift upwards in the yearly average 25OHD increase or if it just a transient trend upwards due to the unique circumstances of living through legislatively enforced measures implemented globally to protect people from a pandemic while the search for solutions - such as the potential benefit of vitamin D - was the highest profile news story.

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In conclusion, we report in Ireland a laboratory-based trend analysis of 25OHD showing that the yearly average 25OHD has increased about 3-fold during the first year of COVID-19 pandemic compared to prior trend analysis. This trend reflects benefit for those with low vitamin D status but risk for those with high vitamin D status, especially since there is a trend for greater availability of high dose supplements. Public health efforts should be redoubled at maximising the provision of specified daily vitamin D supplements in at-risk groups and clinically vulnerable patients and should advise about safe vitamin D supplement

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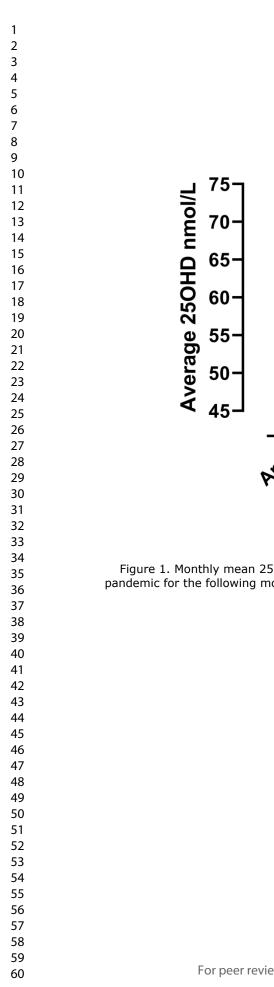
There should be a precautionary approach to population-based blanket use. recommendations for vitamin D supplementation to healthy adults, as well as a caution to consumers about adverse effects of high dose vitamin D supplements on the market. Acknowledgements: For 25OHD data mining, we thank John Hill, Department of Pathology, St Vincent's University Hospital. For data mining of new-to-market vitamin D supplements, we thank Paul Devlin (Freelance Excel Consultant). We did not receive financial support from any source. **Author Contributions:** All authors read, edited, and approved the submitted manuscript. Conception and design: MMcK, OL, MF, RC, PT, MK. Laboratory analysis: PT and MK. FSAI supplement analysis: OL and MF. Statistical analysis and data interpretation: MMcK. Drafting manuscript: MMcK. Critical review and revising manuscript: all authors. MMcK takes responsibility for the integrity of the data analysis. Funding: There was no financial support provided for this study. **Competing Interests:** All authors declare that they have no competing interests. Data sharing statement: Data described in the manuscript, code book, and analytic code will be made available upon request pending application to and approval by the corresponding author. **Research Ethics Approval Statement:**

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25	513	Legen	ds to Figures:
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28	514	Figure	1. Monthly mean 250HD during COVID-19 pandemic was significantly higher than
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30	515	nrior t	o the pandemic for the following months: May, June, July, October, November,
31	212	ρποιτ	o the pandemic for the following months. May, Julie, July, October, November,
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33	516	Decen	nber, February, and March (see results).
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39 40	518	Figure	2. Yearly mean (95% confidence intervals) vitamin D supplement doses.
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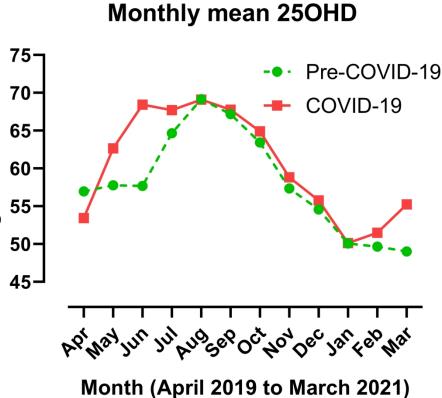
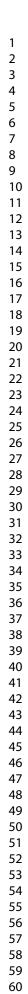


Figure 1. Monthly mean 25OHD during COVID-19 pandemic was significantly higher than prior to the pandemic for the following months: May, June, July, October, November, December, February, and March (see results).

100x87mm (600 x 600 DPI)

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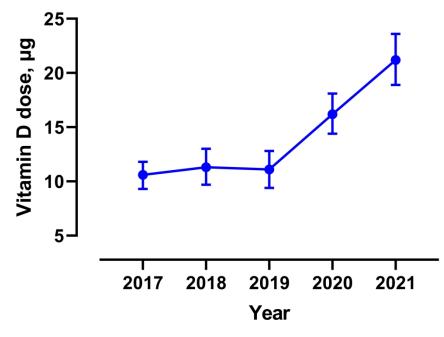


Figure 2. Yearly mean (95% confidence intervals) vitamin D supplement doses

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STROBE Statement for bmjopen-2021-059477

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found. Done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported.
C		Done
Objectives	3	State specific objectives, including any prespecified hypotheses. Done
Methods		
Study design	4	Present key elements of study design early in the paper Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment,
		exposure, follow-up, and data collection Done
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of
		selection of participants. Describe methods of follow-up Consecutive laboratory-
		based samples formed the cohort, as described
		Case-control study—Give the eligibility criteria, and the sources and methods of
		case ascertainment and control selection. Give the rationale for the choice of cases
		and controls
		Cross-sectional study-Give the eligibility criteria, and the sources and methods of
		selection of participants
		(b) Cohort study—For matched studies, give matching criteria and number of
		exposed and unexposed
		Case-control study-For matched studies, give matching criteria and the number of
		controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
		modifiers. Give diagnostic criteria, if applicable Done
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there i
		more than one group Done
Bias	9	Describe any efforts to address potential sources of bias. Bias explained in
		Methods
Study size	10	Explain how the study size was arrived at Sample size was determined by number
		of laboratory samples during the 2-year time period.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,
		describe which groupings were chosen and why. Done
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding.
		Done
		(b) Describe any methods used to examine subgroups and interactions Done
		(c) Explain how missing data were addressed. Not pertinent
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Not
		pertinent
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was
		addressed

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account sampling strategy
		(\underline{e}) Describe any sensitivity analyses Not performed
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible examined for eligibility, confirmed eligible, included in the study, completing follow-up, analysed. Done
		(b) Give reasons for non-participation at each stage Not pertinent
		(c) Consider use of a flow diagram Not pertinent
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and inform on exposures and potential confounders Done
		(b) Indicate number of participants with missing data for each variable of interest Not pertinent
		(c) Cohort study—Summarise follow-up time (eg, average and total amount) Not pertine
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time Done Case-control study—Report numbers in each exposure category, or summary measures or exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for why they were included Not pertinent
		(b) Report category boundaries when continuous variables were categorized Done(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaning
		time period Not pertinent
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Done
Discussion		
Key results	18	Summarise key results with reference to study objectives Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecisi Discuss both direction and magnitude of any potential bias Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multip of analyses, results from similar studies, and other relevant evidence Done
Generalisability	21	Discuss the generalisability (external validity) of the study results Done
Other informati	on	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applica for the original study on which the present article is based No funding for study is state