Title:

RAPID EVIDENCE SUMMARY: VITAMIN D IN COVID-19

Author: CMO Office, Louise Hendrick

Organisation: Department of Health

Date: 27th January 2021

Action required:
☐ For noting
☐ For discussion
☒ For decision

Approved for future publication: YES

RAPID EVIDENCE SUMMARY: VITAMIN D IN COVID-19

24 JANUARY 2021

INTRODUCTION

- National Department of Health guidelines on vitamin D were updated in November 2020 and advise adults aged 65 and older to take a daily vitamin D supplement of 15 micrograms to support bone and muscle health.

- In the context of COVID-19, advice has previously issued recommending that individuals that are self-isolating or unable to go outside should consider supplementation.

- This rapid review was conducted to assess current evidence on the role of vitamin D in the prevention and treatment of COVID-19 and additional considerations which may impact decision-making.

- This review of the available research evidence up to January 2021 considers recent rapid reviews, randomised controlled trial (RCT) evidence, observational studies and laboratory studies.

  o A recently updated rapid review conducted by the National Institute for Health and Care Excellence (NICE) in the UK concluded that there is currently a lack of evidence linking vitamin D and the incidence and severity of COVID-19. The report recommends increasing awareness of existing recommendations relating to vitamin D supplementation.

  o Results from a randomised controlled trial (Entrenas Castillo, 2020) reported reduced admission to ICU and reduced mortality in patients with COVID-19 receiving standard care plus vitamin D compared to standard care alone. However, this trial was noted to have significant methodological limitations including low numbers (n=76) and serious risk of bias.

  o Collectively, other evidence provides conflicting reports of an association between vitamin D supplementation and a reduced risk of and poorer outcomes with COVID-19 infection.

  o A number of studies have suggested an association between low vitamin D status and increased incidence and severity of COVID-19 infection. However, causality has not been confirmed as many of the risk factors for severe COVID-19 outcomes are the same as the risk factors for low vitamin D status.

- Additional considerations outlined within the report include:

  o Modest evidence to suggest that vitamin D may slightly reduce the risk of acute respiratory illness.

- Existing evidence of vitamin D deficiency in Ireland with TILDA results showing that 13.1% of adults over 55 are deficient all year round, rising to 21.3% in winter. Higher levels of deficiency have been reported in those aged 70+ (27.1%) and 85+ (46.6%) in winter, with 11.5% of those aged 70+ reported taking a vitamin D supplementation. A cross-sectional study also reported high levels of deficiency in Irish individuals of South Asian descent (66.7% had vitamin D levels ≤30 nmol/L).

- International public health guidance typically recommends optimisation of vitamin D status in the context of bone and muscle health. Several countries have reiterated existing guidance given increased time spent indoors due to COVID-19 restrictions (England, Scotland, Wales, Northern Ireland, Slovenia, France).

- England and Scotland have recently launched an opt-in scheme offering a free 4-month supply of vitamin D supplements for those listed as extremely clinically vulnerable.

- There is insufficient high-quality evidence to support a change to existing guidance, however this report makes the following recommendations:

  - Increase awareness of existing guidance that adults age 65 and over should take a 15 microgram daily supplement for bone and muscle health

  - Adults spending increased time indoors or are housebound or in long-term residential care or have dark skin are also recommended to take vitamin D supplementation

  - That ongoing developments, particularly RCTs, in this area be monitored with guidance reviewed accordingly

BACKGROUND

This rapid review was conducted to assess the following question:

"What is the current evidence in relation to the role of vitamin D in prevention and treatment of COVID-19?"

The potential role of vitamin D in the prevention and treatment of COVID-19 has been proposed based on:

- Systematic reviews and meta-analyses showing a reduced risk of acute respiratory tract illness with vitamin D supplementation.
- In vitro studies showing the role of vitamin D in induction of antimicrobial peptides in response to both viral and bacterial stimuli,[1] [2] and have demonstrated the responsiveness of several hundred genes to vitamin D, including activated T cells, B cells, dendritic cells and macrophages (immune cells).[3]

- A number of observational studies that have highlighted the relationship between UVB exposure,[4] vitamin D supplementation,[5][6] vitamin D serum levels[7] and deficiency[8] and COVID-19 incidence and outcomes.

Vitamin D is a group of fat-soluble seco-sterols. Vitamin D is obtained through synthesis in the skin from 7-dehydrocholesterol under the influence of ultraviolet-B (UVB) light and through the consumption of vitamin D-rich foods. Vitamin D is metabolised first to 25-hydroxyvitamin D (25[OH]D), then to the bioactive form 1,25-dihydroxyvitamin D.[9] The classic function of vitamin D is in the regulation of calcium absorption and homeostasis, supporting musculoskeletal health. Deficiency which is typically defined as serum 25[OH]D levels <25nmol/L, is associated with osteomalacia, low bone mass, fractures, muscle weakness, increased risk of falls; and rickets in children.[10][11][12] Research suggests that vitamin D may also play a role in immunity owing to the existence of vitamin D receptors on multiple different cell types including immune cells, and studies showing an association between autoimmune disease and vitamin D deficiency.[13]

Ireland resides at the latitude band of 51–55°N resulting in a 5-month period from October to February during which UVB-induced dermal synthesis of vitamin D does not occur and thus supplementation is recommended in certain groups.[14][15] Characteristics, such as skin pigmentation, age, clothing style, sunscreen use, outdoor activity and sun exposure behaviour influence vitamin D status,[16] with deficiency more common in individuals that are institutionalised, elderly, obese and with dark skin.[17]

EXISTING GUIDELINES

Existing guidelines on vitamin D encompass recommendations for infants aged 0 to 12 months; children aged 1 to 4 years and adults aged 65 years and older.

Since 2010 the HSE has recommended a 5 microgram (5µg) daily vitamin D supplement in liquid or drop form babies for babies from birth to 12 months.[18] The initial guidance followed a 2007 review by the FSAI's Scientific Committee which highlighted the re-emergence of rickets in infants in Ireland with 23 cases reported in the early 2000s at two Dublin-based paediatric hospitals.[19] This guidance was updated in 2020 limiting this recommendation to babies that are breastfed or taking less than 300mls of infant formula a day,[20] reflecting the European Food Safety Authority's approval of increased vitamin D levels in fortified infant formula[21] and subsequent FSAI recommendation.[22]

In October 2020 the Department of Health issued guidance recommending a 5 microgram (5µg) vitamin D only supplement in liquid or drop form to be taken daily from Halloween (31st October) to St Patrick's Day (17th March) in children from one to four years (inclusive).[23]

In November 2020 the Department of Health issued guidance advising adults aged 65 and older to take a daily vitamin D supplement of 15 micrograms (15µg), either as a multivitamin, a vitamin D-calcium combination or as a vitamin D only supplement, to support bone and muscle health.[24] The guidance also recommends a diet with regular intakes of natural sources of vitamin D, such as oily fish, eggs, meats and vitamin D-fortified. This follows a 2020 FSAI report, on vitamin D and older adults, recommending that healthy older adults living independently and who get sunlight exposure during summer should take 10µg (400 IU) daily dose during the extended winter months (end of October to March); and for those of darker-skinned ethnicity, this should be taken throughout the full year. The report recommends a 15µg (600 IU) daily dose for housebound older adults with minimal or no sunlight exposure taken throughout the full year. The report notes that such dosing should be sufficient and safe for most older people.[25]

METHODOLOGY

This rapid review aimed to provide a high-level summary of the evidence on vitamin D and COVID-19. A scoping methodology was used and considered research evidence on vitamin D status and prevention of SARS-CoV-2 infection; vitamin D supplementation and COVID-19 outcomes; vitamin D status and prevention of acute respiratory illness, and public health guidance and measures. The research evidence cited includes literature up to 22nd January 2021.

REVIEW OF EVIDENCE FOR THE EFFECTIVENESS OF THE USE OF VITAMIN D IN THE PREVENTION OF COVID-19

Search Results

Due to the limited time available for the completion of this rapid report, a scoping approach was adopted to identify relevant studies published. The following table presents examples of research studies identified, which are discussed under the relevant section.

	Sample articles identified	Publication date
Rapid review informing national policy	NICE rapid review: Vitamin D for COVID-19 [26]	December 2020
Systematic Reviews	Yisak et al. Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review	January 2021
Randomised controlled trials	Entrenas Castillo et al. vitamin D supplementation in the treatment of COVID-19	October 2020

Observational studies	Hastie C et al. Vitamin D concentrations and COVID-19 infection in UK Biobank	April 2020
Laboratory studies	McCarthy et al. Immuno-protection against COVID-19	April 2020

National Institute for Health and Care Excellence (NICE) COVID-19 Rapid Guideline: Vitamin D

The most up-to-date review of the evidence identified within this review comprises a rapid review performed by the NICE in the UK, which was published on 17 December 2020. The results of this rapid review are described below.

This review was performed to inform a policy recommendation based on three questions:

"What is the clinical effectiveness and safety of vitamin D supplementation for the treatment of COVID-19 in adults, young people and children?"

"What is the clinical effectiveness and safety of vitamin D supplementation for the prevention of SARS CoV2 infection (and subsequent COVID-19) in adults, young people and children?"

"Is vitamin D status independently associated with susceptibility to developing COVID-19, severity of COVID-19, and poorer outcomes from COVID-19 in adults, young people and children?"

This review considered the following outcomes of interest:

- Incidence of COVID-19
- COVID-19-related ICU admission
- All-cause and COVID-19-related mortality
- Hospitalisation; ventilation; time to cure; complications; adverse effects and tolerability

Overall, the categories of research incorporated in the review included: direct evidence reporting multivariable models for outcomes of interest, systematic reviews and meta-analyses of Randomised Control Trials (RCTs), observational studies and laboratory studies. Pre-print research (not peer-reviewed) was included.

With respect to evidence for vitamin D supplementation in the treatment of COVID-19, one RCT by Entrenas Castillo et al was included. This study reported a lower likelihood (OR 0.03, 95% CI 0.003-0.25) of admission to ICU in those receiving calcifediol treatment plus standard care compared to those receiving standard care alone. However, the evidence quality was deemed very low due to a very serious of bias and low number of participants (n=76).[27]

With respect to evidence for vitamin D supplementation in the prevention of COVID-19, no articles were identified following review.

With respect to the evidence for an association between vitamin D status and COVID-19 susceptibility and severity 12 studies were included. Six studies explored the association between vitamin D status and COVID-19 incidence. Results were mixed with one study reporting a significant association between vitamin D concentration and risk of COVID-19 diagnosis (OR 0.984, 95% CI 0.983, 0.986, N=191,779)[28]; and two studies reporting no association ((OR 1.00, 95% CI 0.998, 1.01, N=349,017)[29] and (OR 1.00, 95% CI 1.00, 1.00, N=4,510)[30]) between vitamin D status and COVID-19 cases. The latter two studies utilised serum vitamin D measurements from the UK biobank study which were collected between 2006 and 2010, which may differ from the populations included in the analysis.

Three studies assessed vitamin D deficiency and COVID-19 diagnosis. Two reported an association with Meltzer et al reported an association between deficiency ($<$25nmol/L) and COVID-19 cases OR 1.77 (95% CI 1.12, 2.81)[31] and Merzon et al. reporting an association between suboptimal levels ($<$75nmol/L) and COVID cases OR 1.5 (95% CI 1.13 to 1.98)[32]. The former did not adjust for demographic factors (e.g. sex, gender, ethnicity). An additional study found no difference in COVID-19 cases between people above and below the thresholds, $<$25nmol/L OR 0.92 (95% CI 0.71, 1.21) and $<$ 50nmol/L OR 0.88 (95% CI 0.72, 1.08)[29]. The quality of all studies was graded as very low with criticism of methodological approach relating to a failure to adjust for confounding variables (including sex, gender and ethnicity); use of UK Biobank data (based on vitamin D measurements taken between 2006 and 2010); and lack of power.

Seven studies assessed vitamin D status and an association with COVID-19 severity. Hernandez et al. did not identify an association between vitamin D levels and ICU admission, need for mechanical ventilation or in-hospital mortality OR 1.13 (95% CI 0.27, 4.77) n=197[33]. Macaya et al. did not find an association between vitamin D levels (<50nmol/L) and death, ICU admission or need for high-flow oxygen OR 3.2 (95% CI 0.99 to 11.4)[34]. A third study reported a significant association between low vitamin D levels (<30nmol/L) and the composite outcome mechanical ventilation and death, HR 6.12 (95% CI 2.79 to 13.42), n=185.[35] Ye et al. also reported an association between vitamin D levels <50nmol/L and more severe COVID-19, OR 15.18 (95% CI 1.23, 187.45).[36]

Annweiler et al. reported the results of two quasi-experimental studies, and found that supplementation for a year was significantly negatively associated with the likelihood of severe

COVID-19, OR 0.08 (95% CI 0.01, 0.81), but identified no difference if those only receiving a bolus when diagnosed, OR 0.46 (95% CI 0.07, 2.85). These studies also reported on mortality as a single outcome with one study reporting lower mortality risk in those receiving vitamin D3 bolus supplementation during COVID-19 or in the preceding month compared to those receiving no treatment (Hazard ratio (HR) = 0.11 [95 %CI 0.03, 0.48], p = 0.003),[6] and a second study of 77 patients hospitalised with COVID-19 reported a higher risk of 14-day mortality in those receiving no supplementation compared to those receiving supplementation in the preceding year (HR = 0.07 (p = 0.017)) or those supplemented after a COVID-19 diagnosis (HR = 0.37 (p = 0.28)).[37] Both studies had limitations including small sample size, lack of use of a placebo, and use of estimations of vitamin D status based on supplementation which rely on compliance and thus may be incorrect.

A further two studies reported on vitamin D status and mortality with Karahan et al. finding that higher vitamin D levels were negatively associated with death OR 0.92 (95% CI 0.88, 0.98)[28] and Radujkovic et al. reporting higher mortality with serum vitamin D levels <30nmol/L (HR 14.73 (95% CI 4.16, 52.19)).[35]

The review excluded numerous observational studies due to the use of unadjusted analysis and a lack of relevant predictive values.

Taking into consideration all forms of evidence, the recommendations of this review were:

- A lack of evidence supporting the use of vitamin D in the treatment of COVID-19
- A lack of evidence supporting the use of vitamin D in the prevention of COVID-19
- A lack of evidence supporting an association between vitamin D status and the incidence of COVID-19
- A call for urgent research into vitamin D supplementation and prevention of COVID-19, particularly in Black African and Minority Ethnic (BAME) individuals, and people categorised as overweight or obese.

Systematic Review

Yisak et al conducted a review of 9 articles and identified 7 studies that reported a correlation between vitamin D status and COVID-19 infection, prognosis and mortality. 2 studies failed to demonstrate an association. This review did not address the limitations of included studies including unadjusted analysis and an absence of relevant predictive values.[38]

Randomised Control Trials

A pre-publication (not peer reviewed) Brazilian, multicentre, double-blind, RCT randomised patients with 240 hospitalised patients with COVID-19 (1:1) to receive a single oral dose of 200,000 IU (5,000mcg) or placebo. 86.7% of patients in the supplementation arm achieved vitamin D serum levels (≥30ng/mL) compared to 11% in the placebo group; however there was no difference in hospital length of stay in vitamin D and placebo groups (7.0 days [95% CI 6.1, 7.9] and 7.0 days [95% CI 6.2, 7.8 days], HR 1.12, [95% CI 0.9, 1.5]; p = .379) respectively. There was also no difference reported in secondary outcomes including mortality, admission to ICU and requirement for ventilation. Study limitations include low power, and heterogeneity of the patient sample and its treatment. [39]

Rapid Review of evidence for use of vitamin D in the prevention of Acute Respiratory Illness

Systematic Reviews and Meta-Analyses

Seven systematic reviews and meta-analyses were identified that assessed the role of vitamin D in the prevention of acute respiratory illness. These suggest a modest reduced risk of acute respiratory tract infection and asthma exacerbation due to respiratory tract infection with vitamin D supplementation.

In a 2017 systematic review and meta-analysis of 25 RCTs, Martineau et al. identified patient data for 10,933 (96.6%) of 11,321 participants aged 0 to 95 years.[40] Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted OR 0.88, 95% CI 0.81 to 0.96; P for heterogeneity <0.001). Protective effects were seen with daily or weekly dosing between 20μg and 50μg (adjusted OR 0.81, 0.72 to 0.91) with stronger effects in those with baseline deficiency defined as serum 25[OH]D levels<25 nmol/L (adjusted OR 0.30, 0.17 to 0.53). No effect was seen with bolus dosing and no reduction in adverse events was observed.

A 2020 pre-publication, non-peer reviewed systematic review of 45 RCTs conducted by Joliffe et al. reported patient data for 46,331 (98%) of 47,262 individuals in 42 trials (in total 73,384 patients were involved in 45 trials).[41] The study reported a reduced risk of acute respiratory tract infection overall in those receiving vitamin d supplements vs placebo (OR 0.91, 95% CI 0.84, 0.99; P for heterogeneity 0.01). No statistically significant effect of vitamin D was seen for any of the sub-groups defined by baseline 25[OH]D concentration. Protective effects were seen in trials using daily dosing regimen (OR 0.75, 95% CI 0.61, 0.93) at daily dose equivalents of 10 micrograms to 25 micrograms or 400 to 1000 IU, but not above (OR 0.70, 95% CI 0.55, 0.89); and for a duration of ≤12 months (OR 0.82, 95% CI 0.72, 0.94). There was no impact of supplementation on adverse events. Limitations of this research included inconsistency between study results, and differences between vitamin D supplementation doses and regimens, durations, populations, settings and definition of outcomes, between studies.

A 2021 systematic review and meta-analysis on micronutrient supplementation reported a reduced the risk of ARI (risk ratio (RR)=0.97; 95% CI 0.94 to 1.00; p=0.028) based on 20 studies and shortened the duration of symptoms (per cent difference: −6% (95% CI −9% to −2%; p=0.003)), with an optimal dosing regimen proposed as daily dose ≥2000 IU (50mcg) vitamin D and a <60000IU (1500mcg) loading dose.[42]

A 2016 systematic review and meta-analysis of 15 RCTs reported patient data for 7,053 individuals and failed to demonstrate a statistically significant association between vitamin D supplementation and risk of clinical respiratory tract infection (RR 0.94; 95% CI 0.88, 1.00).[43] Similarly, Wang et al. reported data for 2312 healthy participants aged 19 to 61 years in 8 RCTs and reported no different between vitamin D and placebo groups in risk of self-reported cold, cold duration and cold severity.[44] Additionally, included studies differed with respect to population, baseline vitamin D levels and study length.

A 2015 systematic review of 7 RCTs in those aged 18 or younger found insufficient evidence supporting vitamin D supplementation and reduction of acute respiratory illness (relative risk (RR) 0·79, 95%CI 0·55, 1·13), all-cause mortality (RR 1·18, 95% CI 0·71, 1·94), or the rate of hospital admission due to respiratory infection in healthy children (RR 0·95, 95% CI 0·72, 1·26), however this study did identify a reduction in the risk of asthma exacerbation due to acute respiratory illness with vitamin D supplementation (RR 0·26, 95% CI 0·11, 0·59).[45] A 2019 systematic review and meta-analysis incorporating patient data from 7 RCTs and 955 participants reported an overall reduction in the rate of asthma exacerbations requiring treatment with systemic corticosteroids with vitamin D supplementation.[46]

A systematic review on non-skeletal effects of Vitamin D found that those with low levels are underrepresented in RCTs (inclusion criteria in 67 of 210 RCTs),[47] with a systematic review of 83 trials noting the poor quality of many meta-analyses.[48]

Randomised Control Trials

Two randomised, double-blind, placebo-controlled clinical trials were identified that evaluated the administration high dose vitamin D to critically ill patients with vitamin D deficiency (but not COVID-19). A phase 3 trial of 1360 patients reported no difference in 90-day mortality in those receiving early administration of high-dose enteral vitamin D (mortality difference, 2.9%; 95%CI, -2.1-7.9%; P = 0.26).[49] The VITdAL-ICU is the largest published ICU-based RCT on vitamin D supplementation to date. This single-centre study was conducted from May 2010 through September 2012 at 5 ICUs. 492 adult white patients with Vitamin D deficiency (≤20 ng/mL) were randomised to receive high-dose vitamin D_3 or placebo over a 5-month period. The study showed no reduction in hospital length of stay, hospital mortality, or 6-month mortality. Lower hospital mortality was observed in a severely deficient subgroup and requires further study.[50]

Multiple RCTs, included in the systematic reviews and meta-analysis discussed above, show conflicting evidence on vitamin D and prevention of acute respiratory illness. [51] [52] [53]

Laboratory Studies

Several laboratory-based simulation studies, or, mechanistic studies, have been published which demonstrate a role for vitamin D in the induction of antimicrobial peptides in response to both viral and bacterial stimuli. [1] [2] [54] A possible mechanism proposed to explain the association between vitamin D deficiency and poor COVID-19 outcome is that correction of vitamin D deficiency may suppress CD26, reducing adhesion of COVID-19; in addition to attenuation of interferon gamma and interleukin-6 inflammatory responses which are predictors of poorer outcome in critically-ill ventilated patients including those with COVID-19.[55]

It is important to note that vitamin D is a negative acute phase reactant i.e. serum levels fall in response to acute stress response, therefore single sample 25-OHD levels during critical illness may provide an inaccurate assessment of vitamin D status due to several confounders including albumin levels, interstitial extravasation, decreased synthesis of binding proteins, and renal wasting of 25-hydroxyvitamin D.[56]

Conclusions on the evidence

- Significant limitations with existing research were identified:
  - Systematic reviews and meta-analysis identified large heterogeneity and poor study quality;
  - Association studies included use of historic and inaccurate vitamin D status measurements, lack of generalisability, high likelihood of confounding or failure to adjust for confounders and general low quality of the evidence.
- There is no data from interventional trials showing that vitamin D supplementation may prevent COVID-19.[57]
- Circumstantial evidence linking COVID-19 outcomes and Vitamin D status has led to some supporting supplementation in vulnerable populations given safety profile and low risk of harm[58] [59]

Evidence review: additional considerations

Several studies have estimated the prevalence of vitamin D deficiency in the Irish population.

The National Adult Nutrition Survey sampled of 1132 adults between October 2008 and April 2010. This representative survey found 35.7% of adults aged 50-64 years, and 44.0% of adults aged 65-84 years had serum vitamin D levels less than 50nmol/l on a year-round basis, with these figures increasing to 55.4% and 48.1% respectively in winter. This study also assessed dietary intake of vitamin D and reported the mean daily intakes of vitamin D from diet and supplements was 5.2µg for men and 8.5µg for women (≥65 years), and 27% of both men and women regularly consumed a nutritional supplement containing vitamin D (males: 21%; females: 32%). Mean daily intake of vitamin D from natural foods was 3.6µg and increased to

4.7µg when the contribution of fortified foods was included. Fish, meats, eggs, and vitamin D-fortified foods contributed 23%, 19%, 7% and 17%, respectively.[60]

Results from the Irish Longitudinal Study on Ageing (TILDA) measured 25-hydroxyvitamin D levels in 5,356 adults over 50 years of age. The prevalence of deficiency (25OHD < 30 nmol/L) was 13.1% (95% CI: 12.1–14.2), with higher prevalence in winter, in smokers, in obese adults, the physically inactive, those living alone, and in those over 80 years. Through extrapolation they estimate that 1 in 8 (13%, 149,049) adults over 55 are deficient all year round;; 21.3% (244,209) adults over 55 are deficient in winter; 27%.1 (115,536) of Irish adults over 70 that were 'cocooning' in the springtime in 2020 are deficient and 46.6% (31,480) of all adults aged >85 are deficient in winter. The report also identified that 9.4% (107,773) of those aged 55+ and 11.5% (49,028) of those aged 70+ reported taking a vitamin D supplement during winter.[61] [62]

A cross-sectional study of 186 individuals of South East Asian descent between 2013 and 2016 found that 66.7% had vitamin D levels ≤30 nmol/L (i.e. deficient) and 6.7% had levels ≥50 nmol/L (the 25(OH)D concentration defined by the EU as 'sufficient'). Whilst average levels were higher in females than males (25.0 vs. 18.0 nmol/L; p = 0.001) both groups had a significant proportion with deficient status (56% and 76.8%, respectively).[63]

A cross-sectional study assessed 24,302 eligible patient samples processed through University Hospital Galway between January 2011 and December 2015. They reported vitamin D deficiency was more common in nursing home residents compared to inpatients, outpatient clinic patients or community-based patients (42% vs 37% vs 17% vs 13%; p < .001). Inpatients with a LOS (≥3 days) had greater Vitamin D deficiency than those with LOS ≤2 days (p = .007). Vitamin D deficiency was more common in Winter/Spring, in males, and in those aged ≥80 years.[64] Three Irish studies have demonstrated that daily 20µg vitamin D supplementation of at least 10 weeks duration is sufficient to correct deficiency in nursing home residents[65] and adults aged 50 and over.[66] [67]

A prospective cross-sectional study of healthy children attending the Children's University Hospital for elective surgery (26%), medical outpatients (62%), or the emergency department (12%) for a minor complaint conducted from March 2010 to March 2011 found that of 252 children aged 1 to 17 years 21.9% had 25OHD levels <30 nmol/L, 32.7% were between 30 and 50 nmol/L, and 45.4% had levels >50 nmol/L. Higher levels were associated with younger age (<4 years) and April-September sampling.[68] Recent review articles cited the high prevalence of low vitamin D levels (25[OH]D<30nmol/L) in preterm infants and (25OHD<50nmol/L) in older adults, hospital inpatients and nursing home residents, along with the potential anti-inflammatory and immunomodulatory properties of Vitamin D as justification for ensuring baseline Vitamin D sufficiency for potential enhancement of immune-protection against CoVID-19.[69] [70]

International Measures: England and Scotland

From January 2020 the Department of Health and Social Care in the UK are operating a 4-month opt-in scheme for extremely clinically vulnerable people to receive a supply of daily vitamin D supplements, this includes nursing home residents (Appendix A).[71] This follows a Scottish initiative offering a free 4-month supply of daily vitamin D supplements to everyone on the shielding list (Appendix B). Pregnant women, breastfeeding women and children under 12 months are already eligible for free supplements.[72] This followed the NICE rapid review previously referred to which reported insufficient evidence supporting a benefit of vitamin D supplementation in relation to COVID-19 prevention or response but advised supplementation during winter due to increased time indoors and proven bone and muscle health benefits (Appendix C). The NICE review recommended a 10µg (400 IU) dose per day or 25µg (1000IU) if 10mcg unavailable. The review acknowledged that low vitamin D status was associated with more severe outcomes from COVID-19, emphasising that this does not imply causality and given Vitamin D levels fall during a systematic inflammatory response that it has not been determined whether vitamin D status causes poorer outcomes or vice versa.

Conclusion

The role of vitamin D in bone and muscle health is well documented. Public health guidelines support supplementation in older adults based on these benefits and the risk of deficiency in older adults particularly those spending increased time indoors or in long-term nursing home care. A possible immunomodulatory role has been suggested by in vitro studies and association studies. There is currently insufficient evidence linking vitamin D use in the prevention and treatment of COVID-19. Evidence reporting an association between low vitamin D status and poorer outcomes in COVID-19 infection do not confirm causality and in most cases are of low quality. Previous research shows a modest reduction in the risk of acute respiratory illness with daily vitamin D3 supplementation over weeks to months. This evidence also has limitations, including publication and reporting bias and heterogeneity in study populations, interventions, and definitions of respiratory infections that include upper and lower respiratory tract involvement.

Despite this, research has identified a high prevalence of low vitamin D levels in winter months in Ireland, and given its role in bone and muscle health this report recommends the following:

- Increase awareness of existing guidance that adults age 65 and over should take a 15 microgram daily supplement for bone and muscle health
- Adults spending increased time indoors or are housebound or in long-term residential care or have dark skin pigmentation are also recommended to take vitamin D supplementation

- That ongoing developments, particularly RCTs, in this area be monitored with guidance reviewed accordingly

Appendix

Appendix 1: Summary of COVID-19 Treatment Study

Study	Entrenas Castillo 2020 RCT Spain	Murai 2021 RCT Brazil (PRE-PRINT)
Population	N=76 patients admitted to hospital with confirmed COVID-19	N=240 patients admitted to hospital with confirmed COVID-19
	Patients were randomised 2:1 into intervention (n=50) and comparator arms (n=26)	Patients were randomised 1:1 into intervention (n=120) and comparator arms (n=120)
Intervention	Patients in the intervention arm received calcifediol treatment calcifediol (0.532 mg) on admission, then 0.266 mg on days 3 and 7, then weekly until discharge, along with standard care	Patients in the intervention arm received a single oral dose of 200,000 IU (5,000mcg)
	Patients in the comparator arm received standard care only	Patients in the comparator arm received a placebo
Analysis	Univariate and multivariable logistic regressions were used to estimate the probability of admission to intensive care unit (ICU)	Univariate and multivariate regression models for hospital length of stay, admission to ICU and mechanical ventilation requirement were adjusted by potential confounders
	Mortality was reported as number of deaths	Mortality was reported as number of deaths
Outcomes	1) ICU admission 2) COVID-19 mortality	1) Hospital length of stay 2) Mortality, admission to ICU and requirement for ventilation 3) Vitamin D serum levels ≥30ng/mL
Results	Patients in the intervention arm were less likely to be admitted to intensive care versus those in the comparator group (OR 0.03 (95% CI 0.003, 0.25))	No difference in hospital length of stay in vitamin D and placebo groups (7.0 days [95% CI 6.1, 7.9] and 7.0 days [95% CI 6.2, 7.8 days], HR 1.12, [95% CI 0.9, 1.5]; p = .379) respectively
	Patients in the intervention arm had lower mortality versus those in the comparator group (OR 0.097, 95%CI 0.004, 2.099)	No difference in the reported rate of mortality (7.0% vs 5.1%; P = .59); admission to ICU (15.8% vs 21.2%; P = .314), and mechanical ventilation requirement (7.0% vs 14.4%; P = .090)
		86.7% of patients in the supplementation arm achieved vitamin D serum levels ≥30ng/mL compared to 11% in the placebo group
Limitations	Small sample size; serious risk of bias	Low power, and heterogeneity of the patient sample and its treatment

Appendix 2: Summary of COVID-19 Association Studies[26]

Study	Vitamin D Measurement	N	Adjusted for	Association	Quality
Hastie 2020	Vitamin D level (nmol/L)	Cases n=449 Control n=348,598	Ethnicity, sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, SBP, DBP, and longstanding illness, disability or infirmity	OR 1.00 (0.998 to 1.01)	Very low
	Vitamin D level (nmol/L) by ethnicity			OR 0.90 (0.66 to 1.23)	Very low
	Vitamin D deficiency			OR 0.92 (0.71 to 1.21)	Very low
	Vitamin D insufficiency			OR 0.88 (0.72 to 1.08)	Very low
Hernandez 2020	Vitamin D level (ng/ml)	Cases n=197 Control n=197	Age, smoking, hypertension, diabetes mellitus, history of cardiovascular events, immunosuppression, body mass index (BMI), serum corrected calcium, glomerular filtration rate and the month of vitamin D determination	MD: -9.3; p<0.001	Very low
Kaufman 2020	Vitamin D level (ng/ml)	Cohort N=191,779	Gender, age, latitudes, ethnicity	OR 0.984 (0.983 to 0.986)	Very low
Meltzer 2020	Vitamin D insufficiency	Positive n=71 Negative n=418	Hypertension, diabetes, chronic pulmonary disease, pulmonary circulation disorders, depression, immunosuppression, liver disease, and chronic kidney disease.	OR 1.77 (1.12 to 2.81)	Very low
Merzon 2020	Vitamin D suboptimal	Cases n=782 Control n=7025	Age, gender, ethnicity, smoking, depression/anxiety, schizophrenia, dementia, diabetes, hypertension, cardiovascular disease, chronic lung disease, obesity, BMI and socioeconomic status	OR 1.45 (1.08-1.95)	Very low

Raisi-Esrabragh 2020	Vitamin D level (nmol/L)	Cases n=1326 Control n=3184	Sex, age and ethnicity	OR 1 (1 to 1)	Very low

Appendix 3: Summary of Systematic Reviews and Meta-analyses of Vitamin D and Acute Respiratory Illness[73]

Studies	Martineau et al (2017)	Jolliffe et al (2020)
Trials included	25 trials (11,321 participants) from 14 countries up to 31 December 2015	45 trials (73,384 participants) from 18 countries up to 1 May 2020
Individual patient data	10,933 participants	46,331 participants (in 42 trials)
Study duration	7 weeks - 1.5 years	8 weeks - 5 years
Mean baseline 25(OH)D conc.	Reported in 19/25 trials: range 19 - 89 nmol/L	Reported in 34/42 trials: range 19-91 nmol/L
Population	10 (40%) in populations with pre-existing disease (including asthma, chronic obstructive pulmonary disease, pneumonia)	13 (31%) in populations with pre-existing disease (including asthma, chronic obstructive pulmonary disease, pneumonia)
	1 (4%) in low birthweight infants	1 (2.4%) in low birthweight infants and 2 (4.8%) in preterm infants
	1 (4%) in older care home residents with range of comorbidities (including asthma, chronic obstructive pulmonary disease, congestive heart failure, diabetes, dementia)	1 (2.4%) in older care home residents with range of comorbidities (including asthma, chronic obstructive pulmonary disease, congestive heart failure, diabetes, dementia)
Comparison	vitamin D vs placebo	vitamin D vs placebo higher vs lower dose vitamin D
Vitamin D dosing	daily (12 RCTs; 7.5 to 100µg; 7 weeks to 13 months)	daily (21 trials; 7.5 to 100µg; 7 weeks to 2 years)
	weekly (3 RCTs; 35 to 500 µg; 8 weeks to 6 months)	weekly (6 trials; 35 to 500 µg; 8 weeks 3 years)
	bolus (10 RCTs; once, monthly, 2-monthly, 3-monthly; 750-5000µg; 3 to 18 months)	bolus (13 trials; once, monthly, 2- monthly, 3-monthly; 750-5000µg; 3 to 3 years)
	bolus doses combined with daily vitamin D supplementation (3 studies)	bolus doses combined with daily vitamin D supplementation (2 studies
	control group also received vitamin D (2 studies)	control group also received vitamin D (7 studies)
		intervention group given vitamin D + calcium (1 study)
Subgroup analyses	Baseline 25(OH)D <25 nmol/l vs ≥25 nmol/l	Baseline 25(OH)D <25 vs 25-49.9 vs 50-74.9 vs ≥75nmol/l
	Dosing regimen: daily or weekly without bolus vs ≥1 bolus of ≥750µg	Dosing regimen: daily vs weekly vs monthly or less frequent
	Dose size daily equivalent: <20µg vs 20µg to <50µg vs ≥50µg	Dose size daily equivalent: <10µg vs 10-25µg vs > 25-50µg vs >50µg
	Age: ≤1 year vs 1.1-15.9 years vs 16-65 years vs >65 years	Age: ≤1 year vs 1.1-15.9 years vs 16-64.9 years vs >65 years
	Presence versus absence of asthma, COPD and previous influenza vaccination	Presence of airway disease (asthma vs COPD) vs those without airway disease

Results	Vitamin D supplementation reduced the risk of ARI among all participants (adjusted odds ratio 0.88, 95% CI 0.81, 0.96: heterogeneity p < 0.001)	Vitamin D supplementation reduced the risk of ARI among all participants (OR, 0.91; 95% CI, 0.84, 0.99; I 2=37.2% p for heterogeneity =0.014)
	2 step IPD meta-analysis reported a reduced risk of ARI (OR, 0.80; 95% CI, 0.69, 0.93; p=0.004; I^2=53.3%, p= for heterogeneity 0.001)	No statistically significant difference of higher versus lower vitamin D dosing (OR 0.87, 95% CI 0.73, 1.04 (I2 =0.0%, p for heterogeneity 0.496)
Sensitivity analyses	Excluding the 2 studies at unclear risk of bias: (OR, 0.82; 95% CI, 0.70, 0.95, p=0.01; 10,744 participants).	Excluding the 4 studies at unclear risk of bias: (OR, 0.93; 95% CI, 0.86, 1.00)
	Restricted to 14 trials where ARI a primary or coprimary outcome: protective effects with vitamin D supplementation (OR, 0.82; 95% CI, 0.68, 1.00; p=0.05, 5,739 participants)	Restricted to 18 trials with ARI as a primary or coprimary outcome: no significant protective effect (OR, 0.89; 95% CI, 0.77, 1.03; 7,537 participants)
Subgroup analyses: Dosing Frequency	Protective effect of vitamin D seen with daily or weekly vitamin D dosing (OR, 0.81; 95% CI, 0.72, 0.91; p<0.001) but not bolus doses (OR, 0.97; 95% CI, 0.86, 1.10; p=0.05)	Significant protective effect of vitamin D with daily dosing (OR 0.75, 95% CI 0.61, 0.93) but not weekly (OR 0.97, 95% CI 0.88, 1.06) or monthly to 3-monthly (OR 0.98, 95% CI 0.93, 1.03)
Subgroup analyses: Baselined 25(OH)D concentration	Protective effect of vitamin D in those with levels <25 nmol/L (OR, 0.89; 95% CI, 0.77, 1.04; p=0.15; 19 RCTs; 3634 participants)	No significant effect in any of the subgroups

Appendix 4: UK Definition of clinically extremely vulnerable groups: Summary of Systematic Reviews and Meta-analyses of Vitamin D and Acute Respiratory Illness[74]

People who are defined as clinically extremely vulnerable are at very high risk of severe illness from coronavirus. Patients are identified as clinically extremely vulnerable either by addition to the shielded patient list by a clinician or GP; or by having one or more of the following:

- solid organ transplant recipients
- people with specific cancers:
    - people with cancer who are undergoing active chemotherapy
    - people with lung cancer who are undergoing radical radiotherapy
    - people with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment
    - people having immunotherapy or other continuing antibody treatments for cancer
    - people having other targeted cancer treatments that can affect the immune system, such as protein kinase inhibitors or PARP inhibitors
    - people who have had bone marrow or stem cell transplants in the last 6 months or who are still taking immunosuppression drugs
- people with severe respiratory conditions including all cystic fibrosis, severe asthma and severe chronic obstructive pulmonary disease (COPD)
- people with rare diseases that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell disease)
- people on immunosuppression therapies sufficient to significantly increase risk of infection
- problems with your spleen, for example splenectomy (having your spleen removed)
- adults with Down's syndrome
- adults on dialysis or with chronic kidney disease (stage 5)
- women who are pregnant with significant heart disease, congenital or acquired
- other people who have also been classed as clinically extremely vulnerable, based on clinical judgement and an assessment of their needs. GPs and hospital clinicians have been provided with guidance to support these decisions

Appendix 5: Scottish Government Coronavirus (COVID-19): shielding list[75]

Those recognised as being at the highest risk of severe illness from coronavirus will be notified by post by the Chief Medical Officer. This includes the list below. Individuals in this list are advised to contact their GP or specialist care provider if they have not received a letter.

Grouping	How would I know if I am in this group?
Solid organ transplant recipients	People who have had a transplant of heart, lung, stomach or other part of intestine, liver and kidney. This is because of the medication taken to stop rejection of the transplanted organ.
People with specific cancers	• People with cancer who are undergoing active chemotherapy. Or people who have had radical radiotherapy for lung cancer. • People with cancers of the blood or bone marrow who are at any stage of treatment. This includes cancers such as leukaemia, lymphoma or myeloma. • People with cancer who are having immunotherapy or other continuing antibody treatments. • People with cancer who are having specialised treatments that can affect the immune system. This includes protein kinase inhibitors or PARP inhibitors. • People who have had bone marrow or stem cell transplants in the last 6 months. Or people who are still taking immunosuppression drugs.

People with severe respiratory conditions	• People with cystic fibrosis.
	• People who are on home oxygen for a lung condition.
	• People with severe asthma and on regular inhalers and long-term steroid tablets. For example, Prednisolone or regular injections to control your asthma.
	• People with severe COPD. This usually means being on several different inhaler medications in the last year. As well as a steroid inhaler, this must include two long acting preventers. For example, Long Acting Beta Agonists and Long Acting Anti-Muscarinic Antagonists. Severe COPD means that:
	    o You are too breathless to walk 100 yards
	    o You have 2 or more lung infections a year or
	    o You need oxygen to help with your breathing

People with rare diseases including all forms of	This includes inborn errors of metabolism that significantly increase the risk of infections. For example, SCID and homozygous sickle cell disease and adults with Down's syndrome.

Grouping	How would I know if I am in this group?
interstitial lung disease / sarcoidosis	There are many conditions classed as a rare disease. Not everyone with a rare disease will be in the shielding group
People on immunosuppression therapies that significantly increase risk of infection. Or people who have had their spleens removed	Immunosuppressive therapy helps to stop rejection of a bone marrow or organ transplant. It can also treat conditions in which the immune system is overactive. For example, autoimmune diseases and allergies. In some cases these treatments may put people into the shielding group. Your clinician can determine if your medications put you in this group. • People on high dose corticosteroids (equal to Prednisolone 20mg or more) for 4 weeks or more. • People on specific single therapies, e.g. Cyclophosphamide. These medications are usually prescribed by specialists in hospitals. • People on lower dose of corticosteroids in combination with other disease modifying medication. • People on disease modifying medications who also have other chronic medical conditions. • People who take some medication and are otherwise healthy may not need to be in the shielding group. This includes single Disease Modifying medications (DMARD). It also includes Biologic medications such as Methotrexate, Azathioprine, Ciclosporin, Leflunomide plus others. Discuss this with your specialist or GP if you are not sure.
People who are pregnant with significant heart disease, congenital or acquired	If you are being followed up by a specialist heart clinic during your pregnancy.
People who are receiving renal dialysis treatment and people who have chronic kidney disease stage 5	People receiving or starting renal dialysis, and people who have chronic kidney disease stage 5.

Appendix 6: Pre-COVID NHS Vitamin D Recommendations[76]

The NHS recommends that:

- breastfed babies and formula-fed babies consuming ≤500ml of infant formula per day from birth to 1 year of age should be given a daily Vitamin D supplement containing 8.5 to 10 micrograms;
- children aged 1 to 4 years old should be given a daily supplement containing 10 micrograms;
- adults (including women who are pregnant or breastfeeding), young people and children over 4 years should consider taking a daily supplement containing 10 micrograms (400IU) of vitamin D between October and early March;
- adults that are not often outdoors; are in an institution like a care home; usually wear clothes that cover up most of their skin when outdoors; have dark skin (e.g. those from an African, African-Caribbean or south Asian background) should consider taking a daily supplement containing 10 micrograms of vitamin D throughout the year.

Caution should be taken in:

- those under the care of a renal, endocrinology or cancer specialist
- people with high vitamin D levels
- people with kidney stones (now or in the past)
- people with too much parathyroid hormone (hyperparathyroidism),
- people with cancer (some cancers can lead to high calcium levels)
- people with severe kidney disease
- people with a rare illness called sarcoidosis

REFERENCES

[1] Hansdottir S, Monick MM, Hunninghake GW et al. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 2008;356:7090-9 doi:10.4049/jimmunol.181.10.7090 pmid:18981129

[2] Hewison M. Antibacterial effects of vitamin D. Nat Rev Endocrinol. 20117(6):337-45. doi: 10.1038/nrendo.2010.226. Epub 2011 Jan 25. Erratum in: Nat Rev Endocrinol. 2011 Aug;7(8):436. PMID: 21263449

[3] Hossein-nezhad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. PLoS ONE 2013;8, e58725. doi:10.1371/journal.pone.0058725

[4] Moozhipurath RK, Kraft L, Skiera B. Evidence of protective role of Ultraviolet-B (UVB) radiation in reducing COVID-19 deaths. Sci Rep. 2020;10(1):17705. doi: 10.1038/s41598-020-74825-z.

[5] Grant,WB et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients; 2020:12(4): 988

[6] Annweiler C, Hanotte B, Celarier, T et al. Vitamin D and survival in COVID-19 patients: A quasi-experimental study.; The Journal of steroid biochemistry and molecular biology; 2020; 105771

[7] Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of infection and public health;2020:13(10):1373-1380

[8] Israel A, Cicurel AA, Lavie G et al. The link between vitamin D deficiency and Covid-19 in a large population medRxiv 2020.09.04.20188268; doi: https://doi.org/10.1101/2020.09.04.20188268

[9] Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chemistry & biology 2014;21(3): 319-29. doi:10.1016/j.chembiol.2013.12.016

[10] Holick MF. Vitamin D deficiency. N Engl J Med 2020; 357: 266–81

[11] Jones AN, Hansen KE. Recognizing the musculoskeletal manifestations of vitamin D deficiency. J Musculoskelet Med. 2009;26(10):389-396

[12] Scientific Advisory Committee on Nutrition. Vitamin D and health. 2016 Available online at: https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report

[13] Aranow C. Vitamin D and the immune system. J Investig Med. 2011;59(6):881-886. doi:10.2310/JIM.0b013e31821b8755

[14] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D_3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. J Clin Endocrinol Metab 1988;67, 373–378

[15] Webb AR, Engelsen O. Calculated ultraviolet exposure levels for a healthy vitamin D status. Photochem Photobiol 2006; 82, 1697–1703

[16] Cashman KD, Kiely M. Recommended dietary intakes for vitamin D: Where do they come from, what do they achieve and how can we meet them? J Hum Nutr Diet. 2014; 27(5):434-42

[17] Griffin G et al. Vitamin D and COVID-19: evidence and recommendations for supplementation. Royal Society Open Science 2020; 7.12: 201912.

[18] Health Service Executive. HSE Policy on Vitamin D Supplementation for Infants in Ireland (2010), 31 May 2010 https://pdf4pro.com/cdn/policy-on-vitamin-d-supplementation-for-infants-in-ireland-595991.pdf

[19] FSAI. FSAI Advises on National Policy for Vitamin D Supplementation for Infants. 16 May 2007 https://www.fsai.ie/details.aspx?id=6984

[20] Health Service Executive. Vitamin D for babies 0 to 12 months. 2020 https://www2.hse.ie/wellbeing/child-health/vitamin-d-for-babies-0-12-months.html

[21] European Food Safety Authority Scientific Opinion on the Essential Composition of Infant Formula. 2014 https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3760

[22] FSAI Update to 2007 Scientific Committee Report: Recommendations for a National Policy on Vitamin D Supplementation for Infants in Ireland 2020 https://www.fsai.ie/Recommendations_Update_VitaminD/

[23] Department of Health. Vitamin D advice from the Department of Health for children from 1 to 4 years of age https://assets.gov.ie/93353/5b2c0185-e7c9-42df-9b19-05e1afe2882f.pdf

[24] Department of Health. New advice on Vitamin D supplement for people aged 65 years and older. 24 Nov 2020 https://www.gov.ie/en/press-release/7d595-new-advice-on-vitamin-d-supplement-for-people-aged-65-years-and-older/

[25] FSAI Vitamin D Scientific Recommendations for Food-Based Dietary Guidelines for Older Adults in Ireland 2020 https://www.fsai.ie/VitaminD_DietaryGuidelines_OlderAdults_Ireland

[26] NICE. Covid-19 rapid guideline: vitamin D. 17 December 2020. www.nice.org.uk/guidance/ng187

[27] Entrenas Castillo M et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. The Journal of steroid biochemistry and molecular biology 2020; 203): 105751. doi:10.1016/j.jsbmb.2020.105751

[28] Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF (2020) SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLOS ONE 15(9): e0239252. https://doi.org/10.1371/journal.pone.0239252

[29] Hastie CE, Mackay DF, Jill P et al. Vitamin D concentrations and COVID-19 infection in UK Biobank.; Diabetes & metabolic syndrome; 2020;14 (4); 561-565

[30] Raisi-Estabragh Z, McCracken C, Steffen E et al. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank.; Journal of public health; 2020:42(3); 451-460

[31] Meltzer DO, Best TJ, Solway J et al. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results.; JAMA network open; 2020;3(9); e2019722

[32] Merzon E, Tworowski D, Frenkel-Morgenstern M et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. The FEBS journal; 2020

[33] Hernandez JL, Nan D, Hernandez M et al. Vitamin D Status in Hospitalized Patients With SARS-CoV-2 Infection; The Journal of Clinical Endocrinology & Metabolism; 2020; dgaa733, https://doi.org/10.1210/clinem/dgaa733

[34] Macaya F, Espejo P, Miguel A et al. Interaction between age and vitamin D deficiency in severe COVID-19 infection.; Nutricion hospitalaria; 2020;37(5); 1039-1042

[35] Radujkovic A, Hippchen T, Merle U et al. Vitamin D Deficiency and Outcome of COVID-19 Patients. Nutrients; 2020; 12(9)

[36] Ye K, Tang F, Yang J et al. Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity?-A Case-Control Study.; Journal of the American College of Nutrition; 2020; 1-8

[37] Annweiler G, Corvaisier M, Annweiler C et al. Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study. Nutrients. 2020;12(11):3377. doi: 10.3390/nu12113377. PMID: 331478948

[38] Yisak H, Ewunetei A, Kefale B, et al. Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review. Risk Manag Healthc Policy. 2021;14:31-38. Published 2021 Jan 7. doi:10.2147/RMHP.S291584

[39] Murai IH, Fernandes AL, Pereira RMR et al. Effect of Vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: A Multicenter, Double-blind, Randomized Controlled Trial medRxiv 2020.11.16.20232397; doi: https://doi.org/10.1101/2020.11.16.20232397

[40] Martineau AR, Jolliffe DA, Camargo CA Jr et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583. doi: 10.1136/bmj.i6583. PMID: 28202713; PMCID: PMC5310969

[41] Jolliffe DA Camargo CA Jr, Martineau AR et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials medRxiv 2020.07.14.20152728; doi: https://doi.org/10.1101/2020.07.14.20152728

[42] Abioye AI, Bromage S, Fawzi W. Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis. BMJ Global Health 2021;6:e003176.

[43] Vuichard Gysin D, Dao D, Gysin CM, Lytvyn L, Loeb M. Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoSOne2016;356: e0162996. doi:10.1371/journal.pone.0162996 pmid:27631625

[44] Wang MX, Win SS, Pang J et al. Zinc supplementation reduces common cold duration among healthy adults: A systematic review of randomized controlled trials with micronutrients supplementation. Am J Trop Med Hyg. 2020;103(1):86-99. doi: 10.4269/ajtmh.19-0718.

[45] Xiao L, Xing C, Yang Z, et al. Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic review of randomised controlled trials. Br J Nutr. 2015;114(7):1026–1034

[46] Jolliffe, David A., et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. The lancet Respiratory medicine 2017:5(11): 881-890.

[47] Rejnmark L et al. "Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data." PloS one 2017; 12(7):e0180512 doi:10.1371/journal.pone.0180512

[48] Autier P, Mullie P, Boniol M et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. Lancet Diabetes Endocrinol. 2017; 5: 986–1004

[49] National Heart Lung and Blood Institute PCTN, Ginde AA, et al. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. N Engl J Med. 2019;381(26):2529-2540.

[50] Amrein K, Schnedl C, Holl A, et al. Effect of High-Dose Vitamin D_3 on Hospital Length of Stay in Critically Ill Patients With Vitamin D Deficiency: The VITdAL-ICU Randomized Clinical Trial. JAMA. 2014;312(15):1520–1530. doi:10.1001/jama.2014.13204

[51] Bergman P, Norlin AC, Hansen S et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. BMJ Open 2012; 2: e001663. https://doi.org/10.1136/bmjopen-2012-001663

[52] Murdoch DR, Slow S, Chambers ST et al. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. JAMA 2012; 308: 1333–9.

[53] Camargo CA Jr, Sluyter J, Scragg R et al. Effect of Monthly High-Dose Vitamin D Supplementation on Acute Respiratory Infections in Older Adults: A Randomized Controlled Trial, Clinical Infectious Diseases 2020 71(2); 311–317, https://doi.org/10.1093/cid/ciz801

[54] Olliver M, Spelmink L, Bergman P et al. Immunomodulatory effects of vitamin D on innate and adaptive immune responses to Streptococcus pneumoniae. J Infect Dis2013;356:1474-81. doi:10.1093/infdis/jit355 pmid:23922371

[55] McCartney DM, Byrne DG. Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir Med J. 2020;113(4):58. PMID: 32268051

[56] Quraishi SA, Camargo CA Jr. Vitamin D in acute stress and critical illness. Curr Opin Clin Nutr Metab Care. 2012 Nov;15(6):625-34. doi: 10.1097/MCO.0b013e328358fc2b. PMID: 23075939; PMCID: PMC3751798.

[57] Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? The Lancet Diabetes & Endocrinology, 2020; 8(7): 570

[58] Lancet Editorial Vitamin D and COVID-19: why the controversy? The Lancet Diabetes & Endocrinology, Jan 11, 2021 DOI:https://doi.org/10.1016/S2213-8587(21)00003

[59] Laird E, Rhodes J, Kenny RA. Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. Ir Med J. 2020;113(5):81. PMID: 32603576.http://imj.ie/vitamin-d-and-inflammation-potential-implications-for-severity-of-covid-19

[60] Cashman KD, Muldowney S, Flynn A et al. Vitamin D status of Irish adults: findings from the National Adult Nutrition Survey. Br J Nutr. 2013; 109:1248-56. doi: 10.1017/S0007114512003212.

[61] Laird E, Kenny RA. Vitamin D deficiency in Ireland – implications for COVID-19. Results from the Irish Longitudinal Study on Ageing (TILDA) 2020
https://tilda.tcd.ie/publications/reports/pdf/Report_Covid19VitaminD.pdf

[62] Laird E, O'Halloran AM, Kenny RA et al. The prevalence of vitamin D deficiency and the determinants of 25 (OH)D concentration in older Irish adults: Data from The Irish Longitudinal Study on Ageing (TILDA). The Journals of Gerontology: Series A. 2018 ;3(4):519-525
https://academic.oup.com/biomedgerontology/ article/73/4/519/4103040

[63] Laird E, Walsh JB, Healy M et al. A High Prevalence of Vitamin D Deficiency Observed in an Irish South East Asian Population: A Cross-Sectional Observation Study. Nutrients. 2020;12(12):3674. doi: 10.3390/nu12123674. PMID: 33260572; PMCID: PMC7760119

[64] Griffin TP, Wall D, O'Shea PM et al. Vitamin D status of adults in the community, in outpatient clinics, in hospital and in nursing homes in the West of Ireland. J Gerontol A Biol Sci Med Sci. 2020;pii: glaa010. doi: 10.1093/gerona/glaa010

[65] McKenna MJ, Freaney R, Muldowney FP et al. Prevention of hypovitaminosis D in the elderly. Calcified tissue international, 1985;37(2), 112-116.

[66] Cashman KD, Hayes A, Seamans KM. Dietary calcium does not interact with vitamin D3 in terms of determining the response and catabolism of serum 25-hydroxyvitamin D during winter in older adults. The American Journal of Clinical Nutrition, 2014;99(6), 1414-1423

[67] Cashman KD, Seamans KM, Hill TR et al. Relative effectiveness of oral 25-hydroxyvitamin D3 and vitamin D3 in raising wintertime serum 25-hydroxyvitamin D in older adults. The American journal of clinical nutrition, 2012;95(6), 1350-1356

[68] Carroll A, Onwuneme C, Murphy NP et al. Vitamin D status in Irish children and adolescents: value of fortification and supplementation. Clinical pediatrics, 2014;53(14), 1345-1351

[69] Molloy EJ, Murphy N. Vitamin D, Covid-19 and Children. Ir Med J. 2020;113(4):64. PMID: 32268052.

[70] McKenna MJ, Flynn MAT. Covid-19, Cocooning and Vitamin D Intake Requirements. Ir Med J. 2020;113(5):79. PMID: 32603573.

[71] Department of Health and Social Care. Vitamin D and clinically extremely vulnerable (CEV) guidance Jan 2021 https://www.gov.uk/government/publications/vitamin-d-for-vulnerable-groups/vitamin-d-and-clinically-extremely-vulnerable-cev-guidance

[72] NHS Inform Scotland Coronavirus (COVID-19): Shielding Jan 2021
https://www.nhsinform.scot/illnesses-and-conditions/infections-and-poisoning/coronavirus-covid-19/coronavirus-covid-19-shielding

[73] Scientific Advisory Committee on Nutrition. Update of rapid review: Vitamin D and acute respiratory tract infections Dec 2020

[74] Department of Health and Social Care. Guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19. 13 Jan 2021
https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#cev

[75] Scottish Government Coronavirus (COVID-19): shielding advice and support: highest risk group 25 Nov 2020 https://www.gov.scot/publications/covid-shielding/pages/highest-risk-classification/

[76] NHS Vitamin D Recommendations 2020 https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/