Vitamin D supplementation could prevent and treat influenza, coronavirus, and pneumonia infections

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Abstract

Low vitamin D status in winter permits viral epidemics. During winter, people who do not take vitamin D supplements are likely to have low serum 25-hydroxyvitamin D [25(OH)D] concentrations. Vitamin D can reduce the risk of viral epidemics and pandemics in several ways. First, higher 25(OH)D concentrations reduce the risk of many chronic diseases, including cancers, cardiovascular disease, chronic respiratory tract infections (RTIs), diabetes mellitus, and hypertension. Patients with chronic diseases have significantly higher risk of death from RTIs than otherwise healthy people. Second, vitamin D reduces risk of RTIs through three mechanisms: maintaining tight junctions, killing enveloped viruses through induction of cathelicidin and defensins, and reducing production of proinflammatory cytokines by the innate immune system, thereby reducing the risk of a cytokine storm leading to pneumonia. Observational and supplementation trials have reported higher 25(OH)D concentrations associated with reduced risk of dengue, hepatitis, herpesvirus, hepatitis B and C viruses, human immunodeficiency virus, influenza, respiratory syncytial virus infections, and pneumonia. Results of a community field trial reported herein indicated that 25(OH)D concentrations above 50 ng/ml (125 nmol/l) vs. <20 ng/ml were associated with a 27% reduction in influenza-like illnesses. From the available evidence, we hypothesize that raising serum 25(OH)D concentrations through vitamin D supplementation could reduce the incidence, severity, and risk of death from influenza, pneumonia, and the current COVID-19 epidemic.

Key words: ascorbic acid, cathelicidin, coronavirus, COVID-19, cytokine storm, influenza, observational, pneumonia, prevention, respiratory tract infection, solar radiation, treatment, UVB, vitamin C, vitamin D

1.Introduction

The world is now experiencing its third major epidemic of coronavirus (CoV) infections. A new CoV infection epidemic began in Wuhan, Hubei, China, in late 2019, originally called 2019-nCoV [1] and renamed COVID-19 by the World Health Organization on February 11, 2020. Previous CoV epidemics include severe acute respiratory syndrome (SARS)–CoV, which started in China in 2003 [2], and Middle East respiratory syndrome (MERS)–CoV in the Middle East, starting 2012 [3]. Those epidemics all began with animal-to-human infection. The mortality rates were >10% for SARS and >35% for MERS [4]. The direct cause of death is generally due to ensuing severe atypical pneumonia [4], [5].. Pneumonia also is generally the cause of death for people who develop influenza, although the mortality rate is lower (1%–3% for the influenza A H5N1 pandemic of 1918–1919 in the United States) [6].

CoVs also include four types associated with seasonal respiratory tract infections (RTIs): human CoV 229E (HCoV-229E), human CoV OC43 (HCoV-OC43), human CoV NL63 (HCoV-NL63,

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or New Haven CoV), and human CoV HKU1. During surveillance from May 2014 to December 2015, three of those CoVs were detected in children crossing between southern China and Hong Kong mainly around January to February, whereas HCoV-NL63 was detected only in summer and fall [7].

Given the enormous economic impact of CoV epidemics, ways must be found to reduce the risk of infection and death that can be easily applied to large populations at a low cost. Both vitamin C and vitamin D may be appropriate because they have demonstrated antiviral properties [8], [9] as well as antimicrobial properties, which are important in reducing risk of pneumonia [10], [11] and are inexpensive. Although vitamin C can play an important role, as outlined in several studies that have identified mechanisms whereby ascorbic acid reduces risk of RTIs [12], [13], [14], reviewed in [15], this article focuses on a review of the evidence for vitamin D. However, several clinical trials are being conducted on intravenous vitamin C infusion to treat COVID-19 in China (https://clinicaltrials.gov/ct2/show/NCT04264533). Vitamin C and vitamin D can probably work together to minimize the incidence as well as treat the infection.

This review is narrative. Searches were made in PubMed.gov and scholar.google.com for publications regarding influenza, CoVs, and pneumonia with respect to epidemiology, innate and adaptive immune response, vitamin D, 25-hydroxyvitamin D [25(OH)D], and parathyroid hormone.

2.Results

*2.1.*Seasonal influenza

Seasonal influenza accounts for many more deaths annually than any previous CoV epidemics have. A recent estimate of influenza-associated respiratory mortality (291,243–645,832 deaths annually; 4.0–8.8 per 100 000 individuals) [16] are higher than previously published estimates, [17] which estimated 148,000–249,000 annual influenza-associated respiratory deaths, and the WHO-attributed estimate of 250,000–500,000 respiratory and circulatory deaths (3·8–7·7 per 100 000 individuals). In the United States during the 2018–2019 influenza season, an estimated 17,443 people died from influenza A(H3N2), 15,136 from influenza A(H1N1)pdm09, and 1364 from influenza B, for a total of 33,943 deaths [18]. However, the influenza burden is probably higher than what was reported there because a significant number of deaths attributed to pneumonia may be related to what was initially an influenza infection [19]:

Influenza virus affects the respiratory tract by direct viral infection or by damage from the immune system response. Patients who develop pneumonia are more likely to be < 5 years old, > 65 years old, Caucasian, and nursing home residents; have chronic lung or heart disease and history of smoking, and are immunocompromised. [20]

Seasonal influenza infections generally peak in winter [21]. Cannell hypothesized that the winter peak was due in part to the conjunction with the season when solar UVB doses, and thus 25(OH)D concentrations, are lowest in most mid- and high-latitude countries [22], extended in

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[23]. (It is impossible to produce vitamin D from solar UVB exposure in Boston, Massachusetts [42.4°N], for about 6 months of the year [24], [25].) As a result, mean serum 25(OH)D concentrations in north and central regions of the United States are near 21 ng/ml in winter and 28 ng/ml in summer, whereas in the south region, they are near 24 ng/ml in winter and 28 ng/ml in summer [26].] In addition, the winter peak of influenza also coincides with weather conditions of low temperature and relative humidity that allow the influenza virus to survive longer outside the body than under warmer conditions [27], [28], [29].

The "NorthernFlu" consortium involved epidemiologists, clinicians, and researchers from Estonia, Finland, Latvia, Lithuania, Norway, and Sweden. That group collected and analyzed data to determine the effect of meteorological and other factors regarding severe influenza virus infections [30]. A total of 62,296 influenza virus–positive specimens were collected between 1 September 2017 and 31 August 2018. Peak numbers occurred in week 7 of 2018. The Pearson correlation coefficients found were as follows: temperature, 0.51 ± 0.08; UV index, 0.39 ± 0.11; humidity, 0.26 ± 0.15; wind speed, 0.09 ± 0.06; precipitation, 0.07 ± 0.01; and pressure, 0.03 ± 0.02. In vitro laboratory experiments confirmed the findings regarding temperature and UV radiation, although UVC was effective and UVB was not. UVC does not reach Earth's surface. A later article reported a laboratory experiment showing that sunlight exposure reduced the half-life of influenza viruses in aerosols at 20% and 70% relative humidity from 31.6 minutes in darkness to 2.4 minutes in full sunlight [31]. Thus, part of the seasonal variation in influenza incidence is probably affected by the amount of sunlight in inactivating the virus.

Ecological studies suggest that raising 25(OH)D concentrations through vitamin D supplementation in winter would reduce the risk of developing influenza. A comprehensive review of the role of vitamin D and influenza was published in 2018 [32]. On the positive side, vitamin D–related innate and adaptive immune responses to viral infections exist. A vitamin D randomized controlled trial (RCT) conducted on schoolchildren in Japan reported significantly reduced incidence of influenza type A but not B for children in the treatment arm taking 1200 IU/d of vitamin D [33]. Although most other trials did not support a beneficial effect of vitamin D supplementation in reducing risk of influenza infection, another recent RCT did [34]. The Gruber-Bzura article concluded that the evidence of vitamin D's effects on the immune system suggest that it should reduce the risk of influenza but that more RCTs are required to evaluate that possibility.

An observational study conducted in Connecticut on 198 healthy adults in the fall and winter of 2009–2010 examined the relationship between serum 25(OH)D concentration and incidence of acute RTIs (ARTIs) [35]. Only 17% of people who maintained 25(OH)D >38 ng/ml throughout the study developed ARTIs, whereas 45% of the others did. Concentrations of 38 ng/ml or more were associated with a significant ($p < 0.0001$) twofold reduction in risk of developing ARTIs

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and with a marked reduction in percentages of days ill. Eight influenza-like illnesses (ILIs) occurred, seven of which were 2009 H1N1 influenza.

*2.2.*GrassrootsHealth observational field trial

Previously unpublished data from an ongoing prospective cohort study by GrassrootsHealth, a nonprofit organization that researches how nutrients affect public health, shows a reduction in ILIs as 25(OH)D levels increase. In that study, launched January 2009, health and demographic information is collected via online health questionnaires on a rolling basis from voluntary participants who also purchase and submit home blood spot 25(OH)D tests. Liquid chromatography–mass spectroscopy was used by ZRT Laboratory (Beaverton, OR) and Purity Laboratory (Lake Oswego, OR) to analyze the dried blood spot tests and determine serum 25(OH)D concentrations. The intra-assay coefficient of variation was 9% for ZRT and 5% for Purity. ZRT and Purity assays have been validated against the DEQAS liquid chromatography–mass spectroscopy consensus group (R^2 values of 0.998 and 0.994, respectively). No exclusion criteria or requirements related to 25(OH)D concentration or supplement intake dose were in place; however, most participants (>80%) choose to take a supplement with vitamin D. Participants included both sexes and a wide range of ages and geographic locations (55 countries, with 92% in the United States or Canada).

Among participants aged 18 years or older (N = 12,605), a cross-sectional analysis was conducted to determine the percentage of participants who answered "yes" to the question "In the last 6 months, have you had the flu with fever?" for the following 25(OH)D concentration groups: <20, 20–39, 30–39, 40–49, 50–59, and ≥60 ng/ml (Figure 1). **Participants with 25(OH)D concentrations of at least 60 ng/ml had a 43% lower risk of ILI than those with 25(OH)D concentrations less than 20 ng/ml ($p < 0.0001$).** The lower level, 20 ng/ml, is used specifically because it is the point that the Institute of Medicine considered sufficient [36]; the minimum upper level, 60 ng/ml, is used because the GrassrootsHealth Scientists' Panel of 48 vitamin D researchers created a consensus statement that the recommended range is 40–60 ng/ml (https://www.grassrootshealth.net/project/our-scientists/).

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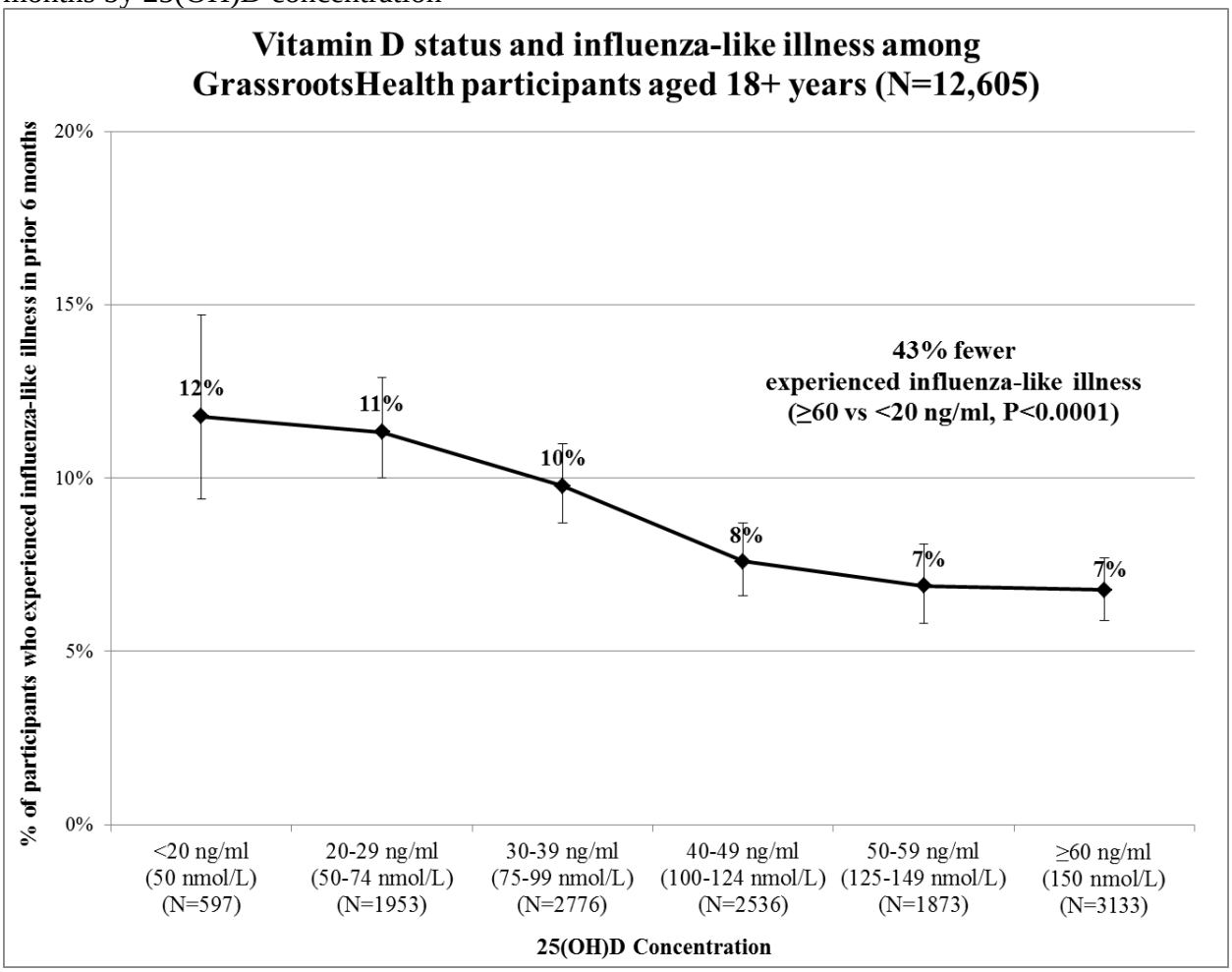
Figure 1. Percentage of GrassrootsHealth participants who experienced ILE in the previous 6 months by 25(OH)D concentration



25(OH)D, 25-hydroxyvitamin D.

Multivariate regression was used to determine the association between 25(OH)D concentration and the risk of ILI, adjusting for age and season (Table 1). People with concentrations of 40–49 ng/ml had a 25% lower risk ($p = 0.04$), those with concentrations of 50–59 had a 30% lower risk ($p = 0.02$), and those with concentrations of at least 60 ng/ml had a 27% lower risk ($p = 0.03$) of ILI than participants with 25(OH)D concentrations of less than 20 ng/ml. Age and season also were significant predictors of ILI ($p < 0.05$). Higher 25(OH)D concentrations were associated with a dose–response decrease in ILI risk, with concentrations ≥40 ng/ml being most protective.

Table 1. Regression results for ILI as a function of 25(OH)D concentration

25(OH)D concn, ng/ml (nmol/L)	Unadjusted Risk Ratio (95% CI)	*p*	Adjusted* Risk Ratio (95% CI)	*p*
<20 (50)	Ref.		Ref.	

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20–29 (50–74)	0.96 (0.74–1.27)	0.78	0.99 (0.76–1.31)	0.96
30–39 ng/ml (75–99)	0.83 (0.64–1.09)	0.17	0.91 (0.70–1.20)	0.50
40–49 (100–124)	0.64 (0.49–0.86)	0.002	0.75 (0.57–0.99)	0.04
50–59 (125–149)	0.58 (0.44–0.79)	0.0003	0.70 (0.52–0.94)	0.02
≥60 (150)	0.57 (0.44–0.76)	<0.0001	0.73 (0.56–0.97)	0.03

95% CI, 95% confidence interval.
*Adjusted for age and season.

In RCTs, participants do not know whether they are in the treatment or control arms, while in open trials they do. A recent review of high-dose vitamin D supplementation trials involving elderly participants concluded that "an open trial is easier to conduct and, when it ends, those taking vitamin D can be offered a continuing supply so that the effect of lifelong treatment can be studied for major diseases and life expectancy, which are unlikely to be affected by individuals knowing whether or not they are taking vitamin D." [37]. This review supports the validity of the GrassrootsHealth open-label field trials such as this one and previous ones [38], [39], [40], [41] as well as those by Pure North S'Energy Foundation [42].

*2.3.*Pandemic influenza

"Pandemic influenzas are unexpected rare events related to the emergence of a reassorted human-pathogenic influenza A virus (IAV) strains that often causes increased morbidity and spreads extremely rapidly in the immunologically naive human population, with huge clinical and economic impact" [43].

Influenza pandemics have outcomes different from those of seasonal influenza. For example, during the 2009 H1N1 pandemic influenza,

> "Adults hospitalized with H1N1pdm09 were younger (median age, 47 years) than those with seasonal influenza (median age, 68 years; $p < 0.01$), and differed in the frequency of certain underlying medical conditions. Whereas there was similar risk for many influenza-associated complications, after controlling for age and type of underlying medical condition, adults hospitalized with H1N1pdm09 were more likely to have lower respiratory tract complications, shock/sepsis, and organ failure than those with seasonal influenza. They were also more likely to be admitted to the intensive care unit, require mechanical ventilation, or die." [44]

*2.4.*Coronavirus infections

CoVs and influenza share several important features: they are enveloped viruses [45], [46], the season of peak infection is generally in winter, and the cause of death is generally from ensuing pneumonia. CoVs also can survive a long time outside the body. A laboratory study reported that

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CoVs could stay viable from 2 hours on aluminum and paper to up to 9 days on plastic at normal room temperature [47]. At temperatures of 30°C to 40°C, survival times were much lower, whereas at 4°C, persistence lasted up to 28 days.

An important reason why COVID-19 cases and deaths have been high in countries such as China and Korea is that serum 25(OH)D concentrations are generally low in those countries, especially in winter. In China, mean wintertime 25OHD concentrations for postmenopausal women from 28°N to 45°N between July 2013 and February 2014 were ~14 ng/ml [48]. In Korea, between October 2011 and May 2014, mean serum 25(OH)D concentrations for people older than 60 years were ~18 ng/ml for males and ~15 ng/ml for females [49]. Food in neither country is fortified with vitamin D, and few inhabitants take vitamin D supplements. A 13-year study conducted in Milan, Italy, reported that summertime mean 25(OH)D concentrations reached about 33–35 ng/ml in summertime for both males and females and ~20 ng/ml for males and 23 ng/ml for females in winter [50]. An analysis of standardized 25(OH)D concentration data from 14 European population studies indicated that 13.0% of the 55,844 European individuals had serum 25(OH)D concentrations <12 ng/ml on average in the year, with 17.7% and 8.3% in those sampled during the extended winter (October–March) and summer (April–November) periods, respectively. The prevalence was 40.4% for 25(OH)D concentrations <20 ng/ml [51].

More important, people with chronic diseases have lower 25(OH)D concentrations and increased inflammation. A study in Triese, Italy, reported that patients with a mean age of 67 ± 12 years who developed acute myocardial infarction had mean serum 25(OH)D concentrations in winter of 11 ± 2 ng/ml [52]. A study conducted in Wenzhou, China (28°N), on diabetics and control subjects aged 43 ± 11 years reported that diabetics had mean 25(OH)D concentration of 13 vs. 16 ng/ml for control subjects [53]. An observational study conducted in Qinhuangdao, China, compared serum 25(OH)D concentrations for hospital patients with pneumonia vs. those without [54]. Serum 25(OH)D concentrations for those with pneumonia were 9 ± 2 ng/ml, whereas those for the nonpneumonia group were 14 ± 4 ng/ml, $p = 0.000$. A study from China reported that prediabetics had lower 25(OH)D concentrations than normal fasting glucose control subjects as well as significantly higher C-reactive protein concentrations as 25(OH)D concentrations decreased [55].

As shown in graphs of cases of the SARS-CoV epidemic as a function of week of onset [56], the SARS-CoV epidemic started in late November 2002. The first peak occurred in late January/early February 2003. Several additional peaks, with the last occurring in mid-April, occurred, with few cases after the end of May. The peaks in April were due to an outbreak in Taiwan [57].

The epidemiological characteristics of the COVID-19 outbreak in China through February 11, 2020, were recently published [58]. Factors of interest included the following:

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1. The case-fatality rate (CFR) increased monotonically from 0.2% for patients younger than 40 years to 14.8% for those ≥80 years.
2. CFRs were higher for men than for women (2.8% vs. 1.7%).
3. Having comorbid conditions greatly increased the CFR (N = none, 0.9%; cancer, 5.6%; hypertension, 6.0%; chronic RTI, 6.3%; diabetes mellitus, 7.3%; cardiovascular disease [CVD], 10.5%).

A possible reason for the monotonic increase in CFR with increasing age could be that the presence of chronic diseases increases with age. For example, the global prevalence of diabetes mellitus increases from about 1% below the age of 20 years to ~10% at 45 years to 19% at 65 years, decreasing to 14% by 95 years [59]. Invasive lung cancer incidence rates for females in the United States in 2015 increased from 1.1/100,000 for those aged 30–34 years, to 51.0/100,000 for those aged 50–54 years, 204.1/100,000 for those aged 65–79 years, and 347.3 for those aged 75–79 years [60]. Several studies report that people with chronic diseases have lower 25(OH)D concentrations than healthy people. A study in Italy reported that male chronic obstructive pulmonary disease patients had mean 25(OH)D concentrations of 16 (95% CI, 13 to 18) ng/ml, whereas female patients had concentrations of 13 (95% CI, 11 to 15) ng/ml [61]. A study in South Korea reported that community-acquired pneumonia (CAP) patients had a mean 25(OH)D concentration at admission of 14 ± 8 ng/ml [62]. A study in Iran reported that hypertensive patients had lower 25(OH)D concentrations than control subjects: males, 13 ± 11 vs. 21 ± 11 ng/ml; females, 13 ± 10 vs. 20 ± 11 ng/ml [63].

A large body of evidence indicates that vitamin D supplementation and higher 25(OH)D concentrations are causally linked to reduced risk of many chronic diseases, including cancers, CVD, and diabetes mellitus [64], [65], [66]. Table 2 presents evidence that the comorbid conditions associated with higher CFR are due in part to low 25(OH)D concentrations.

Table 2. Evidence that relate comorbid conditions to vitamin D deficiency

Outcome	Evidence	Ref.
Cancer	Observational field trials of 25(OH)D	[38], [41]
	Secondary analyses of a 2000-IU/d vitamin D_3 RCT	[67]
Hypertension	Results of an open-label, high-dose vitamin D_3 supplementation field trial	[42]
COPD	Meta-analysis of risk, severity, and exacerbation with respect to 25(OH)D concentration	[68]
Diabetes mellitus	Secondary analyses of a 4000-IU/d vitamin D_3 RCT	[69]
CVD	Meta-analysis of CVD incidence and mortality rates related to 25(OH)D concentration in prospective studies	[70]

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25(OH)D, 25-hydroxyvitamin D; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; RCT, randomized controlled trial.

As for frail health, mortality rates in the United States from CVD and other diseases are about 25% higher in winter than in summer [71]. However, that effect occurs mainly for the elderly who already have CVD, indicating that factors such as cold temperature and low 25(OH)D concentrations finally take their toll. Calcitriol concentrations also vary with season and vitamin D supplementation. A study in Europe involving men aged 40–79 years reported that calcitriol concentrations varied from 54 pg/ml in winter to 67 pg/ml in summer, whereas 25(OH)D concentrations varied from 20 ng/ml in winter to 35 ng/ml in summer [72]. A meta-analysis reported that vitamin D supplementation in trials with low risk of bias increased calcitriol concentrations by 18.1 (95% CI, 9.2 to 28.4) pmol/l [73].

Another factor that affects immune response with age is reduced 1,25-dihydroxyvitamin D [1,25$(OH)_2$D, or calcitriol], the active vitamin D metabolite, with increased age. Parathyroid hormone (PTH) concentration increases with age. A U.S. study was based on 312,962 paired serum PTH and 25(OH)D concentration measurements from July 2010 to June 2011. For participants with 20-ng/ml 25(OH)D concentration, PTH increased from 27 pg/ml for those <20 years to 54 pg/ml for those $\geq$60 years [74]. Serum calcitriol concentrations are inversely related to PTH concentrations. In a study conducted in Norway on patients with a mean age of 50 (SD, 21) years, calcitriol decreased from 140 pmol/l for those aged 20–39 years to 98 pmol/l for those >80 years despite an increase in serum 25(OH)D from 24 ng/ml for those 20–39 years to 27 ng/ml for those >80 years [75].

Evidence also suggests that health outcomes are related to calcitriol concentrations. In a study of infections in 3340 consecutive cardiac surgical patients, the adjusted odds ratio for low vs. high calcitriol concentration was 2.57 (95% CI, 1.47 to 4.49) vs. 1.62 (95% CI, 0.87 to 3.20) for low vs. high 25(OH)D concentration [76]. A study of renal transplant patients reported significantly increased hazard ratio for polyomavirus infection during the first year after transplant for calcitriol concentrations <20 pg/ml [hazard ratio = 2.14 (95% CI, 1.12 to 4.78)] and cytomegalovirus infection [hazard ratio = 2.33 (95% CI, 1.05 to 5.24)] [77].

Another factor relates to age-associated changes in the innate immune response. A review on immunosenescence reported that the innate immune response increases cytokine production with aging [78]. By contrast, young children are more susceptible to severe influenza A infection as a result of differences in the innate immune response [79].

The male-to-female ratio of CFR of 1.6 is probably due largely to the fact that males in China smoke much more than females. A study in Shanghai reported that 48% of adult males and 0.2% of adult females were smokers [80]. That study also reported adjusted odds ratios of tobacco-

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related chronic diseases for smokers in comparison with nonsmokers: cancer, 10.5; hypertension, 1.39; chronic RTI, 2.34; diabetes mellitus, 1.33; coronary diseases, 1.35. However, the fact that the male-to-female ratio is not higher may exist because women have lower mean 25(OH)D concentrations than males [48].

The seasonality of many viral infections is associated with low 25(OH)D concentrations, as a result of low UVB doses owing to winter in temperate climates and the rainy season in tropical climates—such as respiratory syncytial virus infection [81]. That is the case for influenza [21], [22] and SARS-CoV [82]. However, MERS showed a peak in the April–June quarter [83], probably affected by both Hajj pilgrims gathering and that 25(OH)D concentrations show little seasonal variation in the Middle East [84]. In the tropics, seasonality is related more to rainy periods (low UVB doses), for example, for influenza [85] and respiratory syncytial virus [86].

Considerable indirect evidence is inferred from effects found for other enveloped viruses. Higher vitamin D status has been inversely associated with enveloped virus infections such as dengue [87], [88], [89], [90], hepatitis [91], [92], herpesvirus [93], HIV [94], influenza [95], respiratory syncytial virus [96], and rotavirus [97], [98], among others [10], [99]. “An association has been established between low levels of vitamin D and upper respiratory and enteric infections, pneumonia, otitis media, *Clostridium* infections, vaginosis, urinary tract infections, sepsis, influenza, dengue, hepatitis B, hepatitis C, and HIV infections.” [100].

An analysis based on 357 SARS cases and 245 MERS cases reported that 17% of SARS patients required invasive mechanical ventilation and 5% died, whereas for MERS, 37% required invasive mechanical ventilation and 29% died [5]. The differences were partially attributed to differences in host factors such as age and underlying diseases but more importantly to CoV-particular differences in effects. Fatal cases were reported mainly in frail patients such as neonates, the elderly, and immunocompromised patients. However, for four other CoV infections, CFRs were low [5].

One way that CoVs injure the lung epithelial cells and facilitate pneumonia is through increased production of Th1-type cytokines as part of the innate immune response to viral infections, giving rise to the cytokine storm. A laboratory cell study reported that interferon γ is responsible for acute lung injury during the late phase of the SARS-CoV pathology [101].

Proinflammatory cytokine storms from CoV infections have resulted in the most severe cases for SARS-CoV [102] and MERS-CoV [103]. However, COVID-19 infection also initiated increased secretion of Th2 cytokines (e.g., interleukins 4 and 10) that suppress inflammation, which differs from SARS-CoV infection [104], (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020).

*2.5.*Pneumonia

An example of the role of vitamin D in reducing risk of death from pandemic respiratory tract infections is found in a study of CFRs resulting from the 1918–1919 influenza pandemic in the United States [6]. The U.S. Public Health Service conducted door-to-door surveys of 12 communities from New Haven, Connecticut, to San Francisco, California, to ascertain incidence and CFRs. The canvasses were made as soon as possible after the autumn 1918 wave of the epidemic subsided in each locality. A total of 146,203 people, 42,920 cases, and 730 deaths were found. As shown in their Table 25, fatality rates averaged 1.70 per 100 influenza cases but averaged 25.5 per 100 cases of pneumonia. The pneumonia CFR (excluding Charles County, MD, because of inconsistencies in recording cause of death) was 28.8 per thousand for whites and 39.8 per 1000 for blacks. As discussed in an ecological study using those CFR data, communities in the southwest had lower CFR than those in the northeast because of higher summertime and wintertime solar UVB doses [105]. Previous work suggested that higher UVB doses were associated with higher 25(OH)D concentrations, leading to reductions in the cytokine storm and killing of bacteria and viruses that participate in pneumonia. One reason CFRs were higher for blacks than whites is that with darker skin pigmentation, blacks have lower 25(OH)D concentrations. An analysis of serum 25(OH)D concentrations by race for 2001–2004 indicated mean 25(OH)D concentrations for people over 40 years: non-Hispanic whites, ~25–26 ng/ml; non-Hispanic blacks, 14–17 ng/ml; Mexican-Americans, 18–22 ng/ml [106].

A study in China reported that elderly people who developed CAP had lower 25(OH)D concentrations than those in the control group (9 ± 2 vs. 13 ± 4 ng/ml; $p < 0.001$) [54].

Smoking is a significant risk factor for CAP. A study from Spain involving 74,610 adults in Barcelona, of whom 205 developed pneumonia, reported that "smoking any type of tobacco had an odds ratio (OR) of CAP of 2.0 for ever smokers (95% confidence interval [CI], 1.24 to 3.24); 1.88 for current smokers (95% CI, 1.11 to 3.19); and 2.14 for ex-smokers (95% CI, 1.26 to 3.65). A positive trend for increased risk of CAP was observed for an increase in the duration of the habit, the average number of cigarettes smoked daily, and cumulative cigarette consumption." [107].

CAP infections vary seasonally. A U.S. study for 1998 to 2000 reported that CAP infection rates were approximately twice as high in winter as in summer [108].

A prospective study involving 723 men and 698 women aged 53–73 years, free of pneumonia, other pulmonary diseases, and cancer at baseline in 1998–2001, was conducted in Finland [109]. The mean (SD) serum 25(OH)D_3 concentration of the study population was 17 ± 7 ng/ml. Seventy-three subjects had at least one hospitalization episode due to pneumonia during an average follow-up of 9.8 years. After multivariable adjustments, the subjects in the lowest serum 25(OH)D_3 tertile had a 2.6-fold (95% CI, 1.4 to 5.0, p_{trend} across tertiles = 0.005) higher risk of developing pneumonia than subjects in the highest tertile.

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A meta-analysis of vitamin D deficiency and incidence of CAP on the basis of eight observational studies involving 20,966 subjects was reported [110]. The only prospective study was the one from Finland [109]. The others were case–control, cross-sectional, or retrospective. In that meta-analysis, CAP patients with vitamin D deficiency [serum 25(OH)D concentrations <20 ng/mL] experienced a significantly increased risk of CAP (odds ratio [OR] = 1.64; 95% CI, 1.00 to 2.67), and an obvious decrease of –5.63 ng/mL (95% CI, –9.11 to –2.14) in serum 25(OH)D was demonstrated in CAP patients.

A high-dose (250,000 or 500,000 IU) vitamin D_3 trial in ventilated intensive care unit patients in Georgia with mean baseline 25(OH)D concentration of 20–22 ng/ml reported that hospital length of stay was reduced from 36 (SD, 19) days in the control group to 25 (SD, 14) days in the 250,000-IU group [25(OH)D = 45 ± 20 ng/ml] and 18 (11) days in the 500,000-IU group [25(OH)D = 55 ± 14 ng/ml]; $p = 0.03$ [111].

In a pilot trial involving 30 mechanically ventilated critically ill patients, 500,000 IU of vitamin D_3 supplementation significantly increased hemoglobin concentrations and lowered hepcidin concentrations, improving iron metabolism and the blood's ability to transport oxygen [112].

3.Discussion

*3.1.*Hospital-acquired infection

Hospitals are a source of RTIs for both patients and medical personnel. For example, during the SARS-CoV epidemic, a woman returned to Toronto from Hong Kong with SARS-CoV in 2003 and went to a hospital. The disease was transmitted to other people, leading to an outbreak among 257 people in several Greater Toronto Area hospitals [113]. During the 2014–2015 influenza season, 36% of health care workers in Germany developed influenza infection [114].

Working in a hospital dealing with COVID-19 patients is associated with increased risk of COVID-19 infection. For example, 40 of 138 hospitalized COVID-19 patients in Wuhan in the Zhongnan Hospital from 1 to 28 January were medical staff, and 17 more were infected while in the hospital [115]. It was announced on February 14, 2020, that more than 1700 Chinese health workers were infected by COVID-19 and six had died (https://www.huffpost.com/entry/chinese-health-workers-infected-by-virus_n_5e46a0fec5b64d860fc97c1b).

Hospital workers are at high risk of having low 25(OH)D concentrations as a result of long hours working indoors. A sample of 114 female nurses in an Iranian children's hospital had a mean 25(OH)D concentration of 12 ± 9 ng/ml [116]. However, in the United States, practicing physicians had a mean concentration of 22 ± 2 ng/ml, whereas nurses and other health care workers had mean concentrations of 25 ± 4 ng/ml [117].

Vitamin D supplementation to raise serum 25(OH)D concentrations can help reduce hospital-acquired infections [118]. Concentrations at least 40–50 ng/ml (100–125 nmol/l) are indicated on the basis of observational studies such as the one presented here. During the

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COVID-19 epidemic, all people in the hospital, including patients and staff, should take vitamin D supplements to raise 25(OH)D concentrations as an important step in preventing infection and spread. A trial on that hypothesis would be worth conducting. That hypothesis also should be evaluated for people quarantined on cruise ships with COVID-19–infected passengers or crewmembers.

*3.2.*Children

Children have had much lower COVID-19 infection rates than adults, especially the elderly [119]. An editorial reported that prepubertal mice had decreased morbidity and mortality from H1N1 influenza and sepsis than those of mice that reach puberty [120]. The authors hypothesized that the finding relates to a unique prepubertal immune profile characterized by immunocompetence, developmental plasticity, and a lack of exposure to sex hormones. As mentioned, the innate immune response increases cytokine production with aging [78].

*3.3.*Vitamin D and mechanisms to reduce microbial infections

The general metabolism and actions of vitamin D are well known [121]. Vitamin D_3 is produced in the skin through the action of UVB radiation reaching 7-dehydocholesterol in the skin, followed by a thermal reaction. That vitamin D_3 or oral vitamin D is converted to 25(OH)D in the liver and then to the hormonal metabolite, $1,25(OH)_2D$ (calcitriol), in the kidneys or other organs as needed. Most of vitamin D's effect arises from calcitriol entering the nuclear vitamin D receptor, a DNA binding protein that interacts directly with regulatory sequences near target genes and that recruits chromatin active complexes that participate genetically and epigenetically in modifying transcriptional output [122].

Several reviews consider the ways in which vitamin D reduces risk of viral infections [123], [124], [125], [126], [127], [128], [32], [129], [130]. One article noted that UV exposure appears to confer additional benefits [127].

Vitamin D has many mechanisms by which it reduces risk of microbial infection and death. A recent review regarding the role of vitamin D in reducing risk of the common cold grouped those mechanisms into three categories: physical barrier, cellular natural immunity, and adaptive immunity [129]. Vitamin D helps maintain tight junctions, gap junctions, and adherens junctions (e.g., E-cadherin) [131]. Several articles discussed how viruses disturb junction integrity, increasing infection by the virus and other microorganisms [132], [133], [134]. That action by viruses is an important reason why viral infections progress to pneumonia.

Vitamin D enhances cellular natural immunity partly through induction of antimicrobial peptides, including human cathelicidin, LL-37, by 1,25-dihdroxyvitamin D [135], [136] and defensins [137]. Cathelicidins exhibit direct antimicrobial activities against a spectrum of microbes, including gram-positive and gram-negative bacteria, enveloped viruses, and fungi. Those host-derived peptides kill the invaded pathogens by perturbing their cell membranes and can neutralize

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biological activities of endotoxin [138]. They have many more important functions, as described therein. CoVs are enveloped viruses [139]. Human cathelicidin, LL-37, can reduce the production of proinflammatory cytokines in the lungs of mice infected in with influenza A virus, implying a direct effect on the influenza virion [140]. A clinical trial on asthma patients indicated that calcitriol supplementation reduced risk of RTIs related to the increase in LL-37 [141].

Vitamin D also enhances cellular natural immunity in part by reducing the cytokine storm induced by the innate immune system. The innate immune system generates both proinflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients [104]. Vitamin D can reduce the production of proinflammatory Th1 cytokines, such as tumor necrosis factor α and interferon γ, but not Th2 cytokines [142]. Administering vitamin D reduces the expression of proinflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages by upregulating mitogen-activated protein kinase phosphatase 1 and suppressing p38 activation [130] and references therein).

Vitamin D also affects adaptive immunity [129]. However, that effect would be useful if a second epidemic of a viral strain returned, as was observed during the 1918–1919 pandemic influenza. People alive during a previous pandemic influenza H1N1 epidemic had relative immunity, with the result that the age distribution of deaths was shifted to younger people [143].

Serum 25(OH)D concentrations decrease with age [144]. Reasons include less time spent in the sun and reduced production of vitamin D as a result of lower levels of 7-dehydrocholesterol in the skin [145]. In addition, many pharmaceutical drugs reduce serum 25(OH)D concentrations by activating the pregnane-X receptor [146]. Such drugs include antiepileptics, antineoplastics, antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, endocrine drugs, and some herbal medicines. Pharmaceutical drug use increases with age.

Vitamin D supplementation also enhances the expression of genes related to antioxidation (glutathione reductase and glutamate–cysteine ligase modifier subunit) [147]. The increased glutathione production spares the use of ascorbic acid (vitamin C), which has antimicrobial activities.

*3.4.*Proposed actions

The evidence reviewed here supports the role of higher 25(OH)D concentrations in reducing risk of infection and death from ARTIs, including those from influenza, CoV, and pneumonia. The peak season for ARTIs is generally when 25(OH)D concentrations are lowest. Thus, vitamin D_3 supplementation should be started or increased several months before winter to raise 25(OH)D concentrations to the range necessary to prevent ARTIs. Although the degree of protection generally increases as 25(OH)D concentration increases, the optimal range appears to be in the range of 40–60 ng/ml (100–150 nmol/l). To achieve those levels for approximately half the

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population could take at least 2000–5000 IU/d of vitamin D_3 [148]. Various loading doses have been studied for achieving a 25(OH)D concentration of 30 ng/ml. For example, one study used a weekly or fortnightly dose totaling 100,000–200,000 IU over 8 weeks (1800 or 3600 IU/d) [149]. However, to achieve 40–60 ng/ml would take higher loading doses. GrassrootsHealth has results from several volunteers who have taken 10,000 IU/d of vitamin D_3 for extended periods. They reported no adverse health effects. A trial involving Canadian breast cancer patients with bone metastases treated with bisphosphonates but without comorbid conditions reported that doses of 10,000 IU/d of vitamin D_3 over a 4-month period showed no adverse effects but did unmask two cases of primary hyperparathyroidism [150].

The efficacy and safety of high-dose vitamin D supplementation has been demonstrated in a psychiatric hospital in Cincinnati, Ohio [151]. The age range was from 18 to 90 years. Half of the patients were black, and nearly half were white. All patients entering since 2011 were offered supplementation of 5000 or 10,000 IU/d vitamin D_3. For 36 patients who received 5000 IU/d for 12 months or longer, mean serum 25(OH)D concentration rose from 24 ng/ml to 68 ng/ml while for the 78 patients who received 10,000 IU/d, mean concentrations increased from 25 ng/ml to 96 ng/ml. There were no cases of vitamin D-induced hypercalcemia. This article includes a brief review of other high-dose vitamin D studies including that vitamin D doses of 60,000 to 600,000 IU/d were found to treat and control such diseases as asthma, rheumatoid arthritis, rickets, and tuberculosis in the 1930s and 1940s. These doses are much higher than the 10,000 to 25,000 IU/d vitamin D_3 that can be made from solar UVB exposure [152]. However, after reports of hypercalcemia associated with use of supra-physiological doses of vitamin D surfaced, e.g. [153], high-dose vitamin D supplementation fell out of favor.

A recent article on high-dose vitamin D supplementation trial in New Zealand involving 5110 participants found that over a median of 3.3 years, monthly supplementation with 100,000 IU vitamin D_3 did not affect the incidence rate of kidney stone events, or hypercalcemia. [154].

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Cholecalciferol (vitamin D_3) should be used, not ergocalciferol (vitamin D_2). Supplementation studies have shown that vitamin D_3 is better at raising serum 25(OH)D concentrations than vitamin D_2 [155], [156], [157]. More important, vitamin D_3 supplementation has demonstrated better health outcomes than vitamin D_2 supplementation. For example, a meta-analysis of vitamin D supplementation and all-cause mortality rate reported that the risk ratio for all-cause mortality was 0.95 (95% CI, 0.90 to 1.00) for vitamin D_3 and 1.03 (95% CI, 0.98 to 1.09) for vitamin D_2 [158]. Vitamin D_2 is used in the U.S. medical system mainly because the U.S. Federal Medicaid program will pay for prescriptions of vitamin D_2 and not for over-the-counter vitamin D_3, and because the *Physician's Desk Reference* still lists vitamin D_2 but not vitamin D_3 as of March 2020 (https://www.pdr.net/drug-summary/Drisdol-ergocalciferol-1904). However, vitamin D_3 is readily available online and is much cheaper.

Unfortunately, most countries do not have guidelines supporting vitamin D supplementation doses and desirable serum 25(OH)D concentrations that would deal with wintertime RTIs. Guidelines for many countries consider 20 ng/ml (50 nmol/l) adequate. According to the statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases, "attainment of serum 25-hydroxyvitamin D levels well above the threshold desired for bone health cannot be recommended based on current evidence, since safety has yet to be confirmed." [159]. A recent review on the status of vitamin D deficiency worldwide stated that because of inadequate evidence from clinical trials, "a 25(OH)D level of >50 nmol/L or 20 ng/ml is, therefore, the primary treatment goal, although some data suggest a benefit for a higher threshold." [160]. A companion article in the same issue of the journal stated, "although 20 ng/ml seems adequate to reduce risk of skeletal problems and ARTIs, concentrations above 30 ng/ml have been associated with reduced risk of cancer, type 2 diabetes mellitus, and adverse pregnancy and birth outcomes." [161]. However, on the basis of the findings in several studies discussed here, the desirable concentration should be at least 40–50 ng/ml.

The U.S. Institute of Medicine issued vitamin D and calcium guidelines in 2011 [36]. The institute recommended vitamin D supplementation of 600 IU/d for people younger than 70 years, 800 IU/d for those older than 70 years, and a serum 25(OH)D concentration of 20 ng/ml (50 nmol/l) or higher. That recommendation was based on the effects of vitamin D for bone health. The institute recognized that no studies had reported adverse effects of supplementation with less than 10,000 IU/d of vitamin D but set the upper intake level at 4000 IU/d, partly out of concern stemming from observational studies that found U-shaped 25(OH)D concentration–health outcome relationships. However, later investigation determined that most reports of J- or U-shaped relationships were from observational studies that did not measure serum 25(OH)D concentrations and that the likely reason for those relationships was a result of enrolling some participants who had started taking vitamin D supplements shortly before enrolling [162].

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Also in 2011, the Endocrine Society recommended supplementation of 1000–4000 IU/d of vitamin D and a serum 25(OH)D concentration of 30 ng/ml or higher [163]. Those guidelines were for patients. It appears that anyone with chronic disease should be considered in that category.

Measuring serum 25(OH)D concentration may not be useful for everyone. A recent article recommended testing for groups of people who were likely to have low concentrations and could benefit from higher concentrations, such as pregnant women, the obese, people with chronic diseases, and the elderly [161]. Part of the rationale for testing was to increase awareness of actual 25(OH)D concentrations and the benefits of higher concentrations. In addition, increases in 25(OH)D concentration with respect to vitamin D supplementation depend on various personal factors, including genetics, digestive system health, weight, and baseline 25(OH)D concentration. For about half the population, taking 5000 IU/d of vitamin D_3 or 30,000–35,000 IU/wk would raise 25(OH)D concentration to 40 ng/ml.

Vitamin D supplementation is required for many individuals to reach 25(OH)D concentrations above 30 ng/ml, especially in winter [164]. However, vitamin D fortification of basic foods such as dairy and flour products [165], [166] can raise serum 25(OH)D concentrations of those members of various populations with the lowest concentrations by a few nanograms per milliliter. Doing so can result in reduced risk of ARTIs for individuals with extreme vitamin D deficiency. [167], [168].

Magnesium supplementation is recommended when taking vitamin D supplements. Magnesium helps activate vitamin D, which in turn helps regulate calcium and phosphate homeostasis to influence growth and maintenance of bones. All the enzymes that metabolize vitamin D seem to require magnesium, which acts as a cofactor in the enzymatic reactions in the liver and kidneys [169]. The dose of magnesium should be in the range of 250–500 mg/d, along with twice that dose of calcium.

Supplementing with vitamin D has beneficial effects beyond preventing RTIs. The VITamin D and OmegA-3 TriaL (VITAL) reported in the secondary analyses that supplementing participants with 2000 IU/d of vitamin D_3 for a mean follow-up time of 5.3 years significantly reduced overall cancer incidence for participants with body mass index <25 kg/m^2 of body surface area and those who were black [67]. The trial also reported significantly reduced overall cancer mortality rates for all participants if the first 1 or 2 years of deaths were omitted. We consider p = 0.06 to indicate statistical significance on the basis of an opinion piece in *Nature,* titled "Scientists rise up against statistical significance" [170].

The Vitamin **D** and type **2 d**iabetes (**D2d**) study was an RCT to examine whether vitamin D supplementation could reduce the risk of progressing from prediabetes to diabetes mellitus type 2

[69]. Participants with prediabetes were supplemented with 4000 IU/d of vitamin D_3 or placebo for 2.3 years. In the secondary analyses, significant reductions in progression to type 2 diabetes mellitus were reported for people with body mass index <30 kg/m^2, males, people not taking calcium supplements, and those older than 60.9 years.

According to a recent review, the human immune system requires particular micronutrients, such as vitamins A, B_6, B_{12}, C, D, and E, as well as copper, folate, iron, selenium, and zinc. Those nutrients work together; without enough of those in the right proportions, physical barriers and immune cells cannot do their work properly. The review notes that existing daily recommended dietary allowances may not be high enough to reflect what the immune system actually needs. Some people don't get enough micronutrients, and other people under the physiological burdens of infection, stress, and pollution experience greater loss of those nutrients stored in the body. Even slight deficiency in one or more of the essential micronutrients can dampen the immune system. The review continues: "Although contradictory data exist, available evidence indicates that supplementation with multiple micronutrients with immune-supporting roles may modulate immune function and reduce the risk of infection. Micronutrients with the strongest evidence for immune support are vitamins C and D and zinc. Better design of human clinical studies addressing dosage and combinations of micronutrients in different populations are required to substantiate the benefits of micronutrient supplementation against infection." [130]

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References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R., et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* **2020**, 10.1056/NEJMoa2001017, doi:10.1056/NEJMoa2001017.
2. Zhong, N.S.; Zheng, B.J.; Li, Y.M.; Poon; Xie, Z.H.; Chan, K.H.; Li, P.H.; Tan, S.Y.; Chang, Q.; Xie, J.P., et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* **2003**, *362*, 1353-1358, doi:10.1016/s0140-6736(03)14630-2.
3. Assiri, A.; McGeer, A.; Perl, T.M.; Price, C.S.; Al Rabeeah, A.A.; Cummings, D.A.; Alabdullatif, Z.N.; Assad, M.; Almulhim, A.; Makhdoom, H., et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* **2013**, *369*, 407-416, doi:10.1056/NEJMoa1306742.
4. Song, Z.; Xu, Y.; Bao, L.; Zhang, L.; Yu, P.; Qu, Y.; Zhu, H.; Zhao, W.; Han, Y.; Qin, C. From SARS to MERS, Thrusting Coronaviruses into the Spotlight. *Viruses* **2019**, *11*, doi:10.3390/v11010059.
5. Yin, Y.; Wunderink, R.G. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology* **2018**, *23*, 130-137, doi:10.1111/resp.13196.

6. Britten, R. The incidence of epidemic influenza, 1918--19. *Public Health Reports* **1932**, *47*, 303-339.
7. Liu, P.; Shi, L.; Zhang, W.; He, J.; Liu, C.; Zhao, C.; Kong, S.K.; Loo, J.F.C.; Gu, D.; Hu, L. Prevalence and genetic diversity analysis of human coronaviruses among cross-border children. *Virol J* **2017**, *14*, 230, doi:10.1186/s12985-017-0896-0.
8. Zdrenghea, M.T.; Makrinioti, H.; Bagacean, C.; Bush, A.; Johnston, S.L.; Stanciu, L.A. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol* **2017**, *27*, doi:10.1002/rmv.1909.
9. Colunga Biancatelli, R.M.L.; Berrill, M.; Marik, P.E. The antiviral properties of vitamin C. *Expert Rev Anti Infect Ther* **2020**, *18*, 99-101, doi:10.1080/14787210.2020.1706483.
10. Watkins, R.R.; Lemonovich, T.L.; Salata, R.A. An update on the association of vitamin D deficiency with common infectious diseases. *Can J Physiol Pharmacol* **2015**, *93*, 363-368, doi:10.1139/cjpp-2014-0352.
11. Oudemans-van Straaten, H.M.; Spoelstra-de Man, A.M.; de Waard, M.C. Vitamin C revisited. *Crit Care* **2014**, *18*, 460, doi:10.1186/s13054-014-0460-x.
12. Furuya, A.; Uozaki, M.; Yamasaki, H.; Arakawa, T.; Arita, M.; Koyama, A.H. Antiviral effects of ascorbic and dehydroascorbic acids in vitro. *Int J Mol Med* **2008**, *22*, 541-545.
13. Kim, Y.; Kim, H.; Bae, S.; Choi, J.; Lim, S.Y.; Lee, N.; Kong, J.M.; Hwang, Y.I.; Kang, J.S.; Lee, W.J. Vitamin C Is an Essential Factor on the Anti-viral Immune Responses through the Production of Interferon-alpha/beta at the Initial Stage of Influenza A Virus (H3N2) Infection. *Immune Netw* **2013**, *13*, 70-74, doi:10.4110/in.2013.13.2.70.
14. Cai, Y.; Li, Y.F.; Tang, L.P.; Tsoi, B.; Chen, M.; Chen, H.; Chen, X.M.; Tan, R.R.; Kurihara, H.; He, R.R. A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. *Biomed Res Int* **2015**, *2015*, 675149, doi:10.1155/2015/675149.
15. Khomich, O.A.; Kochetkov, S.N.; Bartosch, B.; Ivanov, A.V. Redox Biology of Respiratory Viral Infections. *Viruses* **2018**, *10*, doi:10.3390/v10080392.
16. Iuliano, A.D.; Roguski, K.M.; Chang, H.H.; Muscatello, D.J.; Palekar, R.; Tempia, S.; Cohen, C.; Gran, J.M.; Schanzer, D.; Cowling, B.J., et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* **2018**, *391*, 1285-1300, doi:10.1016/S0140-6736(17)33293-2.
17. Simonsen, L.; Spreeuwenberg, P.; Lustig, R.; Taylor, R.J.; Fleming, D.M.; Kroneman, M.; Van Kerkhove, M.D.; Mounts, A.W.; Paget, W.J.; Teams, G.L.C. Global mortality estimates for the 2009 Influenza Pandemic from the GLaMOR project: a modeling study. *PLoS Med* **2013**, *10*, e1001558, doi:10.1371/journal.pmed.1001558.
18. Chung, J.R.; Rolfes, M.A.; Flannery, B.; Prasad, P.; O'Halloran, A.; Garg, S.; Fry, A.M.; Singleton, J.A.; Patel, M.; Reed, C. Effects of Influenza Vaccination in the United States during the 2018-2019 Influenza Season. *Clin Infect Dis* **2020**, 10.1093/cid/ciz1244, doi:10.1093/cid/ciz1244.
19. Ortiz, J.R.; Neuzil, K.M.; Cooke, C.R.; Neradilek, M.B.; Goss, C.H.; Shay, D.K. Influenza pneumonia surveillance among hospitalized adults may underestimate the burden of severe influenza disease. *PLoS One* **2014**, *9*, e113903, doi:10.1371/journal.pone.0113903.
20. Kalil, A.C.; Thomas, P.G. Influenza virus-related critical illness: pathophysiology and epidemiology. *Crit Care* **2019**, *23*, 258, doi:10.1186/s13054-019-2539-x.

21. Hope-Simpson, R.E. The role of season in the epidemiology of influenza. *J Hyg (Lond)* **1981**, *86*, 35-47, doi:10.1017/s0022172400068728.
22. Cannell, J.J.; Vieth, R.; Umhau, J.C.; Holick, M.F.; Grant, W.B.; Madronich, S.; Garland, C.F.; Giovannucci, E. Epidemic influenza and vitamin D. *Epidemiol Infect* **2006**, *134*, 1129-1140, doi:10.1017/S0950268806007175.
23. Cannell, J.J.; Zasloff, M.; Garland, C.F.; Scragg, R.; Giovannucci, E. On the epidemiology of influenza. *Virol J* **2008**, *5*, 29, doi:10.1186/1743-422X-5-29.
24. Webb, A.R.; Kline, L.; Holick, M.F. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab* **1988**, *67*, 373-378, doi:10.1210/jcem-67-2-373.
25. Engelsen, O. The relationship between ultraviolet radiation exposure and vitamin D status. *Nutrients* **2010**, *2*, 482-495, doi:10.3390/nu2050482.
26. Kroll, M.H.; Bi, C.; Garber, C.C.; Kaufman, H.W.; Liu, D.; Caston-Balderrama, A.; Zhang, K.; Clarke, N.; Xie, M.; Reitz, R.E., et al. Temporal relationship between vitamin D status and parathyroid hormone in the United States. *PLoS One* **2015**, *10*, e0118108, doi:10.1371/journal.pone.0118108.
27. Lowen, A.C.; Mubareka, S.; Steel, J.; Palese, P. Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathog* **2007**, *3*, 1470-1476, doi:10.1371/journal.ppat.0030151.
28. Shaman, J.; Kohn, M. Absolute humidity modulates influenza survival, transmission, and seasonality. *Proc Natl Acad Sci U S A* **2009**, *106*, 3243-3248, doi:10.1073/pnas.0806852106.
29. Shaman, J.; Pitzer, V.E.; Viboud, C.; Grenfell, B.T.; Lipsitch, M. Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS Biol* **2010**, *8*, e1000316, doi:10.1371/journal.pbio.1000316.
30. Ianevski, A.; Zusinaite, E.; Shtaida, N.; Kallio-Kokko, H.; Valkonen, M.; Kantele, A.; Telling, K.; Lutsar, I.; Letjuka, P.; Metelitsa, N., et al. Low Temperature and Low UV Indexes Correlated with Peaks of Influenza Virus Activity in Northern Europe during 2010(-)2018. *Viruses* **2019**, *11*, doi:10.3390/v11030207.
31. Schuit, M.; Gardner, S.; Wood, S.; Bower, K.; Williams, G.; Freeburger, D.; Dabisch, P. The Influence of Simulated Sunlight on the Inactivation of Influenza Virus in Aerosols. *J Infect Dis* **2020**, *221*, 372-378, doi:10.1093/infdis/jiz582.
32. Gruber-Bzura, B.M. Vitamin D and Influenza-Prevention or Therapy? *Int J Mol Sci* **2018**, *19*, doi:10.3390/ijms19082419.
33. Urashima, M.; Segawa, T.; Okazaki, M.; Kurihara, M.; Wada, Y.; Ida, H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* **2010**, *91*, 1255-1260, doi:10.3945/ajcn.2009.29094.
34. Arihiro, S.; Nakashima, A.; Matsuoka, M.; Suto, S.; Uchiyama, K.; Kato, T.; Mitobe, J.; Komoike, N.; Itagaki, M.; Miyakawa, Y., et al. Randomized Trial of Vitamin D Supplementation to Prevent Seasonal Influenza and Upper Respiratory Infection in Patients With Inflammatory Bowel Disease. *Inflamm Bowel Dis* **2019**, *25*, 1088-1095, doi:10.1093/ibd/izy346.
35. Sabetta, J.R.; DePetrillo, P.; Cipriani, R.J.; Smardin, J.; Burns, L.A.; Landry, M.L. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* **2010**, *5*, e11088, doi:10.1371/journal.pone.0011088.

36. Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G., et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* **2011**, *96*, 53-58, doi:10.1210/jc.2010-2704.
37. Rake, C.; Gilham, C.; Bukasa, L.; Ostler, R.; Newton, M.; Peto Wild, J.; Aigret, B.; Hill, M.; Gillie, O.; Nazareth, I., et al. High-dose oral vitamin D supplementation and mortality in people aged 65-84 years: the VIDAL cluster feasibility RCT of open versus double-blind individual randomisation. *Health Technol Assess* **2020**, *24*, 1-54, doi:10.3310/hta24100.
38. McDonnell, S.L.; Baggerly, C.; French, C.B.; Baggerly, L.L.; Garland, C.F.; Gorham, E.D.; Lappe, J.M.; Heaney, R.P. Serum 25-Hydroxyvitamin D Concentrations >/=40 ng/ml Are Associated with >65% Lower Cancer Risk: Pooled Analysis of Randomized Trial and Prospective Cohort Study. *PLoS One* **2016**, *11*, e0152441, doi:10.1371/journal.pone.0152441.
39. McDonnell, S.L.; Baggerly, L.L.; French, C.B.; Heaney, R.P.; Gorham, E.D.; Holick, M.F.; Scragg, R.; Garland, C.F. Incidence rate of type 2 diabetes is >50% lower in GrassrootsHealth cohort with median serum 25-hydroxyvitamin D of 41 ng/ml than in NHANES cohort with median of 22 ng/ml. *J Steroid Biochem Mol Biol* **2016**, *155*, 239-244, doi:10.1016/j.jsbmb.2015.06.013.
40. McDonnell, S.L.; Baggerly, K.A.; Baggerly, C.A.; Aliano, J.L.; French, C.B.; Baggerly, L.L.; Ebeling, M.D.; Rittenberg, C.S.; Goodier, C.G.; Mateus Nino, J.F., et al. Maternal 25(OH)D concentrations >/=40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. *PLoS One* **2017**, *12*, e0180483, doi:10.1371/journal.pone.0180483.
41. McDonnell, S.L.; Baggerly, C.A.; French, C.B.; Baggerly, L.L.; Garland, C.F.; Gorham, E.D.; Hollis, B.W.; Trump, D.L.; Lappe, J.M. Breast cancer risk markedly lower with serum 25-hydroxyvitamin D concentrations >/=60 vs <20 ng/ml (150 vs 50 nmol/L): Pooled analysis of two randomized trials and a prospective cohort. *PLoS One* **2018**, *13*, e0199265, doi:10.1371/journal.pone.0199265.
42. Mirhosseini, N.; Vatanparast, H.; Kimball, S.M. The Association between Serum 25(OH)D Status and Blood Pressure in Participants of a Community-Based Program Taking Vitamin D Supplements. *Nutrients* **2017**, *9*, doi:10.3390/nu9111244.
43. Peteranderl, C.; Herold, S.; Schmoldt, C. Human Influenza Virus Infections. *Semin Respir Crit Care Med* **2016**, *37*, 487-500, doi:10.1055/s-0036-1584801.
44. Reed, C.; Chaves, S.S.; Perez, A.; D'Mello, T.; Daily Kirley, P.; Aragon, D.; Meek, J.I.; Farley, M.M.; Ryan, P.; Lynfield, R., et al. Complications among adults hospitalized with influenza: a comparison of seasonal influenza and the 2009 H1N1 pandemic. *Clin Infect Dis* **2014**, *59*, 166-174, doi:10.1093/cid/ciu285.
45. Schoeman, D.; Fielding, B.C. Coronavirus envelope protein: current knowledge. *Virol J* **2019**, *16*, 69, doi:10.1186/s12985-019-1182-0.
46. Luo, M. Influenza virus entry. *Adv Exp Med Biol* **2012**, *726*, 201-221, doi:10.1007/978-1-4614-0980-9_9.
47. Kampf, G.; Todt, D.; Pfaender, S.; Steinmann, E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. *J Hosp Infect* **2020**, 10.1016/j.jhin.2020.01.022, doi:10.1016/j.jhin.2020.01.022.

48. Xie, Z.; Xia, W.; Zhang, Z.; Wu, W.; Lu, C.; Tao, S.; Wu, L.; Gu, J.; Chandler, J.; Peter, S., et al. Prevalence of Vitamin D Inadequacy Among Chinese Postmenopausal Women: A Nationwide, Multicenter, Cross-Sectional Study. *Front Endocrinol (Lausanne)* **2019**, *9*, 782, doi:10.3389/fendo.2018.00782.
49. Yu, H.J.; Kwon, M.J.; Woo, H.Y.; Park, H. Analysis of 25-Hydroxyvitamin D Status According to Age, Gender, and Seasonal Variation. *J Clin Lab Anal* **2016**, *30*, 905-911, doi:10.1002/jcla.21955.
50. Ferrari, D.; Lombardi, G.; Strollo, M.; Pontillo, M.; Motta, A.; Locatelli, M. Association between solar ultraviolet doses and vitamin D clinical routine data in European mid-latitude population between 2006 and 2018. *Photochem Photobiol Sci* **2019**, *18*, 2696-2706, doi:10.1039/c9pp00372j.
51. Cashman, K.D.; Dowling, K.G.; Skrabakova, Z.; Gonzalez-Gross, M.; Valtuena, J.; De Henauw, S.; Moreno, L.; Damsgaard, C.T.; Michaelsen, K.F.; Molgaard, C., et al. Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* **2016**, *103*, 1033-1044, doi:10.3945/ajcn.115.120873.
52. Aleksova, A.; Belfiore, R.; Carriere, C.; Kassem, S.; La Carrubba, S.; Barbati, G.; Sinagra, G. Vitamin D Deficiency in Patients with Acute Myocardial Infarction: An Italian Single-Center Study. *Int J Vitam Nutr Res* **2015**, *85*, 23-30, doi:10.1024/0300-9831/a000220.
53. Chen, X.; Wu, W.; Wang, L.; Shi, Y.; Shen, F.; Gu, X.; Jia, Z. Association Between 25-Hydroxyvitamin D and Epicardial Adipose Tissue in Chinese Non-Obese Patients with Type 2 Diabetes. *Med Sci Monit* **2017**, *23*, 4304-4311, doi:10.12659/msm.904755.
54. Lu, D.; Zhang, J.; Ma, C.; Yue, Y.; Zou, Z.; Yu, C.; Yin, F. Link between community-acquired pneumonia and vitamin D levels in older patients. *Z Gerontol Geriatr* **2018**, *51*, 435-439, doi:10.1007/s00391-017-1237-z.
55. Zhang, M.; Gao, Y.; Tian, L.; Zheng, L.; Wang, X.; Liu, W.; Zhang, Y.; Huang, G. Association of serum 25-hydroxyvitamin D3 with adipokines and inflammatory marker in persons with prediabetes mellitus. *Clin Chim Acta* **2017**, *468*, 152-158, doi:10.1016/j.cca.2017.02.022.
56. WHO. Epidemic curves - Severe Acute Respiraotry Syndrome (SARD). Availabe online: https://www.who.int/csr/sars/epicurve/epiindex/en/index1.html (accessed on
57. Chan-Yeung, M.; Xu, R.H. SARS: epidemiology. *Respirology* **2003**, *8 Suppl*, S9-14, doi:10.1046/j.1440-1843.2003.00518.x.
58. Team, N.C.P.E.R.E. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi* **2020**, *41*, 145-151, doi:10.3760/cma.j.issn.0254-6450.2020.02.003.
59. Cho, N.H.; Shaw, J.E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.D.; Ohlrogge, A.W.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* **2018**, *138*, 271-281, doi:10.1016/j.diabres.2018.02.023.
60. Henley, S.J.; Gallaway, S.; Singh, S.D.; O'Neil, M.E.; Buchanan Lunsford, N.; Momin, B.; Richards, T.B. Lung Cancer Among Women in the United States. *J Womens Health (Larchmt)* **2018**, *27*, 1307-1316, doi:10.1089/jwh.2018.7397.
61. Malinovschi, A.; Masoero, M.; Bellocchia, M.; Ciuffreda, A.; Solidoro, P.; Mattei, A.; Mercante, L.; Heffler, E.; Rolla, G.; Bucca, C. Severe vitamin D deficiency is associated

with frequent exacerbations and hospitalization in COPD patients. *Respir Res* **2014**, *15*, 131, doi:10.1186/s12931-014-0131-0.

62. Kim, H.J.; Jang, J.G.; Hong, K.S.; Park, J.K.; Choi, E.Y. Relationship between serum vitamin D concentrations and clinical outcome of community-acquired pneumonia. *Int J Tuberc Lung Dis* **2015**, *19*, 729-734, doi:10.5588/ijtld.14.0696.
63. Naghshtabrizi, B.; Borzouei, S.; Bigvand, P.; Seifrabiei, M.A. Evaluation of the Relationship between Serum 25-Hydroxy Vitamin D and Hypertension in Hamadan, Iran-A Case Control Study. *J Clin Diagn Res* **2017**, *11*, LC01-LC03, doi:10.7860/JCDR/2017/25522.10187.
64. Pludowski, P.; Holick, M.F.; Pilz, S.; Wagner, C.L.; Hollis, B.W.; Grant, W.B.; Shoenfeld, Y.; Lerchbaum, E.; Llewellyn, D.J.; Kienreich, K., et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev* **2013**, *12*, 976-989, doi:10.1016/j.autrev.2013.02.004.
65. Wimalawansa, S.J. Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol* **2018**, *175*, 60-81, doi:10.1016/j.jsbmb.2016.09.016.
66. Charoenngam, N.; Shirvani, A.; Holick, M.F. Vitamin D for skeletal and non-skeletal health: What we should know. *J Clin Orthop Trauma* **2019**, *10*, 1082-1093, doi:10.1016/j.jcot.2019.07.004.
67. Manson, J.E.; Cook, N.R.; Lee, I.M.; Christen, W.; Bassuk, S.S.; Mora, S.; Gibson, H.; Gordon, D.; Copeland, T.; D'Agostino, D., et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med* **2019**, *380*, 33-44, doi:10.1056/NEJMoa1809944.
68. Zhu, M.; Wang, T.; Wang, C.; Ji, Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* **2016**, *11*, 2597-2607, doi:10.2147/COPD.S101382.
69. Pittas, A.; Dawson-Hughes, B.; Staten, M. Vitamin D Supplementation and Prevention of Type 2 Diabetes. Reply. *N Engl J Med* **2019**, *381*, 1785-1786, doi:10.1056/NEJMc1912185.
70. Gholami, F.; Moradi, G.; Zareei, B.; Rasouli, M.A.; Nikkhoo, B.; Roshani, D.; Ghaderi, E. The association between circulating 25-hydroxyvitamin D and cardiovascular diseases: a meta-analysis of prospective cohort studies. *BMC Cardiovasc Disord* **2019**, *19*, 248, doi:10.1186/s12872-019-1236-7.
71. Grant, W.B.; Bhattoa, H.P.; Boucher, B.J. Seasonal variations of U.S. mortality rates: Roles of solar ultraviolet-B doses, vitamin D, gene exp ression, and infections. *J Steroid Biochem Mol Biol* **2017**, *173*, 5-12, doi:10.1016/j.jsbmb.2017.01.003.
72. Vanderschueren, D.; Pye, S.R.; O'Neill, T.W.; Lee, D.M.; Jans, I.; Billen, J.; Gielen, E.; Laurent, M.; Claessens, F.; Adams, J.E., et al. Active vitamin D (1,25-dihydroxyvitamin D) and bone health in middle-aged and elderly men: the European Male Aging Study (EMAS). *J Clin Endocrinol Metab* **2013**, *98*, 995-1005, doi:10.1210/jc.2012-2772.
73. Zittermann, A.; Ernst, J.B.; Birschmann, I.; Dittrich, M. Effect of Vitamin D or Activated Vitamin D on Circulating 1,25-Dihydroxyvitamin D Concentrations: A Systematic Review and Metaanalysis of Randomized Controlled Trials. *Clin Chem* **2015**, *61*, 1484-1494, doi:10.1373/clinchem.2015.244913.

74. Valcour, A.; Blocki, F.; Hawkins, D.M.; Rao, S.D. Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. *J Clin Endocrinol Metab* **2012**, *97*, 3989-3995, doi:10.1210/jc.2012-2276.
75. Christensen, M.H.; Lien, E.A.; Hustad, S.; Almas, B. Seasonal and age-related differences in serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone in patients from Western Norway. *Scand J Clin Lab Invest* **2010**, *70*, 281-286, doi:10.3109/00365511003797172.
76. Zittermann, A.; Kuhn, J.; Ernst, J.B.; Becker, T.; Larisch, J.; Dreier, J.; Knabbe, C.; Borgermann, J.; Gummert, J.F. Circulating 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Concentrations and Postoperative Infections in Cardiac Surgical Patients: The CALCITOP-Study. *PLoS One* **2016**, *11*, e0158532, doi:10.1371/journal.pone.0158532.
77. Moscarelli, L.; Antognoli, G.; Buti, E.; Dervishi, E.; Fani, F.; Caroti, L.; Tsalouchos, A.; Romoli, E.; Ghiandai, G.; Minetti, E. 1,25 Dihydroxyvitamin D circulating levels, calcitriol administration, and incidence of acute rejection, CMV infection, and polyoma virus infection in renal transplant recipients. *Clin Transplant* **2016**, *30*, 1347-1359, doi:10.1111/ctr.12829.
78. Fulop, T.; Larbi, A.; Dupuis, G.; Le Page, A.; Frost, E.H.; Cohen, A.A.; Witkowski, J.M.; Franceschi, C. Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? *Front Immunol* **2017**, *8*, 1960, doi:10.3389/fimmu.2017.01960.
79. Coates, B.M.; Staricha, K.L.; Wiese, K.M.; Ridge, K.M. Influenza A Virus Infection, Innate Immunity, and Childhood. *JAMA Pediatr* **2015**, *169*, 956-963, doi:10.1001/jamapediatrics.2015.1387.
80. Wang, R.; Jiang, Y.; Yao, C.; Zhu, M.; Zhao, Q.; Huang, L.; Wang, G.; Guan, Y.; Michael, E.; Zhao, G. Prevalence of tobacco related chronic diseases and its role in smoking cessation among smokers in a rural area of Shanghai, China: a cross sectional study. *BMC Public Health* **2019**, *19*, 753, doi:10.1186/s12889-019-7110-9.
81. Nam, H.H.; Ison, M.G. Respiratory syncytial virus infection in adults. *BMJ* **2019**, *366*, l5021, doi:10.1136/bmj.l5021.
82. Feng, X.; Guo, T.; Wang, Y.; Kang, D.; Che, X.; Zhang, H.; Cao, W.; Wang, P. The vitamin D status and its effects on life quality among the elderly in Jinan, China. *Arch Gerontol Geriatr* **2016**, *62*, 26-29, doi:10.1016/j.archger.2015.09.002.
83. Nassar, M.S.; Bakhrebah, M.A.; Meo, S.A.; Alsuabeyl, M.S.; Zaher, W.A. Global seasonal occurrence of middle east respiratory syndrome coronavirus (MERS-CoV) infection. *Eur Rev Med Pharmacol Sci* **2018**, *22*, 3913-3918, doi:10.26355/eurrev_201806_15276.
84. Grant, W.B.; Fakhoury, H.M.A.; Karras, S.N.; Al Anouti, F.; Bhattoa, H.P. Variations in 25-Hydroxyvitamin D in Countries from the Middle East and Europe: The Roles of UVB Exposure and Diet. *Nutrients* **2019**, *11*, doi:10.3390/nu11092065.
85. Moura, F.E.; Perdigao, A.C.; Siqueira, M.M. Seasonality of influenza in the tropics: a distinct pattern in northeastern Brazil. *Am J Trop Med Hyg* **2009**, *81*, 180-183.
86. Paynter, S.; Ware, R.S.; Sly, P.D.; Weinstein, P.; Williams, G. Respiratory syncytial virus seasonality in tropical Australia. *Aust N Z J Public Health* **2015**, *39*, 8-10, doi:10.1111/1753-6405.12347.

87. Arboleda, J.F.; Urcuqui-Inchima, S. Vitamin D-Regulated MicroRNAs: Are They Protective Factors against Dengue Virus Infection? *Adv Virol* **2016**, *2016*, 1016840, doi:10.1155/2016/1016840.
88. Villamor, E.; Villar, L.A.; Lozano, A.; Herrera, V.M.; Herran, O.F. Vitamin D serostatus and dengue fever progression to dengue hemorrhagic fever/dengue shock syndrome. *Epidemiol Infect* **2017**, *145*, 2961-2970, doi:10.1017/S0950268817002059.
89. Giraldo, D.M.; Cardona, A.; Urcuqui-Inchima, S. High-dose of vitamin D supplement is associated with reduced susceptibility of monocyte-derived macrophages to dengue virus infection and pro-inflammatory cytokine production: An exploratory study. *Clin Chim Acta* **2018**, *478*, 140-151, doi:10.1016/j.cca.2017.12.044.
90. Martinez-Moreno, J.; Hernandez, J.C.; Urcuqui-Inchima, S. Effect of high doses of vitamin D supplementation on dengue virus replication, Toll-like receptor expression, and cytokine profiles on dendritic cells. *Mol Cell Biochem* **2020**, *464*, 169-180, doi:10.1007/s11010-019-03658-w.
91. Fan, H.Z.; Zhang, R.; Tian, T.; Zhong, Y.L.; Wu, M.P.; Xie, C.N.; Yang, J.J.; Huang, P.; Yu, R.B.; Zhang, Y., et al. CYP24A1 genetic variants in the vitamin D metabolic pathway are involved in the outcomes of hepatitis C virus infection among high-risk Chinese population. *Int J Infect Dis* **2019**, *84*, 80-88, doi:10.1016/j.ijid.2019.04.032.
92. Hu, Y.C.; Wang, W.W.; Jiang, W.Y.; Li, C.Q.; Guo, J.C.; Xun, Y.H. Low vitamin D levels are associated with high viral loads in patients with chronic hepatitis B: a systematic review and meta-analysis. *BMC Gastroenterol* **2019**, *19*, 84, doi:10.1186/s12876-019-1004-2.
93. Brice, D.C.; Toth, Z.; Diamond, G. LL-37 disrupts the Kaposi's sarcoma-associated herpesvirus envelope and inhibits infection in oral epithelial cells. *Antiviral Res* **2018**, *158*, 25-33, doi:10.1016/j.antiviral.2018.07.025.
94. Alvarez, N.; Aguilar-Jimenez, W.; Rugeles, M.T. The Potential Protective Role of Vitamin D Supplementation on HIV-1 Infection. *Front Immunol* **2019**, *10*, 2291, doi:10.3389/fimmu.2019.02291.
95. Gui, B.; Chen, Q.; Hu, C.; Zhu, C.; He, G. Effects of calcitriol (1, 25-dihydroxy-vitamin D3) on the inflammatory response induced by H9N2 influenza virus infection in human lung A549 epithelial cells and in mice. *Virol J* **2017**, *14*, 10, doi:10.1186/s12985-017-0683-y.
96. Currie, S.M.; Findlay, E.G.; McHugh, B.J.; Mackellar, A.; Man, T.; Macmillan, D.; Wang, H.; Fitch, P.M.; Schwarze, J.; Davidson, D.J. The human cathelicidin LL-37 has antiviral activity against respiratory syncytial virus. *PLoS One* **2013**, *8*, e73659, doi:10.1371/journal.pone.0073659.
97. Bucak, I.H.; Ozturk, A.B.; Almis, H.; Cevik, M.O.; Tekin, M.; Konca, C.; Turgut, M.; Bulbul, M. Is there a relationship between low vitamin D and rotaviral diarrhea? *Pediatr Int* **2016**, *58*, 270-273, doi:10.1111/ped.12809.
98. Zhao, Y.; Ran, Z.; Jiang, Q.; Hu, N.; Yu, B.; Zhu, L.; Shen, L.; Zhang, S.; Chen, L.; Chen, H., et al. Vitamin D Alleviates Rotavirus Infection through a Microrna-155-5p Mediated Regulation of the TBK1/IRF3 Signaling Pathway In Vivo and In Vitro. *Int J Mol Sci* **2019**, *20*, doi:10.3390/ijms20143562.
99. Laplana, M.; Royo, J.L.; Fibla, J. Vitamin D Receptor polymorphisms and risk of enveloped virus infection: A meta-analysis. *Gene* **2018**, *678*, 384-394, doi:10.1016/j.gene.2018.08.017.

100. Borella, E.; Nesher, G.; Israeli, E.; Shoenfeld, Y. Vitamin D: a new anti-infective agent? *Ann N Y Acad Sci* **2014**, *1317*, 76-83, doi:10.1111/nyas.12321.
101. Theron, M.; Huang, K.J.; Chen, Y.W.; Liu, C.C.; Lei, H.Y. A probable role for IFN-gamma in the development of a lung immunopathology in SARS. *Cytokine* **2005**, *32*, 30-38, doi:10.1016/j.cyto.2005.07.007.
102. Wong, C.K.; Lam, C.W.; Wu, A.K.; Ip, W.K.; Lee, N.L.; Chan, I.H.; Lit, L.C.; Hui, D.S.; Chan, M.H.; Chung, S.S., et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* **2004**, *136*, 95-103, doi:10.1111/j.1365-2249.2004.02415.x.
103. Mahallawi, W.H.; Khabour, O.F.; Zhang, Q.; Makhdoum, H.M.; Suliman, B.A. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine* **2018**, *104*, 8-13, doi:10.1016/j.cyto.2018.01.025.
104. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, 10.1016/S0140-6736(20)30183-5, doi:10.1016/S0140-6736(20)30183-5.
105. Grant, W.B.; Giovannucci, E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918-1919 influenza pandemic in the United States. *Dermatoendocrinol* **2009**, *1*, 215-219, doi:10.4161/derm.1.4.9063.
106. Ginde, A.A.; Liu, M.C.; Camargo, C.A., Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med* **2009**, *169*, 626-632, doi:10.1001/archinternmed.2008.604.
107. Almirall, J.; Gonzalez, C.A.; Balanzo, X.; Bolibar, I. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest* **1999**, *116*, 375-379, doi:10.1378/chest.116.2.375.
108. Jackson, M.L.; Neuzil, K.M.; Thompson, W.W.; Shay, D.K.; Yu, O.; Hanson, C.A.; Jackson, L.A. The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clin Infect Dis* **2004**, *39*, 1642-1650, doi:10.1086/425615.
109. Aregbesola, A.; Voutilainen, S.; Nurmi, T.; Virtanen, J.K.; Ronkainen, K.; Tuomainen, T.P. Serum 25-hydroxyvitamin D3 and the risk of pneumonia in an ageing general population. *J Epidemiol Community Health* **2013**, *67*, 533-536, doi:10.1136/jech-2012-202027.
110. Zhou, Y.F.; Luo, B.A.; Qin, L.L. The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. *Medicine (Baltimore)* **2019**, *98*, e17252, doi:10.1097/MD.0000000000017252.
111. Han, J.E.; Jones, J.L.; Tangpricha, V.; Brown, M.A.; Brown, L.A.S.; Hao, L.; Hebbar, G.; Lee, M.J.; Liu, S.; Ziegler, T.R., et al. High Dose Vitamin D Administration in Ventilated Intensive Care Unit Patients: A Pilot Double Blind Randomized Controlled Trial. *J Clin Transl Endocrinol* **2016**, *4*, 59-65, doi:10.1016/j.jcte.2016.04.004.
112. Smith, E.M.; Jones, J.L.; Han, J.E.; Alvarez, J.A.; Sloan, J.H.; Konrad, R.J.; Zughaier, S.M.; Martin, G.S.; Ziegler, T.R.; Tangpricha, V. High-Dose Vitamin D3 Administration Is Associated With Increases in Hemoglobin Concentrations in Mechanically Ventilated Critically Ill Adults: A Pilot Double-Blind, Randomized, Placebo-Controlled Trial. *JPEN J Parenter Enteral Nutr* **2018**, *42*, 87-94, doi:10.1177/0148607116678197.
113. Centers for Disease, C.; Prevention. Update: severe acute respiratory syndrome--Toronto, Canada, 2003. *MMWR Morb Mortal Wkly Rep* **2003**, *52*, 547-550.

114. Hagel, S.; Ludewig, K.; Moeser, A.; Baier, M.; Loffler, B.; Schleenvoigt, B.; Forstner, C.; Pletz, M.W. Characteristics and management of patients with influenza in a German hospital during the 2014/2015 influenza season. *Infection* **2016**, *44*, 667-672, doi:10.1007/s15010-016-0920-0.
115. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y., et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**, 10.1001/jama.2020.1585, doi:10.1001/jama.2020.1585.
116. Rajebi, H.; Khodadad, A.; Fahimi, G.; Abolhassani, H. Vitamin D Deficiency among Female Nurses of Children's Medical Center Hospital and Its Related Factors. *Acta Med Iran* **2016**, *54*, 146-150.
117. Sowah, D.; Fan, X.; Dennett, L.; Hagtvedt, R.; Straube, S. Vitamin D levels and deficiency with different occupations: a systematic review. *BMC Public Health* **2017**, *17*, 519, doi:10.1186/s12889-017-4436-z.
118. Youssef, D.A.; Ranasinghe, T.; Grant, W.B.; Peiris, A.N. Vitamin D's potential to reduce the risk of hospital-acquired infections. *Dermatoendocrinol* **2012**, *4*, 167-175, doi:10.4161/derm.20789.
119. Wu, Z.; McGoogan, J.M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* **2020**, 10.1001/jama.2020.2648, doi:10.1001/jama.2020.2648.
120. Joachim, R.B.; Kobzik, L. Why are children more resistant to mortality from severe infections? *Future Microbiol* **2018**, *13*, 1549-1552, doi:10.2217/fmb-2018-0221.
121. Holick, M.F. Vitamin D deficiency. *N Engl J Med* **2007**, *357*, 266-281, doi:10.1056/NEJMra070553.
122. Pike, J.W.; Christakos, S. Biology and Mechanisms of Action of the Vitamin D Hormone. *Endocrinol Metab Clin North Am* **2017**, *46*, 815-843, doi:10.1016/j.ecl.2017.07.001.
123. Beard, J.A.; Bearden, A.; Striker, R. Vitamin D and the anti-viral state. *J Clin Virol* **2011**, *50*, 194-200, doi:10.1016/j.jcv.2010.12.006.
124. Hewison, M. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)* **2012**, *76*, 315-325, doi:10.1111/j.1365-2265.2011.04261.x.
125. Greiller, C.L.; Martineau, A.R. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients* **2015**, *7*, 4240-4270, doi:10.3390/nu7064240.
126. Wei, R.; Christakos, S. Mechanisms Underlying the Regulation of Innate and Adaptive Immunity by Vitamin D. *Nutrients* **2015**, *7*, 8251-8260, doi:10.3390/nu7105392.
127. Abhimanyu; Coussens, A.K. The role of UV radiation and vitamin D in the seasonality and outcomes of infectious disease. *Photochem Photobiol Sci* **2017**, *16*, 314-338, doi:10.1039/c6pp00355a.
128. Lang, P.O.; Aspinall, R. Vitamin D Status and the Host Resistance to Infections: What It Is Currently (Not) Understood. *Clin Ther* **2017**, *39*, 930-945, doi:10.1016/j.clinthera.2017.04.004.
129. Rondanelli, M.; Miccono, A.; Lamburghini, S.; Avanzato, I.; Riva, A.; Allegrini, P.; Faliva, M.A.; Peroni, G.; Nichetti, M.; Perna, S. Self-Care for Common Colds: The Pivotal Role of Vitamin D, Vitamin C, Zinc, and Echinacea in Three Main Immune Interactive Clusters (Physical Barriers, Innate and Adaptive Immunity) Involved during an Episode of Common Colds-Practical Advice on Dosages and on the Time to Take

These Nutrients/Botanicals in order to Prevent or Treat Common Colds. *Evid Based Complement Alternat Med* **2018**, *2018*, 5813095, doi:10.1155/2018/5813095.
130. Gombart, A.F.; Pierre, A.; Maggini, S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients* **2020**, *12*, doi:10.3390/nu12010236.
131. Schwalfenberg, G.K. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Mol Nutr Food Res* **2011**, *55*, 96-108, doi:10.1002/mnfr.201000174.
132. Kast, J.I.; McFarlane, A.J.; Globinska, A.; Sokolowska, M.; Wawrzyniak, P.; Sanak, M.; Schwarze, J.; Akdis, C.A.; Wanke, K. Respiratory syncytial virus infection influences tight junction integrity. *Clin Exp Immunol* **2017**, *190*, 351-359, doi:10.1111/cei.13042.
133. Chen, Y.; Leng, K.; Lu, Y.; Wen, L.; Qi, Y.; Gao, W.; Chen, H.; Bai, L.; An, X.; Sun, B., et al. Epidemiological features and time-series analysis of influenza incidence in urban and rural areas of Shenyang, China, 2010-2018. *Epidemiol Infect* **2020**, *148*, e29, doi:10.1017/S0950268820000151.
134. Rossi, G.A.; Fanous, H.; Colin, A.A. Viral strategies predisposing to respiratory bacterial superinfections. *Pediatr Pulmonol* **2020**, 10.1002/ppul.24699, doi:10.1002/ppul.24699.
135. Liu, P.T.; Stenger, S.; Li, H.; Wenzel, L.; Tan, B.H.; Krutzik, S.R.; Ochoa, M.T.; Schauber, J.; Wu, K.; Meinken, C., et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* **2006**, *311*, 1770-1773, doi:10.1126/science.1123933.
136. Adams, J.S.; Ren, S.; Liu, P.T.; Chun, R.F.; Lagishetty, V.; Gombart, A.F.; Borregaard, N.; Modlin, R.L.; Hewison, M. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. *J Immunol* **2009**, *182*, 4289-4295, doi:10.4049/jimmunol.0803736.
137. Laaksi, I. Vitamin D and respiratory infection in adults. *Proc Nutr Soc* **2012**, *71*, 90-97, doi:10.1017/S0029665111003351.
138. Agier, J.; Efenberger, M.; Brzezinska-Blaszczyk, E. Cathelicidin impact on inflammatory cells. *Cent Eur J Immunol* **2015**, *40*, 225-235, doi:10.5114/ceji.2015.51359.
139. Fehr, A.R.; Perlman, S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol* **2015**, *1282*, 1-23, doi:10.1007/978-1-4939-2438-7_1.
140. Barlow, P.G.; Svoboda, P.; Mackellar, A.; Nash, A.A.; York, I.A.; Pohl, J.; Davidson, D.J.; Donis, R.O. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. *PLoS One* **2011**, *6*, e25333, doi:10.1371/journal.pone.0025333.
141. Ramos-Martinez, E.; Lopez-Vancell, M.R.; Fernandez de Cordova-Aguirre, J.C.; Rojas-Serrano, J.; Chavarria, A.; Velasco-Medina, A.; Velazquez-Samano, G. Reduction of respiratory infections in asthma patients supplemented with vitamin D is related to increased serum IL-10 and IFNgamma levels and cathelicidin expression. *Cytokine* **2018**, *108*, 239-246, doi:10.1016/j.cyto.2018.01.001.
142. Sharifi, A.; Vahedi, H.; Nedjat, S.; Rafiei, H.; Hosseinzadeh-Attar, M.J. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. *APMIS* **2019**, *127*, 681-687, doi:10.1111/apm.12982.
143. Short, K.R.; Kedzierska, K.; van de Sandt, C.E. Back to the Future: Lessons Learned From the 1918 Influenza Pandemic. *Front Cell Infect Microbiol* **2018**, *8*, 343, doi:10.3389/fcimb.2018.00343.

144. Vasarhelyi, B.; Satori, A.; Olajos, F.; Szabo, A.; Beko, G. [Low vitamin D levels among patients at Semmelweis University: retrospective analysis during a one-year period]. *Orv Hetil* **2011**, *152*, 1272-1277, doi:10.1556/OH.2011.29187.
145. MacLaughlin, J.; Holick, M.F. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* **1985**, *76*, 1536-1538, doi:10.1172/JCI112134.
146. Grober, U.; Kisters, K. Influence of drugs on vitamin D and calcium metabolism. *Dermatoendocrinol* **2012**, *4*, 158-166, doi:10.4161/derm.20731.
147. Lei, G.S.; Zhang, C.; Cheng, B.H.; Lee, C.H. Mechanisms of Action of Vitamin D as Supplemental Therapy for Pneumocystis Pneumonia. *Antimicrob Agents Chemother* **2017**, *61*, doi:10.1128/AAC.01226-17.
148. Heaney, R.P.; Davies, K.M.; Chen, T.C.; Holick, M.F.; Barger-Lux, M.J. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* **2003**, *77*, 204-210, doi:10.1093/ajcn/77.1.204.
149. van Groningen, L.; Opdenoordt, S.; van Sorge, A.; Telting, D.; Giesen, A.; de Boer, H. Cholecalciferol loading dose guideline for vitamin D-deficient adults. *Eur J Endocrinol* **2010**, *162*, 805-811, doi:10.1530/EJE-09-0932.
150. Amir, E.; Simmons, C.E.; Freedman, O.C.; Dranitsaris, G.; Cole, D.E.; Vieth, R.; Ooi, W.S.; Clemons, M. A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D(3) in breast cancer patients with bone metastases. *Cancer* **2010**, *116*, 284-291, doi:10.1002/cncr.24749.
151. McCullough, P.J.; Lehrer, D.S.; Amend, J. Daily oral dosing of vitamin D3 using 5000 TO 50,000 international units a day in long-term hospitalized patients: Insights from a seven year experience. *J Steroid Biochem Mol Biol* **2019**, *189*, 228-239, doi:10.1016/j.jsbmb.2018.12.010.
152. Holick, M.F. Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr* **1995**, *61*, 638S-645S, doi:10.1093/ajcn/61.3.638S.
153. Howard, J.E.; Meyer, R.J. Intoxication with vitamin D. *J Clin Endocrinol Metab* **1948**, *8*, 895-910, doi:10.1210/jcem-8-11-895.
154. Malihi, Z.; Lawes, C.M.M.; Wu, Z.; Huang, Y.; Waayer, D.; Toop, L.; Khaw, K.T.; Camargo, C.A.; Scragg, R. Monthly high-dose vitamin D supplementation does not increase kidney stone risk or serum calcium: results from a randomized controlled trial. *Am J Clin Nutr* **2019**, *109*, 1578-1587, doi:10.1093/ajcn/nqy378.
155. Tripkovic, L.; Lambert, H.; Hart, K.; Smith, C.P.; Bucca, G.; Penson, S.; Chope, G.; Hypponen, E.; Berry, J.; Vieth, R., et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr* **2012**, *95*, 1357-1364, doi:10.3945/ajcn.111.031070.
156. Shieh, A.; Chun, R.F.; Ma, C.; Witzel, S.; Meyer, B.; Rafison, B.; Swinkels, L.; Huijs, T.; Pepkowitz, S.; Holmquist, B., et al. Effects of High-Dose Vitamin D2 Versus D3 on Total and Free 25-Hydroxyvitamin D and Markers of Calcium Balance. *J Clin Endocrinol Metab* **2016**, *101*, 3070-3078, doi:10.1210/jc.2016-1871.
157. Tripkovic, L.; Wilson, L.R.; Hart, K.; Johnsen, S.; de Lusignan, S.; Smith, C.P.; Bucca, G.; Penson, S.; Chope, G.; Elliott, R., et al. Daily supplementation with 15 mug vitamin D2 compared with vitamin D3 to increase wintertime 25-hydroxyvitamin D status in healthy South Asian and white European women: a 12-wk randomized, placebo-controlled food-fortification trial. *Am J Clin Nutr* **2017**, *106*, 481-490, doi:10.3945/ajcn.116.138693.

158. Zhang, Y.; Fang, F.; Tang, J.; Jia, L.; Feng, Y.; Xu, P.; Faramand, A. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ* **2019**, *366*, l4673, doi:10.1136/bmj.l4673.
159. Cianferotti, L.; Bertoldo, F.; Bischoff-Ferrari, H.A.; Bruyere, O.; Cooper, C.; Cutolo, M.; Kanis, J.A.; Kaufman, J.M.; Reginster, J.Y.; Rizzoli, R., et al. Vitamin D supplementation in the prevention and management of major chronic diseases not related to mineral homeostasis in adults: research for evidence and a scientific statement from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). *Endocrine* **2017**, *56*, 245-261, doi:10.1007/s12020-017-1290-9.
160. Amrein, K.; Scherkl, M.; Hoffmann, M.; Neuwersch-Sommeregger, S.; Kostenberger, M.; Tmava Berisha, A.; Martucci, G.; Pilz, S.; Malle, O. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr* **2020**, 10.1038/s41430-020-0558-y, doi:10.1038/s41430-020-0558-y.
161. Grant, W.B.; Al Anouti, F.; Moukayed, M. Targeted 25-hydroxyvitamin D concentration measurements and vitamin D3 supplementation can have important patient and public health benefits. *Eur J Clin Nutr* **2020**, 10.1038/s41430-020-0564-0, doi:10.1038/s41430-020-0564-0.
162. Grant, W.B.; Karras, S.N.; Bischoff-Ferrari, H.A.; Annweiler, C.; Boucher, B.J.; Juzeniene, A.; Garland, C.F.; Holick, M.F. Do studies reporting 'U'-shaped serum 25-hydroxyvitamin D-health outcome relationships reflect adverse effects? *Dermatoendocrinol* **2016**, *8*, e1187349, doi:10.1080/19381980.2016.1187349.
163. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M.; Endocrine, S. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* **2011**, *96*, 1911-1930, doi:10.1210/jc.2011-0385.
164. Pludowski, P.; Holick, M.F.; Grant, W.B.; Konstantynowicz, J.; Mascarenhas, M.R.; Haq, A.; Povoroznyuk, V.; Balatska, N.; Barbosa, A.P.; Karonova, T., et al. Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol* **2018**, *175*, 125-135, doi:10.1016/j.jsbmb.2017.01.021.
165. Pilz, S.; Marz, W.; Cashman, K.D.; Kiely, M.E.; Whiting, S.J.; Holick, M.F.; Grant, W.B.; Pludowski, P.; Hiligsmann, M.; Trummer, C., et al. Rationale and Plan for Vitamin D Food Fortification: A Review and Guidance Paper. *Front Endocrinol (Lausanne)* **2018**, *9*, 373, doi:10.3389/fendo.2018.00373.
166. Grant, W.B.; Boucher, B.J. A Review of the Potential Benefits of Increasing Vitamin D Status in Mongolian Adults through Food Fortification and Vitamin D Supplementation. *Nutrients* **2019**, *11*, doi:10.3390/nu11102452.
167. Camargo, C.A., Jr.; Ganmaa, D.; Frazier, A.L.; Kirchberg, F.F.; Stuart, J.J.; Kleinman, K.; Sumberzul, N.; Rich-Edwards, J.W. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics* **2012**, *130*, e561-567, doi:10.1542/peds.2011-3029.
168. Martineau, A.R.; Jolliffe, D.A.; Hooper, R.L.; Greenberg, L.; Aloia, J.F.; Bergman, P.; Dubnov-Raz, G.; Esposito, S.; Ganmaa, D.; Ginde, A.A., et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* **2017**, *356*, i6583, doi:10.1136/bmj.i6583.
169. Uwitonze, A.M.; Razzaque, M.S. Role of Magnesium in Vitamin D Activation and Function. *J Am Osteopath Assoc* **2018**, *118*, 181-189, doi:10.7556/jaoa.2018.037.

 doi:10.20944/preprints202003.0235.v1

170. Amrhein, V.; Greenland, S.; McShane, B. Scientists rise up against statistical significance. *Nature* **2019**, *567*, 305-307, doi:10.1038/d41586-019-00857-9.