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Obesity, Hypovitaminosis D, and COVID-19: the Bermuda Triangle in Public Health

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Abstract

Purpose of Review The COVID-19 pandemic has challenged public health to a significant extent by markedly increasing morbidity and mortality. Evidence suggests that obesity and hypovitaminosis D constitute important risk factors for SARS-CoV-2 infection, severity of disease, and poor outcomes. Due to their high prevalence globally, obesity and hypovitaminosis D are considered pandemics. This review presents current epidemiologic and genetic data linking obesity, hypovitaminosis D, and COVID-19, highlighting the importance of the convergence of three pandemics and their impact on public health. We also briefly summarize potential mechanisms that could explain these links.

Recent Findings Epidemiologic data have shown that obesity is an independent risk factor for COVID-19, severe disease and death, and genetic evidence has suggested a causal association between obesity-related traits and COVID-19 susceptibility and severity. Additionally, obesity is independently associated with hypovitaminosis D, which is highly prevalent in subjects with obesity. Hypovitaminosis D is independently associated with a higher risk for COVID-19, severity, hospitalization, infectious complications, acute respiratory distress syndrome, and poor outcomes. However, genome-wide association studies have not revealed any causal association between vitamin D levels and the risk for COVID-19, while there is no robust evidence for a beneficial role of vitamin D supplementation in the prevention and treatment of COVID-19.

Summary In the context of the ongoing COVID-19 pandemic, the epidemiologic impact of obesity and hypovitaminosis D is emphasized. Efforts to increase public awareness and reinforce preventive and therapeutic measures against obesity and hypovitaminosis D are strongly required.

Keywords Body mass index · Hypovitaminosis D · Obesity · Pandemic · SARS-CoV-2 · Vitamin D

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Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 has evoked a challenging pandemic, with more than 5 million deaths worldwide as of November 8, 2021 [1]. The morbidity and mortality burden of the coronavirus disease 2019 (COVID-19) are unprecedented globally. As this infectious disease has spread fast throughout the world and is still growing, public health systems were caught off guard.

Large descriptive epidemiologic studies have revealed that hypertension, diabetes mellitus, and cardiovascular disease are the most prevalent comorbidities among hospitalized patients with COVID-19 [2–4]. Since obesity is a key risk factor for the presence of metabolic syndrome, diabetes mellitus, and related cardiovascular disease, it is not surprising that these patients also present an increased prevalence rate of overweight and obesity. In particular, obesity is associated with a higher risk for COVID-19 and worse outcomes [5•]. Obesity has been characterized a global epidemic by WHO [6]. Additionally, obesity is associated with hypovitaminosis D, which is also highly prevalent globally and may be considered a pandemic [7]. Interestingly, hypovitaminosis D has been traditionally linked to a higher susceptibility to respiratory infections, explaining the renewed interest on vitamin D supplementation as a potential protective measure against COVID-19 [8, 9•].

In this review, we present current epidemiologic and genetic data on the associations between obesity, hypovitaminosis D, and COVID-19 in view of the convergence of these three pandemics. We also summarize potential pathophysiologic mechanisms that may explain these associations.

Obesity and the COVID-19 Pandemic

Soon after the COVID-19 outbreak, obesity emerged as a key risk factor for severe COVID-19. Among a large US cohort of 16,780 patients hospitalized with COVID-19, 77% presented with excess body weight, while almost two-thirds of them had obesity [3]. Large observational studies as well as meta-analyses have demonstrated that obesity is an independent risk factor for SARS-CoV-2 infection, severity of disease, hospitalization, need for invasive mechanical ventilation (IMV), and death due to COVID-19 [5•, 10, 11]. In particular, the prevalence of obesity in large cohorts of hospitalized patients with COVID-19 varies from as little as 8.6% to as high as 60.7% [5•, 12]. A large prospective, community-based cohort study revealed a J-shaped association between body mass index (BMI) and admission to hospital due to COVID-19 and a linear association with admission to an intensive care unit (ICU) [13••]. This study also demonstrated a linear increase in the risk of severe COVID-19 leading to admission to hospital and death and a linear increase in admission to an ICU across the whole BMI range, independently from obesity-related comorbidities. Of note, the relative risk conferred by obesity was higher in younger individuals and those of Black ethnicity.

In a cohort study, 34,128 adult hospitalized patients with confirmed COVID-19 in the USA, South Korea, and Spain were compared to 81,596 previously hospitalized patients with influenza. Obesity was more prevalent in patients with COVID-19 than in patients with influenza (20.6% vs 16.6%) and was associated with a significantly higher risk for COVID-19 (odds ratio (OR): 1.30, 95% CI: 1.12–1.32; $p < 0.0001$) [10]. In large meta-analyses, the risk for SARS-CoV-2 infection in patients with obesity is reported to be 46–78% higher than in those with normal body weight [14, 15]. Furthermore, obesity is independently associated with a higher risk for hospitalization due to COVID-19, with ORs varying from 1.4 to 4.17 among meta-analyses [16–18]. The risk for IMV is 66–113% higher in patients with obesity compared to normal weight patients [14, 17, 18]. Also, the risk for admission to ICU in patients with obesity and COVID-19 is 21–88% higher than in patients with COVID-19 but without obesity, based on results from meta-analyses [19, 20].

Obesity is also an independent risk factor for COVID-19-related death [5•]. In a large cohort study, 34% of patients who died due to COVID-19 suffered from obesity [10]. Meta-analyses have shown that obesity increased the risk of death from COVID-19 with pooled ORs varying from 1.14 to 3.52 [16, 21, 22]. Of note, large observational studies showed that obesity is independently associated with death in patients with COVID-19 after adjustment for age, gender, race, and comorbidities [23, 24]. Specifically, increased BMI was significantly associated with death due to COVID-19, and this association was stronger in patients < 50 years old compared to those aged > 70 years [23]. Also, very severe obesity increased the risk of death by 42% compared to normal body weight independently from age, gender, and comorbidities, with those < 65 years old having the greatest risk [24]. Therefore, the impact of obesity in patients with COVID-19 appears to be greater in younger people.

Noteworthy, a causal association between increased BMI and COVID-19 susceptibility and severity has been demonstrated by Mendelian randomization analyses in a UK Biobank cohort of European subjects with confirmed COVID-19 [25, 26]. Also, obesity-related traits have been found to confer a higher risk of developing severe COVID-19 in a population-based cohort study [27••]. It is postulated that multiple underlying mechanisms, which have been extensively reviewed elsewhere, contribute to this association [5•, 28, 29]. Most importantly, obesity is characterized by impaired immune responses affecting both the innate and adaptive immunity [30, 31]. Chronic low-grade inflammation (referred to as "meta-inflammation") is responsible for the inflammatory preconditioning in obesity, which results in excessive secretion of pro-inflammatory cytokines during

infection [32–34]. Moreover, overactivation of the coagulation cascade and the renin-aldosterone system along with endothelial dysfunction may contribute to the severity of COVID-19 in patients with obesity [35–37]. Interestingly, enhanced expression of angiotensin-converting enzyme 2 receptors, which facilitate SARS-CoV-2 entry into cells, has been observed in the adipose tissue, making it a large reservoir for SARS-CoV-2, promoting viral replication and prolonged shedding, and thereby contributing to the severity of COVID-19 [38]. Also, obesity is characterized by alterations in gut microbiome, which is known to modulate immune responses to infections. Gut dysbiosis has been implicated in aberrant inflammation during COVID-19 [5•]. Additionally, obesity results in decreased functional respiratory capacity and respiratory system compliance, which increase the risk for respiratory failure and need for mechanical ventilation. Treatment of hospitalized patients with excess body weight presents many challenges due to mechanical issues affecting transportation, positioning, diagnostic, and therapeutic techniques. Finally, the psychological impact of obesity along with the discrimination experienced by individuals with obesity in the healthcare environment may contribute to a reluctance to seek medical help, leading to delays in treatment and worse outcomes [5•].

The association of obesity with COVID-19 becomes even more important for public health when considering its high and increasing prevalence worldwide. According to the World Health Organization (WHO), obesity is considered a global epidemic since 1997 [6]. In 2016, 1.6 billion adults had overweight (BMI 25–29.9 kg/m^2), and 650 million had obesity (BMI $\geq$ 30 kg/m^2) [39]. The estimated global prevalence of overweight and obesity in adults was 52% (39% for overweight and 13% for obesity) in 2016, has nearly tripled since 1975, and is expected to rise above 57% by 2030 [39, 40]. Furthermore, it has been estimated that over 4 million people died due to overweight or obesity in 2017 [39]. Thus, obesity has grown into a pandemic, affecting not only developed countries but literally every part of the world [40–42]. Considering that the prevalence of obesity is comparable to COVID-19 globally, we are now facing the concurrence of two pandemics, with interactions that drive COVID-19 morbidity and mortality [43].

Obesity and Hypovitaminosis D

Paradoxically, obesity is associated with malnutrition and micronutrient deficiencies. In this context, hypovitaminosis D (vitamin D deficiency and insufficiency, defined as serum 25-hydroxyvitamin D or 25(OH)D values < 30 nmol/L and 30–50 nmol/L, respectively) is particularly prominent in subjects with obesity, with a reported prevalence of 33% in adults and 37% in children [44•, 45]. Large observational studies and meta-analyses have consistently demonstrated inverse associations of vitamin D status with BMI, which are typically stronger with increasing BMI values [46, 47, 48••]. This inverse relationship has been observed with other measures of adiposity as well, such as fat mass, percentage body fat, and waist-to-hip ratio [49, 50]. A large meta-analysis of 21 cohort studies including more than 42,000 participants showed that each 1 kg/m^2 increase in BMI was associated with 1.15% lower serum 25(OH)D concentrations after adjusting for age, gender, and other confounding variables [48••]. Moreover, obesity was found to be an independent risk factor for low vitamin D status, with hypovitaminosis D being 35–52% more prevalent in individuals with obesity and 24% more prevalent in individuals with overweight compared to individuals with normal body weight [45, 51].

The association between obesity and low vitamin D status has been investigated by Mendelian randomization studies in large populations in order to elucidate the direction and causality of this link. Evidence from these studies suggests that obesity may lead to low vitamin D levels, rather than the opposite [48••, 52••]. Various underlying mechanisms, reviewed elsewhere, have been implicated, including volumetric dilution of vitamin D into a greater body size, sequestration into the expanded adipose tissue due to the increased fat-solubility of vitamin D, and decreased vitamin D synthesis due to limited sunlight exposure [44].

Based on evidence from recent population-based surveys from the USA, Canada, and Europe, the prevalence rates of vitamin D deficiency and insufficiency may be as high as 13% and 40%, respectively [7]. However, there are great variations according to age, race, and socioeconomic status, with children, dark-skinned ethnic groups, and populations of low-income countries being at higher risk for hypovitaminosis D. Despite the lack of global epidemiologic data and important variations between ethnic populations, it is estimated that more than 100 million people in North America and Europe and more than 490 million people in Asia have vitamin D deficiency [7]. These epidemiologic data suggest that vitamin D deficiency is highly prevalent around the world, reaching pandemic levels, and its association with obesity may be in part responsible for this [44•].

Hypovitaminosis D and COVID-19

Vitamin D exerts a plethora of immunomodulatory actions including downregulation of Toll-like receptor expression; inhibition of B-cell proliferation and differentiation; suppression of B-cell antibody production; inhibition of major histocompatibility complex class II expression and differentiation of monocytes to dendritic cells; modulation of T-cell differentiation; and downregulation of pro-inflammatory cytokine expression [8]. These effects are

particularly prominent in the respiratory epithelium due to the locally increased synthesis of active vitamin D, conferring a protective effect against respiratory infections [8]. As shown in recent meta-analyses, hypovitaminosis D is associated with susceptibility to respiratory infections, while vitamin D supplementation reduces the risk of acute respiratory infections and facilitates clinical improvement [8, 9•, 53, 54]. Moreover, hypovitaminosis D has been implicated in the development of acute respiratory failure being independently associated with worse outcomes in critically ill patients [55, 56].

Vitamin D is further implicated in SARS-CoV-2 pathophysiologic processes, involving the renin-angiotensin system (RAS) and the inflammation, coagulation, and oxidative stress induced by angiotensin II [57]. In particular, vitamin D, via its active metabolite $1,25(OH)_2D$, inhibits renin expression and thus angiotensin II synthesis. It also facilitates angiotensin-(1,7) synthesis by upregulating angiotensin converting enzyme 2 (ACE2), thus inhibiting the pro-inflammatory and pro-coagulatory actions of angiotensin II and protecting from systemic inflammation and lung injury induced by SARS-CoV-2 [58]. Additionally, vitamin D induces cathelicidin and defensins, which act against viral infections [59]. Finally, vitamin D upregulates IL-10, an anti-inflammatory cytokine, and downregulates the pro-inflammatory cytokines IL-1, IL-6, and tumor-necrosis factor-alpha, ameliorating inflammation and cytokine storm due to COVID-19 [60].

According to observational studies and meta-analyses, hypovitaminosis D has been associated with a higher risk for COVID-19 infection, disease severity, hospitalization, and poor outcomes [61••, 62–69]. In particular, a large retrospective observational study in over 190,000 patients in the USA has demonstrated a strong inverse association between SARS-CoV-2 positivity and circulating 25(OH)D levels that remained significant after adjustment for age, gender, race, and latitude [61••]. Also, hypovitaminosis D was highly prevalent in hospitalized patients with COVID-19, reported to be as high as 100% in one study [62]. A meta-analysis of 27 studies found that vitamin D deficiency rates were 64% higher in patients with severe COVID-19 than in those with mild COVID-19 [68]. Furthermore, meta-analyses have revealed that the risk for COVID-19 was 26–171% higher; the risk for severe disease was 90–160% higher; the risk for hospitalization was 81–117% higher; and the risk for death due to COVID-19 was 22–208% higher in subjects with hypovitaminosis D [64–69]. Additionally, hypovitaminosis D was found to be an independent risk factor for SARS-CoV-2 infection and hospitalization due to COVID-19 after adjustment for demographic variables (age, gender, and BMI) and comorbidities [70]. A recent study has shown that pre-infection vitamin D deficiency was associated with increased COVID-19 severity, independently of age, gender, BMI, and comorbidities and also with higher mortality due to COVID-19 [71]. Of note, the researchers used a cosinor model to account for any influence of the seasonal variation of vitamin D status. Moreover, studies in critically ill patients with COVID-19 have demonstrated that hypovitaminosis D is associated with a higher rate of infectious complications (respiratory infection, bacteremia, and sepsis) as well as a higher risk for acute respiratory distress syndrome (ARDS) and poor outcomes [72]. Also, vitamin D sufficiency (defined as $25(OH)D \geq 30$ ng/mL) was independently associated with decreased risk for ARDS and severe sepsis or septic shock among hospitalized patients with COVID-19, after adjustment for potential confounding factors (age, sex, BMI, insurance, race, smoking, alcohol drinking, and comorbidities), as well as with a decreased risk of death in elderly and patients without obesity [73]. Finally, a meta-analysis found that low vitamin D was associated with a higher mortality risk due to COVID-19 [74].

Since a causal relationship cannot be inferred from observational studies and due to the many confounding factors that may affect vitamin D levels, Mendelian randomization studies were used to explore causal associations between vitamin D status and the risk for COVID-19 and its outcomes. Evidence from a genome-wide association study (GWAS) of 443,734 European participants, which investigated genetic variants related to 25(OH)D levels, does not support an association between genetically-predicted vitamin D levels and COVID-19 susceptibility, hospitalization, or severe disease [75].

The effects of vitamin D supplementation on viral clearance, inflammatory biomarkers, clinical improvement, and outcome in patients with COVID-19 have been evaluated in numerous studies. The SHADE study, which is an RCT, reported that the administration of a short term high-dose course of vitamin D (60,000 IU daily for 7–14 days) in 40 individuals infected with SARS-CoV-2 (16 in the intervention group and 24 in the control group) restored vitamin D levels, decreased inflammatory biomarkers, and resulted in a significantly higher rate of viral clearance compared to controls [76]. Another RCT compared the administration of pulse vitamin D supplementation (60,000 IU daily for 8–10 days) in 44 patients with mild to moderate COVID-19 and hypovitaminosis D with standard treatment in 43 patients (matched on age, BMI, and comorbidities) with mild to moderate COVID-19 and hypovitaminosis D [77]. This study also reported that vitamin D supplementation significantly restored vitamin D levels and reduced all inflammatory biomarkers in contrast to the control group, where the reduction in inflammatory biomarkers was insignificant. Although the sample size of the abovementioned RCTs is small, the corresponding statistical power was more than 80% in both studies.

Evidence from retrospective, observational studies has indicated that vitamin D supplementation was associated with a better clinical course and improved survival in patients with COVID-19 [78–80]. However, a large RCT in 240 hospitalized patients with moderate to severe COVID-19 failed to demonstrate any benefit of a single high-dose of vitamin D3 (200,000 IU orally) in reducing hospital stay, in-hospital mortality, or need for mechanical ventilation and ICU admission, despite restoring vitamin D levels [81•]. Noteworthy, a meta-analysis of 13 studies (10 observational studies and 3 RCTs, including the abovementioned RCT) and almost 3,000 patients with COVID-19 showed that vitamin D supplementation significantly reduced ICU admission and mortality by almost 60% and reduced the risk for adverse outcomes by more than 70% after adjustment for age, gender, BMI, and comorbidities [82]. Improved clinical outcomes were found only in those who received vitamin D after the COVID-19 diagnosis [82]. However, none of these studies have explored whether patients with hypovitaminosis D or obesity had a greater clinical benefit from vitamin D supplementation. Nevertheless, other meta-analyses of cohort studies and RCTs in patients with COVID-19 failed to confirm any beneficial effect of vitamin D supplementation on COVID-19 outcomes, mainly due to methodological heterogeneity of the studies [83, 84]. Apparently, more prospective studies are needed to elucidate the role of vitamin

Table 1 Epidemiologic and genetic associations and underlying mechanisms linking obesity, hypovitaminosis D and COVID-19

Epidemiologic data	Genetic data	Pathogenetic mechanisms
Obesity and COVID-19		
BMI is positively correlated with the risk for severe COVID-19 and ICU admission, independently from related comorbidities [13••]	Genetically determined higher BMI is causally associated with increased risk of COVID-19 (OR: 1.15, 95% CI: CI: 1.05–1.26, per 1 SD increase in BMI) according to Mendelian randomization analyses [25]	Impaired innate and adaptive immunity Meta-inflammation enhances inflammatory response Activation of the coagulation cascade Activation of the renin-aldosterone system Endothelial dysfunction and oxidative stress Aberrant activation of the complement cascade Increased expression of ACE2 receptors Obesity-associated comorbidities Gut dysbiosis Hypovitaminosis D Mechanical issues related to obesity Physical inactivity due to obesity Psychological issues in obesity [30–38]
Obesity is present in 8.6–60.7% of patients with COVID-19 and 34% of patients who died due to COVID-19 [5•, 10, 12]	Genetically determined higher BMI is a causal risk factor for COVID-19 susceptibility and severity, with a significantly higher risk for hospitalization due to COVID-19 (OR: 1.14, 95% CI: CI: 1.07–1.21, per 1 kg/m^2 increase in BMI) [26]	
Obesity is associated with poorer COVID-19 related outcomes: •46–78% higher risk for COVID-19 [14, 15] •40–317% higher risk for hospitalization [16–18] •66–113% higher risk for IMV [14, 17, 18] •21–88% higher risk for ICU admission [19, 20] •14–252% higher risk of death [16, 21, 22]	Obesity-related traits and genetic predisposition for obesity are associated with higher risk of developing severe COVID-19 in a population-based cohort study [27••]	
Hypovitaminosis D and obesity		
Vitamin D status is inversely associated with BMI [46, 47, 48••]	Vitamin D-related genetic variants are not associated with obesity [48••, 52••]	Volumetric dilution Sequestration into the adipose tissue Decreased vitamin D synthesis [44•]
Obesity is an independent risk factor for hypovitaminosis D [44•]		
Hypovitaminosis D is present in 33% of adults and 37% of children with obesity [44•, 45]		
Hypovitaminosis D is 35–52% more prevalent in obesity and 24% more prevalent in overweight [45]		
Serum 25(OH)D is 1.15% lower for every 1 kg/m2 increase in BMI [48••]		
Hypovitaminosis D and COVID-19		
Hypovitaminosis D is an independent risk factor for SARS-CoV-2 infection and hospitalization [70, 71]	Evidence from Mendelian randomization analyses in populations without vitamin D deficiency does not support an association between genetically predicted vitamin D level and COVID-19 susceptibility, hospitalization or severe disease [75]	Upregulation of TLR, MHC II expression, antibody production, and B-cell proliferation and differentiation Upregulation of pro-inflammatory cytokine expression [60] Downregulation of anti-inflammatory cytokine expression [8, 60] Upregulation of RAS and angiotensin II synthesis [57, 58] Downregulation of ACE2 expression and angiotensin-(1,7) synthesis [58] Downregulation of cathelicidin and defensins [59]
Hypovitaminosis D is 64% more prevalent in severe COVID-19 [68]		
Hypovitaminosis D is associated with poorer COVID-19 related outcomes: •26–171% higher risk for COVID-19 •90–160% higher risk for severe disease •81–117% higher risk for hospitalization •22–208% higher risk of death [64–69]		

ACE2 angiotensin-converting enzyme 2; *BMI* body mass index; *CI* confidence interval; *COVID-19* coronavirus disease 2019; *ICU* intensive care unit; *IMV* invasive mechanical ventilation; *MHC* major histocompatibility complex; *OR* odds ratio; *RAS* renin-angiotensin system; *SD* standard deviation; *TLR* toll-like receptors; *25(OH)D* 25-hydroxyvitamin D

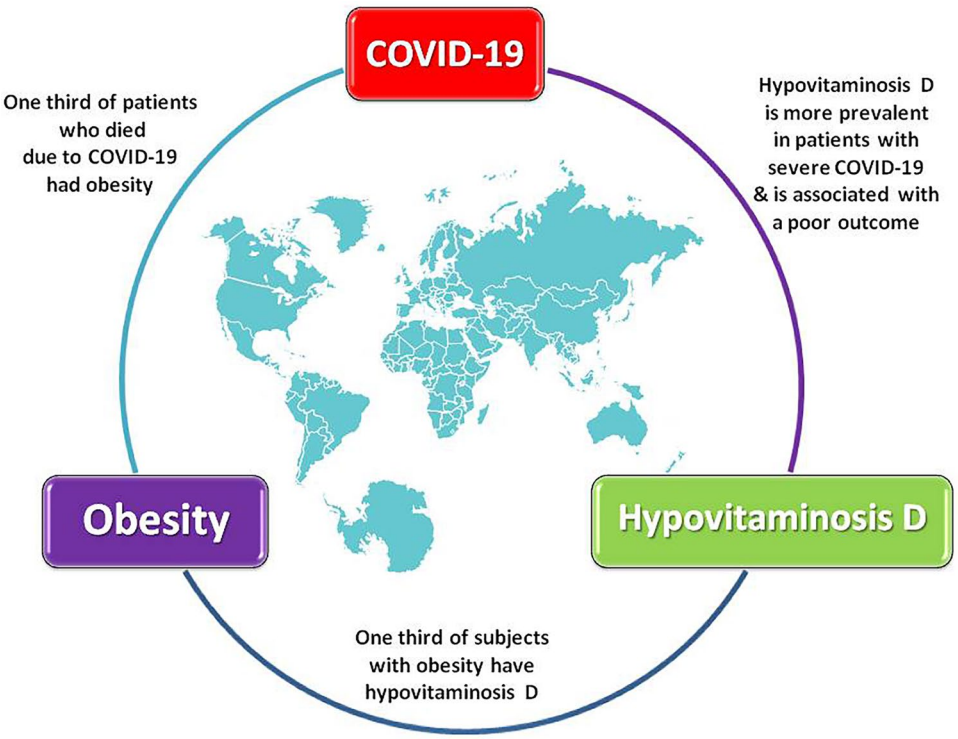

Fig. 1 Global convergence of the three pandemics of obesity, hypovitaminosis D and COVID-19

D supplementation in COVID-19. Despite the lack of robust evidence, a recommendation for vitamin D supplementation has been proposed as a preventive measure against SARS-CoV-2 infection and severe COVID-19, since it is considered safe, inexpensive, and widely available [63, 72, 85].

Hypovitaminosis D at the Intersection of Obesity and COVID-19

A large study of 353,299 UK Biobank participants from England have demonstrated that metabolically unhealthy obesity combined with vitamin D insufficiency could highly increase the risk of SARS-CoV-2 infection and COVID-19 severity, especially in elderly men [86••]. Normal body weight and vitamin D status are mainly dependent on the availability and adherence to a healthy diet [87]. Obesity, as well as hypovitaminosis D, is driven by multiple underlying factors, many of which lead to poor dietary quality owing to low socio-economic status. Low and middle-income countries present high rates of malnutrition, but also obesity. In addition, disparities related to racial, environmental, educational, and social factors are associated with higher obesity rates and worse COVID-19 outcomes [88].

The emergence of the COVID-19 pandemic has taken place at a time when the world population is vulnerable due to the widespread obesity and hypovitaminosis D. The coincidence of two preexisting pandemics (obesity and hypovitaminosis D) with a new infectious one (COVID-19) has resulted in a public health crisis. Table 1 summarizes epidemiologic data, genetic evidence, and underlying pathogenetic mechanisms linking obesity, hypovitaminosis D, and COVID-19. As both obesity and hypovitaminosis D have been implicated in COVID-19 severity, it is reasonable to assume that their high prevalence may in part be responsible for the heavy impact of COVID-19 (Fig. 1). Had the occurrence of obesity and hypovitaminosis D been limited, COVID-19 pandemic might have presented with a different trajectory and a potentially less severe impact.

Conclusion

Obesity and hypovitaminosis D are interrelated epidemiologically and are highly prevalent reaching pandemic levels. Due to their associations with a higher risk for COVID-19 morbidity and mortality, there are important implications regarding the currently active COVID-19 pandemic. The convergence of these three pandemics may be at least in part responsible for the severe impact of COVID-19. As both hypovitaminosis D and obesity are modifiable risk factors for COVID-19, renewed efforts to increase public awareness are warranted. Also, health policies and preventive strategies should focus not only on

COVID-19, but also on improving public health status in the long term by preventing and treating obesity and hypovitaminosis D to mitigate the impact of COVID-19 but also the impact of future viral infectious disease outbreaks.

Author Contribution IK designed the manuscript, performed literature search, wrote and edited the manuscript. NV wrote and edited the manuscript. FM and CMA edited and reviewed the manuscript. MD conceived the idea, designed, supervised, edited and reviewed the manuscript.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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