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

Irene Karampela1 · Natalia Vallianou2 · Faidon Magkos3 · Caroline M. Apovian4 · Maria Dalamaga5

Accepted: 2 March 2022 / Published online: 7 April 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

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

This article is part of the Topical Collection on Metabolism

1 Second Department of Critical Care, Medical School, Attikon General University Hospital, National and Kapodistrian University of Athens, 1 Rimini St, 12462 Haidari, Greece

2 Department of Internal Medicine and Endocrinology, Evangelismos General Hospital of Athens, 45-47 Ypsilantou St., 10676 Athens, Greece

3 Department of Nutrition, Exercise, and Sports, University of Copenhagen, Copenhagen, Denmark

4 Division of Endocrinology, Diabetes and Hypertension, Brigham and Womens Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA

5 Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias St, 11527 Athens, Greece

Springer
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
studies and meta-analyses have consistently demonstrated that 250 adults had overweight (BMI 25–29.9 kg/m²), and 650 considered a global epidemic since 1997 [6]. In 2016, 1.6 billion had 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/m² 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•].

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

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, including 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 ≥ 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: 1.05–1.26, per 1 SD increase in BMI) according to Mendelian randomization analyses [25] | Impaired innate and adaptive immunity |
| 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: 1.07–1.21, per 1 kg/m² increase in BMI) [26] | Meta-inflammation enhances inflammatory response |
| Obesity is associated with poorer COVID-19 related outcomes: | 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••] | Activation of the coagulation cascade |
| •46–78% higher risk for COVID-19 [14, 15] | | Activation of the renin-angiotensin system |
| •40–317% higher risk for hospitalization [16–18] | | Endothelial dysfunction and oxidative stress |
| •66–113% higher risk for IMV [14, 17, 18] | | Aberrant activation of the complement cascade |
| •21–88% higher risk for ICU admission [19, 20] | | Increased expression of ACE2 receptors |
| •14–252% higher risk of death [16, 21, 22] | | Obesity-associated comorbidities |
| **Hypovitaminosis D and obesity** | | Gut dysbiosis |
| Vitamin D status is inversely associated with BMI [46, 47, 48••] | Vitamin D-related genetic variants are not associated with obesity [48••, 52••] | Hypovitaminosis D |
| Obesity is an independent risk factor for hypovitaminosis D [44•] | | Mechanical issues related to obesity |
| Hypovitaminosis D is present in 33% of adults and 37% of children with obesity [44•, 45] | | Physical inactivity due to obesity |
| Hypovitaminosis D is 35–52% more prevalent in obesity and 24% more prevalent in overweight [45] | | Psychological issues in obesity [30–38] |
| Serum 25(OH)D is 1.15% lower for every 1 kg/m² increase in BMI [48••] | | |

**Hypovitaminosis D and COVID-19**

| | | |
| 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 |
| Hypovitaminosis D is an independent risk factor for SARS-CoV-2 infection and hospitalization [70, 71] | | Upregulation of pro-inflammatory cytokine expression [60] |
| Hypovitaminosis D is 64% more prevalent in severe COVID-19 [68] | | Downregulation of anti-inflammatory cytokine expression [8, 60] |
| Hypovitaminosis D is associated with poorer COVID-19 related outcomes: | | Upregulation of RAS and angiotensin II synthesis [57, 58] |
| •26–171% higher risk for COVID-19 | | Downregulation of ACE2 expression and angiotensin (1,7) synthesis [58] |
| •90–160% higher risk for severe disease | | Downregulation of cathelicidin and defensins [59] |
| •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**
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. 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.

Disclosures CMA reports receiving personal fees from Abbott Nutrition, Allergan, Inc., Altimmune, Inc., Bariatritx Nutrition, Cowen and Company, LLC, Curavit Clinical Research, Enteromedics, Gelesis, SrL, Janssen, Jazz Pharmaceuticals, Inc., L-Nutra, Inc., Novo Nordisk, Inc., Nutrisystem, Real Appeal, Riverview School, Rhythm Pharmaceuticals, Roman Health Ventures, Inc., SetPoint Health, Scientific Intake Ltd, Co., Tivity Health, Inc., Xeno Biosciences and Zafgen Inc. outside of the funded work. CMA Real Appeal, Riverview School, Rhythm Pharmaceuticals, Roman Health Disclosures of the authors.

Conflict of Interest The manuscript.

Author Contribution MD conceived the idea, designed, supervised, edited and reviewed the manuscript. FM and CMA edited and reviewed the manuscript.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

• Of major importance

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available from: https://covid19.who.int/ [Accessed 8 Nov 2021].

2. Kalyanaraman Marcello R, Dolle J, Grami S, Adule R, Li Z, Tatem K, et al. New York city health + hospitals COVID-19 population health data team. Characteristics and outcomes of COVID-19 patients in New York city’s public hospital system. PLoS One 2020;15(12): e0243027. https://doi.org/10.1371/journal.pone.0243027.

3. Chawla D, Rizzo S, Zaloucysky K, Keebler D, Chia J, Lindsay L, et al. Descriptive epidemiology of 16,780 hospitalized COVID-19 patients in the United States. 2020:2020.07.17.20156265. medRxiv. https://doi.org/10.1101/2020.07.17.20156265.

4. Vallianou NG, Evangelopoulos A, Kounatidis D, Stratigou T, Christodoulatos GS, Karampela I, et al. Diabetes mellitus and SARS-CoV-2 infection: pathophysiologic mechanisms and implications in management. Curr Diabetes Rev. 2020. https://doi.org/10.2174/157339981766210110111253.

5. Dalamaga M, Christodoulatos GS, Karampela I, Vallianou N, Apovian CM. Understanding the co-epidemic of obesity and COVID-19: current evidence, comparison with previous epidemics, mechanisms, and preventive and therapeutic perspectives. Curr Obes Rep. 2021;1:1–30. https://doi.org/10.1007/s13679-021-00436-y. This interesting review summarizes current epidemiologic data on the association between obesity and COVID-19, compares data from previous pandemics and highlights the pathophysiologic role of obesity-related meta-inflammation with regard to COVID-19.

6. Obesity: preventing and managing the global epidemic: report of a WHO Consultation on Obesity, Geneva, 3–5 June 1997. World Health Organization. Available form: https://apps.who.int/iris/handle/10665/63584. [Accessed 17 July 2021]

7. Cashman KD, Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. Calcif Tissue Int. 2020;106:14–29. https://doi.org/10.1007/s00223-019-00559-4.

8. Hughes DA, Norton R. Vitamin D and respiratory health. Clin Exp Immunol. 2009;158(1):20–5. https://doi.org/10.1111/j.1365-2249.2009.04001.x.

9. Jolliffe DA, Camargo CA Jr, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021;9(5):276–292. https://doi.org/10.1016/S2213-8587(21)00051-6. This meta-analysis of 46 RCTs and more than 48,400 participants suggests that vitamin D supplementation is safe and is associated with a small reduction in the risk of acute respiratory infections.

10. Burn E, You SC, Sena AG, Kostka K, Abdedash H, Abrahão MTF, et al. An international characterisation of patients hospitalised with COVID-19 and a comparison with those previously hospitalised with influenza. medRxiv. 2020. https://doi.org/10.1101/2020.04.22.20074336.

11. Sattar N, Valabhji J. Obesity as a risk factor for severe COVID-19: summary of the best evidence and implications for health care. Curr Obes Rep. 2021;10(3):282–9. https://doi.org/10.1007/s13679-021-00448-8.

12. Gu T, Mack JA, Salvatore M, Sankar SP, Valley TS, Singh K, et al. COVID-19 outcomes, risk factors and associations by race: a comprehensive analysis using electronic health records data in Michigan Medicine. medRxiv. 2020. https://doi.org/10.1101/2020.06.16.20133140.

13. Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O’Rahilly S, Aveyard P, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol. 2021. https://doi.org/10.1016/S2213-8587(21)00089-9. This large, prospective, community-based, cohort study in more than 6.9 million participants in England, UK demonstrated a J-shaped association between BMI and hospitalised with COVID-19 and a comparison with those previously hospitalised with influenza.

14. Popkin BM, Du S, Green WD, Beck MA, Algaita T, Herbst CH, et al. Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. Obes Rev. 2020;21: e13128. https://doi.org/10.1111/obr.13128.

15. Soeroto AY, Soetedjo NN, Purwiga A, Santoso P, Kalsum ID, Suryadinata H, et al. Effect of increased BMI and obesity on the outcome of COVID-19 adult patients: a systematic review and meta-analysis. Diabetes Metab Syndr. 2020;14:1897–904. https://doi.org/10.1016/j.dsx.2020.09.029.

16. Yang J, Tian C, Chen Y, Zhu C, Chi H, Li J. Obesity aggravates COVID-19: an updated systematic review and meta-analysis. J Med Virol. 2020. https://doi.org/10.1002/jmv.26677.

17. Chu Y, Yang J, Shi J, Zhang P, Wang X. Obesity is associated with increased severity of disease in COVID-19 pneumonia: a
systematic review and meta-analysis. Eur J Med Res. 2020;25:64. https://doi.org/10.1186/s40001-020-00464-9.

18. Chang TH, Chou CC, Chang LY. Effect of obesity and body mass index on coronavirus disease 2019 severity: a systematic review and meta-analysis. Obes Res Clin Pract. 2020;21(11): e13089. https://doi.org/10.1111/obrcp.13089.

19. Földi M, Farkas N, Kiss S, Zádori N, Vénás S, Szakó L, et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: a systematic review and meta-analysis. Obes Res Clin Pract. 2020;21:e13095. https://doi.org/10.1111/obrcp.13095.

20. Malik P, Patel U, Patel K, Martin C, Shah C, Mehta D, et al. Obesity a predictor of outcomes of COVID-19 hospitalized patients—a systematic review and meta-analysis. J Med Virol. 2021;93(2):1188–93. https://doi.org/10.1002/jmv.26555.

21. Hoong CWS, Hussain I, Aravamudan VM, Phyu EE, Lin JHX, Koh H. Obesity is associated with poor covid-19 outcomes: a systematic review and meta-analysis. Horm Metab Res. 2021;53(2):85–93. https://doi.org/10.1055/a-1326-2125.

22. Seidu S, Gillies C, Zaccardi F, Knutsor SK, Hartmann-Boye J, Yates T, et al. The impact of obesity on severe disease and mortality in people with SARS-CoV-2: a systematic review and meta-analysis. Endocrinol Diabetes Metab. 2020;4(1): e00176. https://doi.org/10.1002/edm2.176.

23. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, et al. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. Circulation. 2021;143:135–44. https://doi.org/10.1161/circulationaha.120.033630.

24. Eastment MC, Berry K, Locke E, Green P, O’Hare A, Crothers J, Yates T, et al. The impact of obesity on severe disease and mortality in patients-a systematic review and meta-analysis. J Med Virol. 2021;93(2):1188–93. https://doi.org/10.1002/jmv.26555.

25. Aung N, Khaniy MY, Munroe PB, Petersen SE. Causal inference for genetic obesity, cardiometabolic profile and COVID-19 susceptibility: a Mendelian randomization study. Front Genet. 2020;11:586308. https://doi.org/10.3389/fgen.2020.586308.

26. Leong A, Cole JB, Brenner LN, Meigs JB, Florez JC, Mercader JM. Cardiometabolic risk factors for COVID-19 susceptibility and severity: a Mendelian randomization analysis. PLoS Med. 2021;18:e1003553.

27. ● Zha Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA Jr, Liang L. Association of obesity and its genetic predisposition with the risk of severe COVID-19: analysis of population-based cohort data. Metabolism. 2020;112:154345. https://doi.org/10.1016/j.metabol.2020.154345. In this study, the analysis of data from almost 0.5 million people from the UK Biobank showed that individuals with higher than normal BMI were at increased risk for severe COVID-19 in a dose-response way. For BMI above 25 kg/m², the ORs ranged from 1.40 to 3.30, being higher for BMI ≥ 40 kg/m². Also, the study concluded that central obesity and genetic predisposition for obesity are associated with a higher risk for severe COVID-19.

28. Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Commentary: obesity: the “Achilles heel” for COVID-19? Metabolism. 2020;108:154251. https://doi.org/10.1016/j.metabol.2020.154251.

29. Kuperberg SJ, Navetta-Modrov B. The role of obesity in the immunopathogenesis of COVID-19 respiratory disease and critical illness. Am J Respir Crit Care Med. 2021;18(5):13–21. https://doi.org/10.1016/j.iccm.2020.02367TR.

30. Dhurandhar NV, Bailey D, Thomas D. Interaction of obesity and infections. Obes Rev. 2015;16:1017–29. https://doi.org/10.1111/obr.12320.

31. McLaughlin T, Ackerman SE, Shen L, Engleman E. Role of innate and adaptive immunity in obesity-associated metabolic disease. J Clin Invest. 2017;127:5–13. https://doi.org/10.1172/jci88876.

32. Korakes E, Ikonomidou I, Kousathana F, Balampanis K, Kountouri A, Raptis A, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab. 2020;319:E105–9. https://doi.org/10.1152/ajpendo.00198.2020.

33. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. Diabetes Res Clin Pract. 2005;69:29–35. https://doi.org/10.1016/j.diabres.2004.11.007.

34. Karampela I, Christodoulouss GS, Dalamaga M. The role of adipose tissue and adipokines in sepsis: inflammatory and metabolic considerations, and the obesity paradox. Curr Obes Rep. 2019;8(4):434–457. https://doi.org/10.1007/s13679-019-00360-2.

35. Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. Curr Opin Hematol. 2013;20:437–44. https://doi.org/10.1097/MOH.0b013e3283644443.

36. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11:875–9. https://doi.org/10.1038/nm1267.

37. van der Heijden DJ, van Leeuwen MAH, Janssens GN, Lenzen MJ, van de Ven PM, Eringa EC, et al. Body mass index is associated with microvascular endothelial dysfunction in patients with treated metabolic risk factors and suspected coronary artery disease. J Am Heart Assoc. 2017;6. https://doi.org/10.1161/jaha.117.006082.

38. Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. Obesity (Silver Spring). 2020;28:1187–90. https://doi.org/10.1002/oby.22856.

39. World Health Organization. Obesity and overweight. Geneva, Switzerland: World Health Organization. Available form: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. [Accessed 17 July 2021]

40. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes. 2008;32:1431–7. https://doi.org/10.1038/ijo.2008.102.

41. Roth J, Qiang X, Marbán SL, Redelt H, Lowell BC. The obesity paradox: where have we been and where are we going? Obes Res. 2004;12(Suppl 2):88S-101S. https://doi.org/10.1038/oby.2004.273.

42. Koliaki C, Liatis S, Dalamaga M, Kokkinos A. Sarcoptic obesity: epidemiologic evidence, pathophysiology, and therapeutic perspectives. Curr Obes Rep. 2019;8(4):458–71. https://doi.org/10.1007/s13679-019-00359-9.

43. Hill MA, Sowers JR, Mantzoros CS. Commentary: COVID-19 and obesity pandemics converge into a syndemic requiring urgent and multidisciplinary action. Metabolism. 2020;114:154408. https://doi.org/10.1016/j.metabol.2020.154408.

● Karampela I, Sakelliau E, Vavlianau NS, Christodoulouss GS, Magkos F, Dalamaga M. Vitamin D and obesity: current evidence and controversies. Curr Obes Rep. 2021;10(2):162–180. https://doi.org/10.1007/s13679-021-00433-1. This review summarizes current evidence from meta-analyses regarding vitamin D status in obesity, weight loss and post-bariatric surgery, highlights important methodological limitations of relevant studies, and discusses potential pathophysiological mechanisms and important controversies. The authors conclude that obesity is associated with low vitamin D status, but weight loss has little effect on improving vitamin D levels. Moreover, vitamin D supplementation is not associated with weight loss, while it has shown contradicting results after bariatric surgery.
45. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16:341–9. https://doi.org/10.1111/obr.12239.

46. Rafiq S, Jeppesen PB. Body mass index, vitamin D, and type 2 diabetes: a systematic review and meta-analysis. Nutrients. 2018;10:1182. https://doi.org/10.3390/nu10091182.

47. Saneei P, Salehi-Abargouei A, Esmailzadeh A. Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis. Obes Rev. 2013;14:393–404. https://doi.org/10.1111/obr.12016.

48. Vimala'swaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bidirectional Mendelian randomization analysis of multiple cohorts. PLoS Med. 2013;10:e1001383. https://doi.org/10.1371/journal.pmed.1001383. This seminal study investigated the causality and direction of the association between BMI and vitamin D, by using a bi-directional Mendelian randomization analysis.

49. More than 42,000 participants from 21 adult cohorts, 12 BMI-related SNPs and 4 vitamin D-related SNPs were studied. The analysis showed that a higher BMI leads to lower vitamin D, while lower vitamin D has a rather small effect if any on increasing BMI.

50. Goldsaim and HollisBW, Mirmiran P, Wagner CL, Shah-Bidar S. Vitamin D supplementation and body fat mass: a systematic review and meta-analysis. Eur J Clin Nutr. 2018;72:1345–57. https://doi.org/10.1038/s41430-018-0132-z.

51. Baccoupolou F, Kolias E, Efthymiou V, Antonopoulos CN, Charranadari E. Vitamin D predictors in polycystic ovary syndrome: a meta-analysis. Eur J Clin Invest. 2017;47:746–55. https://doi.org/10.1111/eci.12800.

52. Shanmugalingam T, Crawley D, Bosco C, Melvin J, Rohrmann S, Chowdhury S, et al. Obesity and cancer: the role of vitamin D. BMJ Cancer. 2014;14:712. https://doi.org/10.1186/1471-2407-14-712.

53. Li et al. Vitamin D deficiency in hospitalised patients with COVID-19: an Italian retrospective study. J Am Coll Nutr. 2021;1–16. https://doi.org/10.1080/07315724.2021.1877580.

54. Jain A, Chaurasia R, Sengar NS, Singh M, Mahar S, Nairn S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Sci Rep. 2020;10(1):20919. https://doi.org/10.1038/s41598-020-77093-z.

55. Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. Int J Infect Dis. 2021;104:58–64. https://doi.org/10.1016/j.ijid.2020.12.077.

56. Wang Z, Joshi A, Leopold K, Jackson S, Christensen S, Nayfeh T, et al. Association of vitamin D deficiency with COVID-19 infection severity: systematic review and meta-analysis. Clin Endocrinol (Oxf). 2021. https://doi.org/10.1111/cen.14540.

57. Akbar MR, Wibowo A, Pranata R, Setiabudiawan B. Low serum 25-hydroxyvitamin D (vitamin D) level is associated with susceptibility to COVID-19, severity, and mortality: a systematic review and meta-analysis. Front Nutr. 2021:8;660420. https://doi.org/10.3389/fnut.2021.660420.

58. Petrelli F, Luciani A, Perego G, Dognini G, Colombelli PL, Ghidini A. Therapeutic and prognostic role of vitamin D for COVID-19 infection: a systematic review and meta-analysis of 43 observational studies. J Steroid Biochem Mol Biol. 2021;211:105883. https://doi.org/10.1016/j.jsbmb.2021.105883.

59. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2020:1–9. https://doi.org/10.1080/10408398.2020.1841090.

60. Teshome A, Adane A, Girma B, Meekonnen ZA. The impact of vitamin D level on COVID-19 infection: systematic review and meta-analysis. Front Public Health. 2021;9:624559. https://doi.org/10.3389/fpubh.2021.624559.

61. Merzon E, Tworowski D, Gorohovskiy A, Vinker S, Golan Cohen A, Green I, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J. 2020;287(17):3693–702. https://doi.org/10.1111/febs.15495.

62. Dror AA, Morozov N, Daoud A, Namir Y, Yakir O, Shachar Y, et al. Pre-infection 25-hydroxyvitamin D3 levels and association...
with severity of COVID-19 illness. PLoS ONE. 2022;17(2):e0263069. https://doi.org/10.1371/journal.pone.0263069.

72. Vassiliou AG, Jahaj E, OrfanoS SE, Dimopoulou I, Kotanidou A. Vitamin D in infectious complications in critically ill patients. Endocr Pract. 2021;27(4):271–8. https://doi.org/10.1016/j.eprac.2021.02.013.

73. Charoenngarn N, Shirvani A, Reddy N, Vodopiev DM, Apovian CM, Holick MF. Association of vitamin D status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. Metabol Open. 2021:100106. https://doi.org/10.1016/j.metop.2021.100106.

74. Borsche L, Glauner B. von Mendel J. COVID-19 mortality risk correlates inversely with vitamin D3 status, and a mortality rate close to zero could theoretically be achieved at 50 ng/mL 25(OH)D3: results of a systematic review and meta-analysis. Nutrients. 2021;13(10):3596. https://doi.org/10.3390/nu13103596.

75. Butler-Laporte G, Nakanishi T, Mooser V, Morrison DR, Abdullah T, AdelEye O, et al. Vitamin D and COVID-19 susceptibility and severity in the COVID-19 host genetics initiative: a Mendelian randomization study. PLoS Med. 2021;18(6):e1003605. https://doi.org/10.1371/journal.pmed.1003605.

76. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, Puri GD, Malhotra P. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled study (SHADE study). Postgrad Med J. 2020;postgradmedj-2020–139065. https://doi.org/10.1136/postgradmedj-2020-139065.

77. Lakhireddy M, Gadiga SG, Malathi RD, Karra ML, Raju ISS-VPM, Ragini, et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID-19 disease. Sci Rep. 2021;11(1):10641. https://doi.org/10.1038/s41598-021-90189-4.

78. Ling SF, Broad E, Murphy R, Pappachan JM, Pardesi-Newton S, Kong MF, et al. High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with COVID-19: a cross-sectional multi-centre observational study. Nutrients. 2020;12(12):3799. https://doi.org/10.3390/nu12123799.

79. Giannini S, Passeri G, Tripepi G, Sella S, Fusaro M, Arcidiacono G, et al. Effectiveness of in-hospital cholecalciferol use on clinical outcomes in comorbid COVID-19 patients: a hypothesis-generating study. Nutrients. 2021;13(1):219. https://doi.org/10.3390/nu13010219.

80. Anwiler C, Hanotte B, Grandin de l’Eprevier C, Sabatier JM, Lafae L, Célarié T, Vitamin D and survival in COVID-19 patients: a quasi-experimental study. J Steroid Biochem Mol Biol. 2020:204:105771. https://doi.org/10.1016/j.jsbmb.2020.105771.

81. • Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA. 2021;325(11):1053–1060. https://doi.org/10.1001/jama.2020.26848. This RCT on 240 hospitalized patients with moderate to severe COVID-19 failed to show any benefit from vitamin D supplementation, regarding hospital length of stay, in-hospital mortality and need for mechanical ventilation.

82. Pal R, Banerjee M, Bhadada SK, Shetty AJ, Singh B, Vyas A. Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. J Endocrinol Invest. 2021:1–16. https://doi.org/10.1007/s40618-021-01614-4.

83. Stroelein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021:5:CD015043. https://doi.org/10.1002/14651858.CD015043.

84. Chen J, Mei K, Xie L, Yuan P, Ma J, Yu P, Zhu W, Zheng C, Liu X. Low vitamin D levels do not aggravate COVID-19 risk or death, and vitamin D supplementation does not improve outcomes in hospitalized patients with COVID-19: a meta-analysis and GRADE assessment of cohort studies and RCTs. Nutr J. 2021;20(1):89. https://doi.org/10.1186/s12937-021-00744-y.

85. Rubin R. Sorting out whether vitamin D deficiency raises COVID-19 risk. JAMA. 2021;325(4):329–30. https://doi.org/10.1001/jama.2020.24127.

86. •• Li S, Cao Z, Yang H, Zhang Y, Xu F, Wang Y. Metabolic healthy obesity, vitamin D status, and risk of COVID-19. Aging Dis. 2021;12(1):61–71. https://doi.org/10.14336/AD.2020.1108. This study used data from more than 350,000 UK Biobank participants to investigate whether the addition of metabolic disorders and vitamin D insufficiency increased obesity associations with COVID-19 hospitalization, confirmed COVID-19, and severe COVID-19. The multivariate logistic regression analysis showed that obesity combined with metabolic disorders and hypovitaminosis D is associated with a significantly increased risk of COVID-19 severity, especially in adults 65 years and older.

87. Dalamaga M, Muscogiuri G, Paganitsa G, Parvouleskou G, Syriou V, Karagkoynis P, et al. Adherence to the Mediterranean diet and vitamin D status in COVID-19 hospitalization, confirmed COVID-19, and severe COVID-19. The Multivariate logistic regression analysis showed that obesity combined with metabolic disorders and hypovitaminosis D is associated with a significantly increased risk of COVID-19 severity, especially in adults 65 years and older.