

COVID-19 and obesity: the confrontation of two pandemics

P. OBOZA¹, N. OGAREK¹, M. OLSZANECKA-GLINIANOWICZ², P. KOCELAK³

¹Students' Scientific Society at the Pathophysiology Unit, Department of Pathophysiology, Medical Faculty in Katowice, The Medical University of Silesia, Katowice Poland

²Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical Faculty in Katowice, The Medical University of Silesia, Katowice, Poland

³Pathophysiology Unit, Department of Pathophysiology, Medical Faculty in Katowice, The Medical University of Silesia, Katowice, Poland

Abstract. – In 2009, obesity was identified for the first time as a risk factor for increased disease severity and mortality in patients infected with the H1N1 influenza A virus. During the current COVID-19 pandemic, overweight and obesity have been described as independent risk factors of disease severity and mortality due to COVID-19. Excess visceral fat is associated with systemic chronic microinflammation, changes in adipokine release, and oxidative stress. These disturbances result in an impaired immune response, including dysfunction in lymphocyte action and antibody production. Moreover, obesity is a cause of endothelial dysfunction, pro-coagulation state, and enhanced expression of angiotensin-converting enzyme 2 (ACE-2), which contributes to the infection itself and the severity of the disease. We analyzed both the impact of obesity on the severity of COVID-19 and the potential mechanism that influences this severity. Moreover, we discuss the effect of obesity complications on the severity of disease and mortality of patients with COVID-19. Furthermore, we summarize the effectiveness of COVID-19 vaccination in patients with obesity. Finally, we analyzed the effect of the COVID-19 pandemic on mood disturbances and emotional eating and, as a consequence, the development of obesity or an increase in its severity.

In summary, the studies conducted during the COVID-19 pandemic indicate that effective obesity treatment should be initiated at once. In addition, the data confirm the need to organize efficient obesity treatment systems for the sake of not only the individual but also society.

Key Words:

Obesity, SARS-CoV-2, COVID-19.

SARS-CoV-2 the New "King" of the Acute Pandemic

Coronaviruses are enveloped positive-sense single-stranded RNA viruses. Two beta coro-

naviruses have caused large-scale pandemics: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)¹. Currently, a novel SARS-like coronavirus 2 (SARS-CoV-2) is rapidly spreading all over the world. The most common clinical symptoms of infected patients are fever, dry cough, dyspnea, pneumonia, headache, loss of taste and smell, and numerous other symptoms related to a new mutation. The disease received the name coronavirus disease 2019 (COVID-19), and on March 11, 2020, was characterized by the World Health Organization (WHO) as a pandemic^{2,3}.

Obesity a Global Chronic Pandemic and its Effects on Acute COVID-19 Pandemic

Since the last century, the prevalence of obesity has been increasing around the world. The global increase in the number of patients with obesity has already reached the scale of the pandemic. Both obesity and its complications negatively affect the health care system. Globally, in 2016, 1.9 billion adults were diagnosed as overweight and 650 million as obese⁴. Obesity can cause numerous complications, including, among others, type 2 diabetes mellitus (DM), hypertension, cardiovascular disease, obstructive sleep apnea, pulmonary arterial hypertension, secondary chronic hypoxia, and increased risk for cancer development^{5,6}. At first, a higher risk for Invasive Mechanical Ventilation (IMV) and Intensive Care Unit (ICU) admission due to COVID-19 among patients with type 2 DM and hypertension was reported. Later, numerous studies performed in various parts of the world showed that overweight and obesity are direct, significant risk factors for severity and

higher mortality for COVID-19 infection. The first data come from a single-center study performed in Wuhan, in which it was found that obesity significantly increased the risk of severe and critical course of COVID-19⁷. These data were confirmed by a retrospective review from New York City⁸. In addition, an early report from Shenzhen in China revealed that overweight and obesity were associated with increased risk of a more severe course of COVID-19 infection after adjusting for age, sex, epidemiological characteristics, days from disease onset to hospitalization, presence of selected comorbidities, and drug used for treatment⁹. Similarly in Italy, during the first wave of the pandemic, an increased risk of death in patients with obesity and COVID-19 was observed¹⁰. Obesity was also the most important risk factor for mortality among young Chinese patients¹¹. Numerous subsequent studies confirmed the primary observations.

The results of a prospective, community-based, cohort study analyzing 6,910,695 subjects diagnosed with SARS-CoV-2 infection from 1,500 English general practices demonstrated non-linear associations between Body Mass Index (BMI) above 23 kg/m² and increased risk of hospitalization (adjusted HR (hazard ratio) per kg/m² from the nadir at a BMI of 23 kg/m² - 1.05, 95% CI 1.05-1.05) and death (HR - 1.04, 95% CI 1.04-1.05). Moreover, a linear association between BMI and ICU admission was shown (HR - 1.1, 95% CI: 1.09-1.1). However, it should be noted that results showed a J-shaped relationship between BMI, hospital admission, and death due to COVID-19 infection. An increased risk of mortality was found in those with a BMI of 28kg/m² and above regardless of the occurrence of type 2 DM and hypertension. This association decreased with age and loss in subjects aged 80 years and above. Among subjects aged 20-39 years, a BMI of 23 kg/m² and above increased the risk of hospital admission (HR 1.09, 95% CI 1.08-1.10), ICU admission (HR 1.13, 95% CI 1.11-1.16), and death due to SARS-CoV-2 infection (1.17, 95% CI 1.11-1.23). It should be noted that BMI is a weak marker of fat mass excess in the elderly and this age increased the occurrence of sarcopenic obesity associated with lower BMI levels. In addition, BMI is a weak marker of visceral obesity and its metabolic complication in younger people.

It has also been shown that race may modify the impact of obesity on COVID-19 severity. Specifically, Black race, more significantly than White race, amplified BMI-related risk of hospital admission

(HR 1.07 95% CI 1.06-1.08 vs. HR 1.04, 95% CI 1.04-1.05) and COVID-19-related death (HR 1.08, 95% CI 1.06-1.10 vs. HR 1.04, 95% CI 1.03-1.04)¹².

The studies that described the impact of obesity on the course of COVID-19 and mortality due to this infection are summarized in Table I.

The results of single studies were confirmed by a meta-analysis, showing an association between obesity and the risk of ICU admission, IMV, and COVID-19 progression in both children and adults^{13,14}. The results of meta-analyses on the course of COVID-19 in patients with obesity are presented in Table II.

Obesity, Viral Transmission, and Re-Infection

Obesity-related inflammation and the dysfunction of innate and adaptive immune responses are associated with prolonged COVID-19 infection¹⁵. It has been shown that the time of shedding the symptomatic influenza A virus (IAV) is longer by 42% and asymptomatic by 104% in patients with obesity. These results may indicate that obesity has an impact on influenza A virus transmission¹⁶. By analogy, it is hypothesized that obesity may also play a role in the transmission of COVID-19¹⁷. Super-spreaders is the term used to describe people with a greater propensity to infect more than the mean number of people¹⁸. The results of an Italian study suggest that patients with obesity are potentially more contagious than those with normal weight since a positive correlation between BMI and infectious viral load in exhaled breath was found¹⁹. In addition, an observational cohort study showed that the number of exhaled aerosol particles increased with an increased BMI and is multiplied by age (BMI-years), which confirmed the 20/80 rule observed for other infectious diseases²⁰. This contributes to a disproportionate increase in the number of COVID-19 cases²¹. Thus, extending the quarantine and isolation period of patients with obesity with COVID-19 should be considered.

Importantly, obesity affects the variety of influenza A viruses through the enhancement of mutations. A reduced interferon response supports increased viral replication and permits the emergence of virulent IAV strains²². Similarly, there may be an increased risk of SARS-CoV-2 mutation in patients with obesity by prolonging viral shedding and blunting the immune response.

It has also been shown that obesity may be a risk factor for COVID-19 re-infection²³. Moreover, obesity is associated with a lack of return-

Table I. Results of studies on the course of COVID-19 in patients with obesity.

Author	Characteristics of population	Type of study	Results
Zhang et al ⁷ , 2021	463 patients (38.7% with overweight, 9.1% with obesity) hospitalized from January 2 to February 20, 2020; China	Single-center, retrospective	Obesity increased the risk of severe and critical course of COVID-19 by 359% (OR 3.586, 95% CI 1.550-8.298, $p = 0.003$)
Filardo et al ⁸ , 2020	337 patients (41.8% with obesity) hospitalized from March 9 to April 8, 2020; USA	Retrospective chart review	Obesity increased risk of mortality due to COVID-19 by 37% (RR 1.37, 95% CI 1.07-1.74)
Cai et al ⁹ , 2020	383 adult patients (32.0% with overweight, 10.7% with obesity), admitted to the hospital from January 11 to 16 February 2020; China	Case series	Overweight increased risk of severe course of COVID-19 by 84% (OR 1.84, 95% CI 0.99-3.43, $p = 0.05$) and obesity by 340% (OR 3.40, 95% CI 1.40-2.86, $p = 0.007$)
Giacomelli et al ¹⁰ , 2020	233 patients (16.3% with obesity), hospitalized from February 21 to March 19, 2020; Italy	Prospective cohort	Obesity increased the risk of death by 304% (HR 3.04, 95% CI 1.42-6.49)
Zhang et al ¹¹ , 2020	53 patients (mean BMI 24.38 ± 4.00 kg/m ²), hospitalized from February 7 to March 27, 2020; China	Retrospective	Obesity increased risk of mortality by 135% (OR 1.354, 95% CI 1.075-1.704, $p = 0.010$)
Huang et al ⁹¹ , 2020	202 patients (14% with BMI ≥ 28 kg/m ²) hospitalized from January 22 to February 10, 2020; China	Multi-centre, retrospective	BMI ≥ 28 kg/m ² increased risk of severe course of COVID-19 by 587% (OR 5.872, 95% CI 1.595-21.621, $p = 0.008$)
Steinberg et al ⁹² , 2020	210 patients (47.6% with obesity), reported to one of two emergency departments from March 8 to April 4, 2020; USA	Two - center, retrospective cohort	Obesity increased risk of mortality by 629% (OR 6.29, 95% CI 1.76-22.46, $p = 0.0046$), risk of IMV by 601% (OR 6.01, 95% CI 2.5-14.48, $p = 0.0001$) and risk of admission to hospital by 261% (OR 2.61, 95% CI, 1.49-4.58, $p = 0.0008$)
Kompaniyets et al ⁵¹ , 2021	148,494 patients (28.3% with overweight, 50.8% with obesity), March to December 2020; USA	Report	Obesity increased risk of ICU admission by 6-16% (BMI 40-44.9 kg/m ² : RR 1.06, 95% CI 1.03-1.10; BMI ≥ 45 kg/m ² : RR 1.16, 95% CI 1.11-1.20), risk of IMV by 208% (BMI ≥ 45 kg/m ² : RR 2.08, 95% CI 1.89-2.29) and risk of death by 8-61% (BMI 30-34.9 kg/m ² : 1.08, 95% CI 1.02-1.14; BMI ≥ 45 kg/m ² : RR 1.61, 95% CI 1.47-1.76)
Al-Sabah et al ⁹³ , 2020	1,158 patients (41.8% with overweight; 13.5% with I degree of obesity; 5.5% with II degree of obesity; 2.6% with morbid obesity) admitted to the hospital from February 24 to April 7, 2020; Kuwait	Retrospective cohort	Overweight increased risk of admission to ICU by 245% (OR 2.45, 95% CI 1.26-4.74; $p = 0.008$), I degree of obesity by 351% (OR 3.51, 95% CI 1.60-7.69), and morbid obesity by 518% (OR 5.18, 95% CI 1.50-17.85)
Hajifathalian et al ⁹⁴ , 2020	770 patients (36% with obesity), recorded between March 4 and April 9, 2020; USA	Retrospective review	Obesity increased risk of ICU admission by 176% (RR 1.76, 95% CI 1.24-2.48, $p = 0.001$), risk of intubation by 172% (R 1.72, 95% CI 1.22-2.44, $p = 0.002$) and risk of death by 115% (RR 1.15, 95% CI 0.62-2.14, $p = 0.663$)
Simonnet et al ⁵⁵ , 2020	124 patients (47.6% with obesity, 28.2% with severe obesity) admitted to ICU between February 27 and April 5, 2020; France	Retrospective cohort	BMI >35 kg/m ² increased risk of IMV by 736% (OR 7.36, 95% CI 1.63-33.14, $p = 0.021$)
Palaodimos et al ⁹⁵ , 2020	200 patients (23% with severe obesity), admission of 1st patient March 9, 2020; 200 th patient: March 22, 2020; completion of 3-week follow-up: April 12, 2020; USA	Retrospective cohort	Obesity increased risk of oxygen requirement by 309% (OR 3.09, 95% CI 1.43-6.69, $p = 0.004$), risk of intubation by 387% (OR 3.87, 95% CI, 1.47-10.18 $p = 0.006$), and risk of in-hospital mortality by 378% (OR 3.78, 95% CI 1.45-9.83, $p = 0.006$)
Hameret al ⁹⁶ , 2020	334,329 participants (66.6% were overweight or obese) with prospective linkage to national registry on hospitalization for COVID-19 from 16 March 2020 to 26 April 2020; ~0.2% hospitalized for COVID-19, UK	Community-based cohort	Overweight increased risk of hospitalization by 139% (OR 1.39, 95% CI 1.13-1.71), BMI 30-34.9 kg/m ² by 170% (OR 1.70; 95% CI 1.34-2.16), and BMI ≥ 35 kg/m ² by 338% (OR 3.38, 95% CI 2.60-4.40)

BMI - body mass index, IMV - Intensive mechanical ventilation, OR - odds ratio, UK - the United Kingdom, ICU - Intensive Care Unit, HR - hazard ratio, RR - relative risk, CI - confidence interval.

Table II. Results of meta-analyses on the course of COVID-19 in patients with obesity.

Author	Characteristics of population	Results
Chu et al ¹³ , 2020	22 studies; 12,591 patients	Obesity increased risk of ICU admission by 157% (OR 1.57, 95% CI 1.18-2.09, $p = 0.002$, $I^2 = 0\%$, $p = 0.60$), risk of IMV by 213% (OR 2.13, 95% CI 1.10-4.14, $p = 0.03$, $I^2 = 54\%$, $p = 0.14$), and risk of disease progression by 417% (OR 4.17, 95% CI 2.32-7.48, $p < 0.00001$, $I^2 = 0\%$)
Tsankov et al ¹⁴ , 2021	42 studies; 285,004 pediatric patients, 3.3% with at least one comorbidity	Obesity (children without complications) increased risk of severe COVID-19 by 287% (RR 2.87, 95% CI 1.16 - 7.07, $\chi^2 = 7.81$, $p = 0.17$; $I^2 = 36\%$)
Yang et al ⁹⁷ , 2020	50 studies; 18,260,378 patients	Obesity increased risk of SARS-CoV-2 infection by 139% (OR 1.39, 95% CI 1.25-1.54, $p < 0.00001$), risk of hospitalization by 245% (OR 2.45, 95% CI 1.78-3.39, $p < 0.00001$), risk of severe cases by 374% (OR 3.74, 95% CI 1.18-11.87, $p = 0.02$), risk of ICU admission by 130% (OR 1.30, 95% CI 1.21-1.40, $p < 0.00001$), risk of IMV by 159% (OR 1.59, 95% CI 1.35-1.88, $p < 0.00001$), and risk of mortality by 165% (OR 1.65, 95% CI 1.21-2.25, $p = 0.001$)
Yang et al ⁹⁸ , 2020	41 studies; 219,543 subjects and 115,635 COVID-19 patients	Obesity increased risk of hospitalization by 154% (OR 1.54, 95% CI 1.33-1.78, $I^2 = 60.9\%$), risk of ICU admission by 148% (OR 1.48, 95% CI 1.24-1.77, $I^2 = 67.5\%$), risk of IMV by 147% (OR 1.47, 95% CI 1.31-1.65, $I^2 = 18.8\%$), and risk of in-hospital mortality by 114% (OR 1.14, 95% CI 1.04-1.26, $I^2 = 74.4\%$)
Zhao et al ⁹⁹ , 2020	11 studies for COVID-19; 9,787 patients	Morbid obesity increased risk of hospitalization by 308% (OR 3.08, 95% CI 1.43-6.62, $I^2 = 92\%$, $n=6$), obesity increased risk of severe outcomes of COVID-19 by 207% (OR 2.07, 95% CI 1.53-2.81, $I^2 = 70.9\%$, $n=9$), and morbid obesity increased risk of severe outcomes and death of COVID-19 by 376% (OR 3.76, 95% CI 2.67-5.28, $I^2 = 0\%$, $n = 3$)
Földi et al ¹⁰⁰ , 2020	6 studies; 2,770 patients; ICU admission 5 studies; 509 patients; IMV requirement	Obesity increased risk of ICU admission by 121% (OR 1.21, 95% CI 1.002-1.46, $I^2 = 0.0\%$), risk of IMV by 205% (OR 2.05, 95% CI 1.16-3.64, $I^2 = 34.86\%$)

BMI - body mass index, IMV - Intensive mechanical ventilation, OR - odds ratio, UK - the United Kingdom, ICU - Intensive Care Unit, HR - hazard ratio, RR - relative risk, CI - confidence interval.

ing to usual health 14-21 days after a SARS-CoV-2 positive test (OR 2.31, 95% CI 1.21-4.42)²⁴. In addition, it has been shown that pulmonary fibrosis, a severe COVID-19 complication, may be more frequent in patients with obesity than in normal-weight individuals²⁵.

Multiple Mechanisms of the Impact of Obesity on the Course of COVID-19 Infection

Immune Response, and Oxidative Stress

Obesity is a cause of chronic systemic microinflammation that influences immune responses to infectious diseases through direct, indirect, and

epigenetic mechanisms²⁶. Adipose tissue is an endocrine organ that produces adipokines with anti- or pro-inflammatory properties. Pro-inflammatory adipokines include leptin, tumor necrosis factor-alpha (TNF- α), interleukin 6 (IL-6), resistin, retinol-binding protein 4 (RBP-4), lipocalin 2, interleukin 18 (IL-18), and angiopoietin-like protein 2²⁷. Their production increases with an increasing volume of adipocytes in visceral fat. Higher IL-6 levels have been correlated with a decreased number of natural killer (NK) cells with granzyme expression that decreased cytotoxic potential²⁸. Furthermore, during antigen presentation, obesity-related chronic microinflammation decreased macrophage activation and their pro-inflammatory cytokines production

upon stimulation¹⁹. Moreover, impaired functions of effector T cells, helper T cells, and a reduction in memory T cell responses were observed. Moreover, an experimental study showed changes in metabolic programming of memory T cells after weight loss¹⁵. In addition, it has been suggested that impaired B and T cell responses related to obesity increased susceptibility and reduced influenza virus clearance¹⁹.

Obesity is also the cause of oxidative stress development related to hyperleptinemia, low antioxidant defense, chronic inflammation, and postprandial reactive oxygen species generation. Oxidative stress impairs adaptive immunity and enhances infection severity and tissue damage²⁹. Oxidative stress may modify the structure and function of CD4⁺ lymphocytes, resulting in impaired interaction between CD4⁺ and B cells, a lower antibody titer, and depleted CD4⁺ lymphocytes^{30,31}. It has also been shown that oxidative stress, enhanced by SARS-CoV-2 infection, directly increased NF-kappaB expression and initiated cell apoptosis³². Increased reactive oxygen species generation may hamper the immune system function and result in worse viral infection outcomes in patients with obesity³³.

In a paper by Mazzone et al³⁴, it was shown that patients with COVID-19, especially those requiring intensive care, had not only decreased numbers of circulating T CD4⁺, T CD8⁺, and NK cells but also displayed reduced antiviral cytokine production. In addition, patients requiring intensive care had a higher level of IL-6 and less frequency of granzyme A-expressing NK cells.

Obesity and Endothelial Dysfunction

Obesity-related inflammation and insulin resistance are causes of endothelial dysfunction resulting in an imbalance between pro-inflammatory/procoagulant and anti-inflammatory/anticoagulant factors. These alterations predispose to the formation of atherosclerotic plaque and platelet activation²⁵. In addition, obesity is associated with impaired fibrinolysis due to increased expression and production of plasminogen activator inhibitor-1 (PAI-1)³⁵. It has also been suggested that higher levels of D-dimer and fibrin degradation products are commonly associated with COVID-19 pneumonia-related death³⁶. In addition, higher D-dimer levels were found in patients with obesity than in normal-weight patients hospitalized due to COVID-19^{37, 38}. This may indicate an increased risk of death from COVID-19 pneumonia in

patients with impaired coagulation associated with obesity-related endothelial dysfunction and hemostatic disturbances. Zhang et al¹¹ showed that increased coagulation activity, aggravated inflammatory responses, and cardiac injury are mechanisms that contribute to higher mortality due to COVID-19. Moreover, hypoxia, inflammation, and oxidative stress in perivascular adipose tissue (PVAT) are mediators of obesity-related endothelial dysfunction and result in the impaired release of vasoactive factors. Changes in PVAT analyzed by computed tomography can be used to quantify COVID-19-induced vascular inflammation and could be a valuable prognostic tool for in-hospital outcomes³⁹.

In addition, in obesity, increased endothelial expression of angiotensin-converting enzyme 2 (ACE-2), transmembrane protease serine 2, and furin was observed. Collectively, these may cause higher vulnerability to SARS-CoV-2 infection and intensify endothelial damage^{25,40}. In lung autopsies obtained from patients who died from COVID-19, severe endothelial injury associated with the presence of intracellular virus and disruption of cell membranes was shown. Importantly, a nine times higher incidence of alveolar-capillary microthrombi than in the lungs of those who died from acute respiratory distress syndrome (ARDS) secondary to influenza A (H1N1) was found in these patients⁴¹. It seems that these mechanisms mediate increased mortality in patients with obesity.

ACE-2 Receptor Expression

The relationship between high ACE-2 receptor expression and COVID-19 morbidity and severity was observed. SARS-CoV-2 presumably uses ACE-2 receptors to infect human cells. The ACE-2 receptor is a functional receptor expressed in 6,738 normal tissues. A high number of these receptors are localized in the small intestine, kidney, heart, thyroid, adipose tissues, salivary glands, and lungs⁴². Although the expression of ACE-2 receptors is higher in adipose tissue than lung tissue, the latter is the main target for SARS-CoV-2⁴³. However, adipose tissue may be an important reservoir of SARS-CoV-2 and may allow the virus to spread to other organs and prolong viral clearance⁶.

The molecular mechanism of virus invasion *via* ACE-2 receptors suggests that SARS-CoV-2 enhances the classical pathway of the renin-angiotensin system (RAS). RAS activation and subsequent hyperactivity cause an intensification

of vasoconstriction, oxidative stress, and pro-inflammatory action which results in an exacerbation of infection symptoms⁴⁴.

The Mammalian Target of Rapamycin (mTOR)

In obesity, hyperactivation of the mTOR pathway in multiple tissues was observed. Hyperactivated mTOR regulates cap-dependent mRNA translation. The hypothesis that coronaviruses are RNA viruses that hijack the host cap-dependent translation machinery to replicate, explains the increased virus replication and enhancement of cap-dependent translation⁴⁵.

The Impact of SARS-CoV2 on the Respiratory System of Patients with Obesity

A reduced functional residual capacity, expiratory residual volume, and less commonly, total lung capacity was shown in patients with obesity⁴⁶. In patients with visceral obesity in a supine position, lung function was additionally impaired by a reduced diaphragm excursion⁴⁷. Disturbed respiratory mechanics and gas exchange in patients with obesity, especially in the supine position, cause expiratory flow limitation. This results in gravitational atelectasis and severe hypoxemia⁴⁸. It has been found that in non-intubated patients with obesity and COVID-19-related pneumonia, the prone position ameliorates blood oxygenation. However, this effect was not sustained after resupination⁴⁹. Improvements in oxygenation by increasing the aerated areas of the lungs in the prone position have also been observed in mechanically ventilated patients⁵⁰. Moreover, obesity may impair motile cilia in airway epithelial cells⁵¹. Furthermore, obesity and its complications increased the risk of developing type 2 inflammation which affects the bronchi and parenchyma of the lungs⁵². In addition, obesity is associated with surfactant dysfunction resulting in the development of severe ARDS during COVID-19⁵³.

NIV (non-invasive ventilation) in patients with obesity is recommended for both the prevention and treatment of acute respiratory failure. It should be noted that due to the high risk of lung collapse, mechanically ventilated patients with obesity require higher positive end-expiratory pressure⁵⁴. In addition, the increased necessity of IMV during hospitalization of patients with obesity and COVID-19 has been shown in several studies. In a single-center, retrospective study,

the need for IMV was significantly associated with 2nd and 3rd-grade obesity, independent of other diseases⁵⁵. In an Italian study involving over 100 patients, pneumonia due to SARS-CoV-2 infection developed in 65.2% of patients who were overweight or obese. Moreover, overweight or patients with obesity were 10 years younger than normal-weight patients. They also more frequently required intensive ventilation support, breathing support in addition to regular oxygen therapy (IMV and NIV), and were more often admitted to ICU and semi-intensive respiratory units⁵³. In addition, the results of a large US study showed that the need for using IMV increased with BMI⁵⁶. Moreover, in a retrospective cohort study, overweight or obesity, especially in patients under 65 years, were associated with a higher risk of requiring IMV⁵⁷. A higher risk of death in younger patients with COVID-19 who were overweight was also confirmed by another study involving nearly 7,000 patients⁵⁸. In another study, Kompaniyets et al⁵¹ showed that overweight or obesity are risk factors for the need for IMV in patients aged 65 years and over.

The difficulty in treating patients with obesity is an estimation of the optimal drug dose. Obesity significantly impacts organs related to the pharmacokinetics and pharmacodynamics of drugs⁵⁹. Inadequate dosing contributes to therapy failure or drug toxicity. Individualized dosing should be based on the patient's lean body mass. Moreover, monitoring the concentrations of the therapeutic level of drugs and clinical responses is also recommended⁶⁰.

Obesity Complications and COVID-19 Outcomes

As described above, obesity is an independent risk factor of worse prognosis in the course of COVID-19. Moreover, obesity complications including hypertension, type 2 DM, and respiratory and cardiovascular disease additionally increase the severity and mortality due to COVID-19⁶¹. The highest risk was for patients with a combination of type 2 DM and hypertension, followed by type 2 DM alone and coexisting obesity, type 2 DM, and hypertension simultaneously. Moreover, for the combination of type 2 DM and obesity, the risk of hospitalization was lower, as well for obesity, only. The risk of death was highest in the group of patients with obesity, type 2 DM, and hypertension. Patients with only one comorbidity had a lower risk of death in comparison to patients with more than one of these diseases⁶². The results of another

er study showed an increased risk of COVID-19 lethality was associated with obesity, type 2 DM, early-onset DM (<40 years), and an increase in the number of comorbidities. Particularly in cases of early-onset type 2 DM, a higher mortality risk was found. In addition, obesity mediates 49.5% of the effect of type 2 DM on COVID-19 lethality⁶³. A significant association between an increased risk of composite outcomes in patients with obesity and type 2 DM was also found⁶⁴. The intubation rate was statistically higher for patients with than without type 2 DM (difference 24.85%; $p < 0.01$; 95% CI 7.4-34.8), and in patients with HbA1C $\geq 7.5\%$ (31.5% vs. 17.8%; $p < 0.05$)⁶⁵. The prevalence of hypertension was higher in severe cases of COVID-19 (47.65%; 95% CI 35.04-60.26) compared to total cases (14.34%; 95% CI 6.60-28.42); moreover, in fatal cases, hypertension (47.90%; 95% CI 40.33-55.48 vs. 14.34%; 95% CI 6.60-28.42), type 2 DM (24.89%; 95% CI 18.80-32.16 vs. 9.65%; 95% CI 6.83-13.48), and respiratory disease (10.89%; 95% CI 7.57-15.43 vs. 3.65%; 95% CI 2.16-6.1) were common⁶⁶. A meta-analysis that included 3,994 patients showed that obesity complications such as hypertension, type 2 DM, cardiovascular disease, and chronic kidney disease increased the risk of a serious event (ICU admission, ARDS, mechanical ventilation, pneumonia) during SARS-CoV-2 infection⁶⁷. In addition, obstructive sleep apnea (OSA) was associated with more frequent hospitalization for respiratory failure in the course of COVID-19 infection⁶⁸.

All described data showed that both obesity and its complications are risk factors for a worse COVID-19 infection prognosis and outcome.

Studies on the impact of obesity complications on the course and mortality due to COVID-19 are summarized in Table III.

Patients with Obesity and the Effectiveness of COVID-19 Vaccination

Increased risk of COVID-19 infection and mortality in patients with obesity should focus specifically on the effectiveness of vaccination in this group. As was mentioned above, obesity-related chronic microinflammation decreased macrophage activation and impairment of memory T cell responses which may worsen vaccination outcomes¹⁹. It should be noted that a previously published study analyzing the effectiveness of the influenza vaccination showed that vaccinated patients with obesity have a two-fold relative risk of developing influenza or an influenza-like illness than normal-weight subjects (RR 2.01, 95% CI

1.12-3.60, $p=0.020$), despite the lack of significant differences in seroconversion or seroprotection. This may indicate a risk of misleading using antibody titers in determining the effectiveness of vaccines⁶⁹.

In a study analyzing the effectiveness and safety of the BNT162b2 mRNA COVID-19 vaccine in a population of patients aged between 16-64 years and over 65 years without and with obesity, the effectiveness of the vaccine was 95.2% and 94.9%, 91.8% and 100%, respectively⁷⁰. Other studies have also shown similar effectiveness in obese and non-obese subjects. In a Pfizer-BioNTech trial, vaccine efficacy from 7 days after a second dose was 95.4% in people with obesity (95% CI 86.0-99.1) and 94.8% in people without obesity (95% CI 87.4-98.3). In a Moderna trial, vaccine efficacy from 14 days after the second dose was 94.1% overall (95% CI 89.3-96.8), and 91.2% in the subgroup with severe obesity (95% CI 32.0-98.9)⁷¹. However, research from the Istituto Fisioterapici Ospitalieri (IFO) indicated that obesity may reduce the immune response to a vaccine. This study analyzed the antibody titer 7 days after the second dose of the BNT162b2 mRNA vaccine in 248 healthcare workers (158 women, median age: 47 years). The effectiveness was compared with age, BMI, and sex. Neutralizing antibodies were present in 93% of vaccinated individuals, and S1/S2 subunits-binding antibody titers were between 3.8-2460 AU/mL and antibody geometric mean concentrations exceeded those observed in convalescent plasma (286 vs. 39 AU/mL, respectively). Women and younger subjects had a higher antibody titer; however, BMI exerted a strong effect on the ability to induce a humoral response⁷². These preliminary results may incite the development of more efficient strategies for vaccinated patients with obesity, for instance, they might need an additional or higher dose of the vaccine. Another study assessing the effectiveness of the Moderna mRNA COVID-19 vaccine did not assess the effectiveness in BMI categories⁷³. No published studies have assessed the impact of BMI on the effectiveness of the adenovirus vector vaccines⁷⁴.

COVID-19 Pandemic Time Anxiety, Mood Disturbances, Emotional Eating (EE) and Risk of the Development of Obesity or Increase its Severity

The introduction of lockdowns during the COVID-19 pandemic has had a positive impact on the epidemiological situation; however, it has

Table III. Results of studies on the course of COVID-19 in patients with complications of obesity.

Author	Characteristics of population	Type of the study	Results
Carrillo-Vega et al ⁶² , 2020	10.544 patients with positive SARS-CoV-2 (57.68% men) 21.74% with hypertension, 20.05% with obesity and 17.65% with type 2 DM	Retrospective data released by the Epidemiological Surveillance System for Vira Respiratory Diseases of the Mexican Ministry of Health	Hypertension increased the risk of hospitalization by 154% (OR 1.54, 95% CI 1.26-1.88), type 2 DM by 214% (OR 2.14, 95% CI 1.70-2.69); obesity, the coexistence of type 2 DM and hypertension by 260% (OR 2.60, 95% CI 2.04-3.31); type 2 DM and hypertension simultaneously by 185% (OR 1.85, 95% CI 1.34-2.56) hypertension increased the risk of death by 49% (OR 1.49, 95% CI 1.15-1.92), COPD by 68% (OR 1.68, 95% CI 1.22-2.31), the coexistence of type 2 DM and hypertension by 92% (OR 1.92, 95% CI 1.48-2.49), the coexistence of obesity and type 2 DM by 206% (OR 2.06, 95% CI 1.35-3.12), the coexistence of obesity, hypertension and type 2 DM by 210% (OR 2.1, 95% CI 1.50-2.93)
Bello-Chavolla et al ⁶³ , 2020	177.133 patients, 51.633 with a positive test for SARS-CoV-2 (57.7% male, mean age 46.65 ± 15.83, 20.7% with obesity)	Retrospective data from the General Directorate of Epidemiology of the Mexican Ministry of Health	Higher mortality risk at early-onset DM (HR 2.754; 95% CI, 2.259-3.359)
Tchang et al ⁶⁴ , 2021	3533 patients; 59% male, median age 65 (IQR 53-75) years admitted to New York-Presbyterian (NYP) Weill Cornell Medical Center, NYP-Queens Hospital, or NYP Lower Manhattan Hospital in New York City between 1 March to 13 May 2020 with positive SARS-CoV-2 test, 32% with type 2 DM, 36%, with obesity: 12% with obesity and type 2 DM\	Retrospective cohort study	The composite outcome increased in subjects with moderate and severe obesity (HR 1.43 95% CI 1.13-1.80, $p = 0.003$ and HR 1.49 95% CI 1.12-2.00, $p = 0.007$, respectively), with type 2 DM (HR 1.14 95% CI 1.01, 1.30), $p = 0.037$); and mortality (HR 1.19 95% CI 1.02- 1.38, $p = 0.024$) Obesity increased risk for ICU admission/intubation (HR 1.41 95% CI 1.16-1.71, $p = 0.001$). Obesity and type 2 DM increased the risk of the composite outcome compared to normal-weight subjects (HR 1.34 95% CI 1.04-1.74), $p=0.025$), especially moderate and severe obesity (HR 1.57 95% CI 1.08-2.28, $p= 0.019$ and HR 2.00 95% CI 1.26-3.18, $p= 0.003$, respectively)
Nandy et al ⁶⁷ , 2020	16 studies included 3994 patients reported outcome of COVID-19	Systematic review and meta-analysis	Increased risk of a serious event (ICU admission, ARDS, mechanical ventilation, pneumonia) was observed in patients with: hypertension (OR 2.95, 95% CI 2.21-3.94, $p < 0.001$), type 2 DM (OR 3.07, 95% CI 2.02-4.66, $p < 0.001$), cardiovascular disease (OR 4.58, 95% CI 2.81-7.47, $p < 0.001$), COPD (OR 6.66, 95% CI 3.09-14.34, $p < 0.001$), CKD (OR 5.32, 95% CI 1.86-15.19, $p = 0.002$) increased risk of mortality in type 2 DM (OR 2.28 95% CI 1.40-5.55; $p = 0.004$)

Continued

Table III (Continued). Results of studies on the course of COVID-19 in patients with complications of obesity.

Author	Characteristics of population	Type of the study	Results
Maas et al ⁶⁸ , 2020	9405 patients with COVID-19, 45.9% male, 34% hospitalized and 9% diagnosed with respiratory failure	Retrospective data from 10 hospitals in the Chicago metropolitan area, from 1 January to 25 June 2020	Patients with more often required hospitalization OSA (OR 1.65 95% CI 1.36-2.02), and had increased risk of respiratory failure (OR 1.98; 95% CI 1.65-2.37)
Huang et al ¹⁰¹ , 2020	30 studies; 6452 patients with COVID-19 and with information on DM	Meta-analysis	Type DM 2 increased risk of composite poor outcome (RR 2.38 95% CI 1.88-3.03, $p < 0.001$; I ² : 62%), mortality (RR 2.12 [1.44, 3.11], $p < 0.001$; I ² : 72%), severe COVID-19 course (RR 2.45 95% CI 1.79-3.35, $p < 0.001$; I ² : 45%), ARDS (RR 4.64 95%CI 1.86-11.58], $p = 0.001$; I ² : 9%) and disease progression (RR 3.31 95% CI 1.08-10.14], $p = 0.04$; I ² : 0%)
Zheng et al ¹⁰² , 2020	13 studies; 3027 patients with COVID-19	Meta-analysis	Increased risk of severe COVID-19 courses and mortality in patients with: type 2 DM (OR 3.68 95% CI 2.68-5.03), hypertension (OR 2.72 95% CI 1.60-4.64), cardiovascular disease (OR 5.19, 95% CI 3.25-8.29), respiratory disease (OR 5.15 95% CI 2.51-10.57)
Aveyard et al ¹⁰³ , 2021	8 256 161 included 193,520 with COPD, 14 271 were admitted to hospital with COVID-19; records from 1205 general practices in England, January 24 and April 30, 2020	Population cohort study	COPD increased the risk of hospitalization (HR 1.54; 95% CI 1.45-1.63 and was associated with a 54% higher risk of death due to COVID-19 infection (HR 1.54; 95% CI 1.42-1.67)
Alqahtani et al ¹⁰⁴ , 2020	15 studies; 2473 with COVID-19 patients, 2.3% with COPD	Meta-analysis	COPD increased risk of more severe course of disease (RR 1.88 95% CI 1.4-2.4) and mortality (RR 1.10 95% CI 0.6-1.8)

BMI - body mass index, IMV - Intensive mechanical ventilation, OR - odds ratio, UK - the United Kingdom, ICU - Intensive Care Unit, COPD - Chronic Obstructive Pulmonary Disease, ARDS - Acute Respiratory Distress Syndrome, OSA - Obstructive Sleep Apnea, HR - hazard ratio, RR - relative risk, CI - confidence interval.

had substantial negative consequences on the development of obesity and its complications as well as deterioration of mental health and social functioning⁷⁵. Quarantine may contribute to weight gain, deterioration of overall health, and as a consequence worsen COVID-19 outcomes⁷⁶. The increased frequency of anxiety and psychological distress was observed in the early stages of the pandemic related to becoming infected, the health of relatives, and the social consequences. Depressive symptoms were more frequently observed in women⁷⁷ who also more often demonstrated post-traumatic stress disorder symptoms⁷⁸. In addition, a study performed in the USA showed that the later phases of the pandemic were also associated with an increased

risk of mental health problems. Symptoms of anxiety or depressive disorder and reporting of an unmet mental health care need from August 2020 to February 2021 increased from 36.4% to 41.5% and from 9.2% to 11.7%, respectively. This was observed more often among people aged 18-29 years and those with a lower level of education, while the percentage of people reporting taking prescription medication or receiving counseling for their mental health increased especially among people aged 30-39 years (from 23.1% to 27.1%)⁷⁹.

Pandemic-related stress activates the hypothalamic-adrenal-pituitary axis (HPA), which in turn, increases cortisol levels and decreases dopamine levels in the brain's reward system

resulting in depressed mood and increased food consumption, especially with high sugar, fat, and sodium [EE to relieve negative feelings] content. Moreover, the negative impact of stress on brain areas responsible for self-regulation disturbs behavioral control and disrupts sleep⁸⁰. In addition, reducing energy expenditure as a result of mobility restrictions staying at home is a risk factor for a positive energy balance. In the Italian population, the predictors of EE during lockdown were a higher level of anxiety, depression, the quality of personal relationships, and the quality of life (expressed as a measure that combines the quantity and the quality of the personal space at home and the family income)⁸¹. In addition, in a population of 24,968 Norwegians, EE during the COVID-19 pandemic was found in 54%, more often in women (OR 1.9; 95% CI 1.8-2.0), and in younger people (OR 1.3; 95% CI 1.1-1.4). EE was strongly related to psychological distress (OR 4.2, 95% CI 3.9-4.4). Interestingly, EE was strongly associated with worries related to the personal economic situation (OR 1.7, 95% CI 1.5-1.9) than with health (OR 1.3, 95% CI 1.2-1.5)⁸². The increased prevalence of EE among young women during the COVID-19 pandemic was also confirmed by another study. It should be noted that women with obesity are more frequently emotional eaters than women with normal weight⁸³. In addition, a retrospective study showed a higher tendency of EE among pregnant women living in severely affected Chinese areas of COVID-19 and with lower physical activity levels⁸⁴.

Unfavorable trends in lifestyle behaviors have also been demonstrated in Italian children with obesity. During the lockdown, increased intake of potato chips, red meat, and sugary drinks was reported, while the time spent undertaking sports activities decreased and sleep time increased⁸⁵. The development of mental health disturbances may be a cause of increased alcohol consumption which further contributes to weight gain⁸⁶.

It should also be noted that in people with eating disorders during the early stages of the pandemic, a significant exacerbation of illness symptoms such as increased restricting (64.5%), binge eating (35.5%), and purging behaviors (18.9%) was observed. There is a need to acknowledge and monitor the potential long-term effects of the COVID-19 pandemic on eating and exercise behaviors in the general population, however, it is crucial to provide greater psychological support to individuals with EE and eating disorders⁸⁷. To help patients, new management strategies and on-

line therapy could be introduced, which can lead to more personalized treatment with greater flexibility⁸⁸. Pharmacotherapy in mental disorders and the supportive pharmacotherapy of obesity should also be adequately initiated^{89,90}.

Conclusions

Obesity, as a disease with complex pathogenesis and multiple causes resulting in numerous complications, presents a challenge to the health care system, especially during and after the COVID-19 pandemic. The effects of the COVID-19 pandemic and the obesity epidemic are two-way. Obesity, via numerous mechanisms, worsens the course and prognosis of the SARS-CoV-2 infection. Conversely, the time of the pandemic and limitations related to lockdown has increased the EE frequency related to anxiety and depression mood which promotes the development of obesity. Studies conducted during the COVID-19 pandemic have indicated that effective obesity treatment should be swiftly initiated. Six Polish Medical Associations have developed guidelines for methods that should be used in the treatment of obesity during the COVID-19 pandemic⁹⁰. In addition, the data confirm the need to organize efficient obesity treatment systems for the sake of not only the individual but also society.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.
- 2) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. Addendum: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 588: E6
- 3) Available at: <https://www.who.int/director-general/speeches/detail/who-director-general-s-open>

- ing-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
- 4) Available at: https://www.who.int/health-topics/obesity#tab=tab_1
 - 5) de Siqueira JVV, Almeida LG, Zica BO, Brum IB, Barceló A, de Siqueira Galil AG. Impact of obesity on hospitalizations and mortality, due to COVID-19: A systematic review. *Obes Res Clin Pract* 2020; 14: 398-403.
 - 6) Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and Outcomes in COVID-19: When an Epidemic and Pandemic Collide. *Mayo Clin Proc* 2020; 95: 1445-1453.
 - 7) Zhang J, Xu Y, Shen B, He H, Liu M, Zhao M, Liu J, Xu S, Pan W, Ye J, Wang Z, Ye D, Liu M, Li D, Luo Z, Feng Y, Wang M, Wan J. The Association between Obesity and Severity in Patients with Coronavirus Disease 2019: a Retrospective, Single-center Study, Wuhan. *Int J Med Sci* 202; 18: 1768-1777.
 - 8) Filardo TD, Khan MR, Krawczyk N, Galitzer H, Karmen-Tuohy S, Coffee M, Schaye VE, Eckhardt BJ, Cohen GM. Comorbidity and clinical factors associated with COVID-19 critical illness and mortality at a large public hospital in New York City in the early phase of the pandemic (March-April 2020). *PLoS One* 2020; 15: e0242760.
 - 9) Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L, Chen J, Xu L. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. *Diabetes Care* 2020; 43: 1392-1398.
 - 10) Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, Bonazzetti C, Covizzi A, Schiuma M, Passerini M, Piscaglia M, Coen M, Gubertini G, Rizzardini G, Cogliati C, Brambilla AM, Colombo R, Castelli A, Rech R, Riva A, Torre A, Meroni L, Rusconi S, Antinori S, Galli M. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study. *Pharmacol Res* 2020; 158: 104931.
 - 11) Zhang F, Xiong Y, Wei Y, Hu Y, Wang F, Li G, Liu K, Du R, Wang CY, Zhu W. Obesity predisposes to the risk of higher mortality in young COVID-19 patients. *J Med Virol* 2020; 92: 2536-2542.
 - 12) Gao M, Piernas C, Astbury N, Hippisley-Cox J, O'Rahilly S, Aveyard P, Jebb S. 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; 9: 350-359.
 - 13) 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.
 - 14) Tsankov BK, Allaire JM, Irvine MA, Lopez AA, Sauvé LJ, Vallance BA, Jacobson K. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. *Int J Infect Dis* 2021; 103: 246-256.
 - 15) Honce R, Schultz-Cherry S. Impact of Obesity on Influenza A Virus Pathogenesis, Immune Response, and Evolution. *Front Immunol* 2019; 10: 1071.
 - 16) Milner JJ, Rebeles J, Dhungana S, Stewart DA, Sumner SC, Meyers MH, Mancuso P, Beck MA. Obesity Increases Mortality and Modulates the Lung Metabolome during Pandemic H1N1 Influenza Virus Infection in Mice. *J Immunol* 2015; 194: 4846-4859.
 - 17) Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev* 2020; 21: e13034.
 - 18) Stein RA. Super-spreaders in infectious diseases. *Int J Infect Dis* 2011; 15: e510-513.
 - 19) Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. *Acta Diabetol* 2020; 57: 759-764.
 - 20) Edwards DA, Ausiello D, Salzman J, Devlin T, Langer R, Beddingfield BJ, Fears AC, Doyle-Meyers LA, Redmann RK, Killeen SZ, Maness NJ, Roy CJ. Exhaled aerosol increases with COVID-19 infection, age, and obesity. *Proc Natl Acad Sci USA* 2021; 118: e2021830118.
 - 21) Kumar S, Jha S, Rai SK. Significance of super spreader events in COVID-19. *Indian J Public Health* 2020; 64: 139-141.
 - 22) Honce R, Karlsson EA, Wohlgemuth N, Estrada LD, Meliopoulos VA, Yao J, Schultz-Cherry S. Obesity-Related Microenvironment Promotes Emergence of Virulent Influenza Virus Strains. *mBio* 2020; 11: e03341-19.
 - 23) Adrielle Dos Santos L, Filho PGG, Silva AMF, Santos JVG, Santos DS, Aquino MM, de Jesus RM, Almeida MLD, da Silva JS, Altmann DM, Boyton RJ, Alves Dos Santos C, Santos CNO, Alves JC, Santos IL, Magalhães LS, Belitardo EMMA, Rocha DJPG, Almeida JPP, Pacheco LGC, Aguiar ERGR, Campos GS, Sardi SI, Carvalho RH, de Jesus AR, Rezende KF, de Almeida RP. Recurrent COVID-19 including evidence of reinfection and enhanced severity in thirty Brazilian healthcare workers. *J Infect* 2021; 82: 399-406.
 - 24) Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, Gibbs KW, Erickson HL, Steingrub JS, Smithline HA, Gong MN, Aboodi MS, Exline MC, Henning DJ, Wilson JG, Khan A, Qadir N, Brown SM, Peltan ID, Rice TW, Hager DN, Ginde AA, Stubblefield WB, Patel MM, Self WH, Feldstein LR; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 993-998.
 - 25) Ritter A, Kreis NN, Louwen F, Yuan J. Obesity and COVID-19: Molecular Mechanisms Linking Both Pandemics. *Int J Mol Sci* 2020; 21: 5793.
 - 26) Petrakis D, Margină D, Tsarouhas K, Tekos F, Stan M, Nikitovic D, Kouretas D, Spandidos DA,

- Tsatsakis A. Obesity - a risk factor for increased COVID-19 prevalence, severity and lethality (Review). *Mol Med Rep* 2020; 22: 9-19.
- 27) Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011; 11: 85-97.
 - 28) Cecchetto i G, Albini A, Malerba M, Noonan DM, Pochetti P, Polosa R. COVID-19 and Obesity: Dangerous Liaisons. *J Clin Med* 2020; 9: 2511.
 - 29) Schönrich G, Raftery MJ, Samstag Y. Devilishly radical NETwork in COVID-19: Oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression. *Adv Biol Regul* 2020; 77: 100741.
 - 30) Moro-García MA, Mayo JC, Sainz RM, Alonso-Arias R. Influence of Inflammation in the Process of T Lymphocyte Differentiation: Proliferative, Metabolic, and Oxidative Changes. *Front Immunol* 2018; 9: 339.
 - 31) Lima JE. The Role of Glutathione in Viral Diseases of the Central Nervous System. *Glutathione in Health and Disease* 2018. Doi: 10.5772/intechopen.76579.
 - 32) Pieniazek A, Gwozdzinski K. Apoptosis and necrosis induced by hydrogen peroxide and cyanate in human lymphocytes. *Free Radic Biol Med* 2017; 108: 92.
 - 33) Bakadia BM, Boni BOO, Ahmed AAQ, Yang G. The impact of oxidative stress damage induced by the environmental stressors on COVID-19. *Life Sci* 2021; 264: 118653.
 - 34) Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, Mencarini J, Caporale R, Peruzzi B, Antonelli A, Trotta M, Zammarchi L, Ciani L, Gori L, Lazzeri C, Maticci A, Vultaggio A, Rossi O, Almerigogna F, Parronchi P, Fontanari P, Lavorini F, Peris A, Rossolini GM, Bartoloni A, Romagnani S, Liotta F, Annunziato F, Cosmi L. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J Clin Invest* 2020; 130: 4694-4703.
 - 35) Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. *Curr Opin Hematol* 2013; 20: 437-444.
 - 36) Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020; 18: 844-847.
 - 37) Mehanna O, El Askary A, Ali E, El Esawy B, Fath-Alla T, Gharib AF. Impact of Obesity and Its Associated Comorbid Conditions on COVID-19 Presentation. *Diabetes Metab Syndr Obes* 2021; 14: 409-415.
 - 38) McNeill JN, Lau ES, Paniagua SM, Liu EE, Wang JK, Bassett IV, Selvaggi CA, Lubitz SA, Foulkes AS, Ho JE. The role of obesity in inflammatory markers in COVID-19 patients. *Obes Res Clin Pract* 2021; 15: 96-99.
 - 39) Available at: https://www.ahajournals.org/doi/10.1161/circ.142.suppl_3.16467.
 - 40) Korakas E, Ikonomidis I, Kousathana F, Balampanis K, Kountouri A, Raptis A, Palaiodimou L, Kokkinos A, Lambadiari V. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. *Am J Physiol Endocrinol Metab* 2020; 319: E105-E109.
 - 41) Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120-128.
 - 42) Han T, Kang J, Li G, Ge J, Gu J. Analysis of 2019-nCoV receptor ACE2 expression in different tissues and its significance study. *Ann Transl Med* 2020; 8: 1077.
 - 43) Al-Benna S. Association of high-level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients. *Obes Med* 2020; 19: 100283.
 - 44) Wiese OJ, Allwood BW, Zemlin AE. COVID-19 and the renin-angiotensin system (RAS): A spark that sets the forest alight? *Med Hypotheses* 2020; 144: 110231.
 - 45) Bolourian A, Mojtahedi Z. Obesity and COVID-19: The mTOR pathway as a possible culprit. *Obes Rev* 2020; 21: e13084.
 - 46) Bokov P, Delclaux C. Impact fonctionnel respiratoire de l'obésité [The impact of obesity on respiratory function]. *Rev Mal Respir* 2019; 36: 1057-1063.
 - 47) Dietz W, Santos-Burgoa C. Obesity and its Implications for COVID-19 Mortality. *Obesity (Silver Spring)* 2020; 28: 1005.
 - 48) Lemyze M, Courageux N, Maladobry T, Arumadura C, Pauquet P, Orfi A, Komorowski M, Mallat J, Granier M. Implications of Obesity for the Management of Severe Coronavirus Disease 2019 Pneumonia. *Crit Care Med* 2020; 48: e761-e767.
 - 49) Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, Cairo M, Mori S, Messinesi G, Contro E, Bonfanti P, Benini A, Valsecchi MG, Antolini L, Foti G. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. *Lancet Respir Med* 2020; 8: 765-774.
 - 50) Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, Hibbert KA, Thompson BT, Hardin CC. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. *Am J Respir Crit Care Med* 2020; 201: 1560-1564.
 - 51) Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucusky MS, Lange SJ, Gundlapalli AV, Boehmer TK, Blanck HM. Body Mass Index and Risk for COVID-19-Related Hospitalization, Intensive Care Unit Admission, Invasive Mechanical Ventilation, and Death — United States, March-December 2020. *MMWR Morb Mortal Wkly Rep* 2021; 70: 355-361.
 - 52) Zhang X, Zheng J, Zhang L, Liu Y, Chen GP, Zhang HP, Wang L, Kang DY, Wood LG, Wang G. Systemic inflammation mediates the detrimental

- effects of obesity on asthma control. *Allergy Asthma Proc* 2018; 39: 43-50.
- 53) Busetto L, Bettini S, Fabris R, Serra R, Dal Pra C, Maffei P, Rossato M, Fioretto P, Vettor R. Obesity and COVID-19: An Italian Snapshot. *Obesity (Silver Spring)* 2020; 28: 1600-1605.
 - 54) De Jong A, Wrigge H, Hedenstierna G, Gattinoni L, Chiumello D, Frat JP, Ball L, Schetz M, Pickers P, Jaber S. How to ventilate obese patients in the ICU. *Intensive Care Med* 2020; 46: 2423-2435.
 - 55) Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* 2020; 28: 1195-1199.
 - 56) Kalligeros M, Shehadeh F, Mylona EK, Benitez G, Beckwith CG, Chan PA, Mylonakis E. Association of Obesity with Disease Severity Among Patients with Coronavirus Disease 2019. *Obesity (Silver Spring)* 2020; 28: 1200-1204.
 - 57) Anderson MR, Geleris J, Anderson DR, Zucker J, Nobel YR, Freedberg D, Small-Saunders J, Rajagopalan KN, Greendyk R, Chae SR, Natarajan K, Roh D, Edwin E, Gallagher D, Podolanczuk A, Barr RG, Ferrante AW, Baldwin MR. Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection: A Retrospective Cohort Study. *Ann Intern Med* 2020; 173: 782-790.
 - 58) Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, Li Z, Shaw SF, Caparosa SL, Nau CL, Saxena T, Rieg GK, Ackerson BK, Sharp AL, Skarbinski J, Naik TK, Murali SB. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. *Ann Intern Med* 2020; 173: 773-781.
 - 59) Meng L, Mui E, Holubar MK, Deresinski SC. Comprehensive Guidance for Antibiotic Dosing in Obese Adults. *Pharmacotherapy* 2017; 37: 1415-1431.
 - 60) Barras M, Legg A. Drug dosing in obese adults. *Aust Prescr* 2017; 40: 189-193.
 - 61) Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marra LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; 323: 2052-2059.
 - 62) Carrillo-Vega MF, Salinas-Escudero G, García-Peña C, Gutiérrez-Robledo LM, Parra-Rodríguez L. Early estimation of the risk factors for hospitalization and mortality by COVID-19 in Mexico. *PLoS One* 2020;15: e0238905.
 - 63) Bello-Chavolla OY, Bahena-López JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, Fermín-Martínez CA, Naveja JJ, Aguilar-Salinas CA. Predicting Mortality Due to SARS-CoV-2: A Mechanistic Score Relating Obesity and Diabetes to COVID-19 Outcomes in Mexico. *J Clin Endocrinol Metab* 2020; 105: dgaa346.
 - 64) Tchang BG, Askin G, Sahagun A, Hwang J, Huang H, Mendelsohn Curanaj FA, Seley JJ, Safford MM, Alonso LC, Aronne LJ, Shukla AP. The Independent Risk of Obesity and Diabetes and Their Interaction in COVID-19: A Retrospective Cohort Study. *Obesity (Silver Spring)* 2021; 29: 971-975.
 - 65) Smith SM, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, Dobesh DP, Brufsky A, Connor RI. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol* 2021; 93: 409-415.
 - 66) Gold MS, Sehayek D, Gabrielli S, Zhang X, McCusker C, Ben-Shoshan M. COVID-19 and comorbidities: a systematic review and meta-analysis. *Postgrad Med* 2020; 132: 749-755.
 - 67) Nandy K, Salunke A, Pathak SK, Pandey A, Doctor C, Puj K, Sharma M, Jain A, Warikoo V. Coronavirus disease (COVID-19): A systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. *Diabetes Metab Syndr* 2020; 14: 1017-1025.
 - 68) Maas MB, Kim M, Malkani RG, Abbott SM, Zee PC. Obstructive Sleep Apnea and Risk of COVID-19 Infection, Hospitalization and Respiratory Failure. *Sleep Breath* 2021; 25: 1155-1157.
 - 69) Neidich SD, Green WD, Rebeles J, Karlsson EA, Schultz-Cherry S, Noah TL, Chakladar S, Hudgens MG, Weir SS, Beck MA. Increased risk of influenza among vaccinated adults who are obese. *Int J Obes (Lond)* 2017; 41: 1324-1330.
 - 70) Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; 383: 2603-2615.
 - 71) Townsend MJ, Kyle TK, Stanford FC. COVID-19 Vaccination and Obesity: Optimism and Challenges. *Obesity (Silver Spring)* 2021; 29: 634-635.
 - 72) Available at: <https://depts.washington.edu/pandemicalliance/2021/02/26/obesity-may-hamper-sars-cov-2-vaccine-immunogenicity/>.
 - 73) Jackson LA, Anderson EJ, Roupheal NG, Roberts PC, Makhene M, Coler RN, McCullough MP, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott A, Flach B, Doria-Rose NA, Corbett KS, Morabito KM, O'Dell S, Schmidt SD, Swanson PA 2nd, Padilla M, Mascola JR, Neuz-

- il KM, Bennett H, Sun W, Peters E, Makowski M, Albert J, Cross K, Buchanan W, Pikaart-Tautges R, Ledgerwood JE, Graham BS, Beigel JH; mRNA-1273 Study Group. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med* 2020; 383: 1920-1931.
- 74) Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, Voysey M, Aley PK, Angus B, Babbage G, Belij-Rammerstorfer S, Berry L, Bibi S, Bittaye M, Cathie K, Chappell H, Charlton S, Cicconi P, Clutterbuck EA, Colin-Jones R, Dold C, Emary KRW, Fedosyuk S, Fuskova M, Gbesemete D, Green C, Hallis B, Hou MM, Jenkin D, Joe CCD, Kelly EJ, Kerridge S, Lawrie AM, Lelliott A, Lwin MN, Makinson R, Marchevsky NG, Mujadidi Y, Munro APS, Pacurar M, Plested E, Rand J, Rawlinson T, Rhead S, Robinson H, Ritchie AJ, Ross-Russell AL, Saich S, Singh N, Smith CC, Snape MD, Song R, Tarrant R, Themistocleous Y, Thomas KM, Villafana TL, Warren SC, Watson MEE, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Faust SN, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021; 396: 1979-1993.
- 75) Clemmensen C, Petersen MB, Sørensen TIA. Will the COVID-19 pandemic worsen the obesity epidemic?. *Nat Rev Endocrinol* 2020; 16: 469-470.
- 76) Krams IA, Jöers P, Luoto S, Trakimas G, Lietuviotis V, Krams R, Kaminska I, Rantala MJ, Krama T. The Obesity Paradox Predicts the Second Wave of COVID-19 to Be Severe in Western Countries. *Int J Environ Res Public Health* 2021; 18: 1029.
- 77) Petzold MB, Bendau A, Plag J, Pyrkosch L, Mascarell Maricic L, Betzler F, Rogoll J, Große J, Ströhle A. Risk, resilience, psychological distress, and anxiety at the beginning of the COVID-19 pandemic in Germany. *Brain Behav* 2020; 10: e01745.
- 78) Cardel MI, Manasse S, Krukowski RA, Ross K, Shakour R, Miller DR, Lemas DJ, Hong YR. COVID-19 Impacts Mental Health Outcomes and Ability/Desire to Participate in Research Among Current Research Participants. *Obesity (Silver Spring)* 2020; 28: 2272-2281.
- 79) Vahratian A, Blumberg SJ, Terlizzi EP, Schiller JS. Symptoms of Anxiety or Depressive Disorder and Use of Mental Health Care Among Adults During the COVID-19 Pandemic - the United States, August 2020-February 2021. *MMWR Morb Mortal Wkly Rep* 2021; 70: 490-494.
- 80) Abbas AM, Fathy SK, Fawzy AT, Salem AS, Shawky MS. The mutual effects of COVID-19 and obesity. *Obes Med* 2020; 19: 100250.
- 81) Cecchetto C, Aiello M, Gentili C, Ionta S, Osimo SA. Increased emotional eating during COVID-19 associated with lockdown, psychological and social distress. *Appetite* 2021; 160: 105122.
- 82) Bermanian M, Mæland S, Blomhoff R, Rabben ÅK, Arnesen EK, Skogen JC, Fadnes LT. Emotional Eating in Relation to Worries and Psychological Distress Amid the COVID-19 Pandemic: A Population-Based Survey on Adults in Norway. *Int J Environ Res Public Health* 2020; 18: 130.
- 83) Al-Musharaf S. Prevalence and Predictors of Emotional Eating among Healthy Young Saudi Women during the COVID-19 Pandemic. *Nutrients* 2020; 12: 2923.
- 84) Zhang J, Zhang Y, Huo S, Ma Y, Ke Y, Wang P, Zhao A. Emotional Eating in Pregnant Women during the COVID-19 Pandemic and Its Association with Dietary Intake and Gestational Weight Gain. *Nutrients* 2020; 12: 2250.
- 85) Pietrobelli A, Pecoraro L, Ferruzzi A, Heo M, Faith M, Zoller T, Antoniazzi F, Piacentini G, Fearnbach SN, Heymsfield SB. Effects of COVID-19 Lockdown on Lifestyle Behaviors in Children with Obesity Living in Verona, Italy: A Longitudinal Study. *Obesity (Silver Spring)* 2020; 28: 1382-1385.
- 86) Lourenço S, Oliveira A, Lopes C. The effect of current and lifetime alcohol consumption on overall and central obesity. *Eur J Clin Nutr* 2012; 66: 813-818.
- 87) Phillipou A, Meyer D, Neill E, Tan EJ, Toh WL, Van Rheenen TE, Rossell SL. Eating and exercise behaviors in eating disorders and the general population during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *Int J Eat Disord* 2020; 53: 1158-1165.
- 88) Fernández-Aranda F, Casas M, Claes L, Bryan DC, Favaro A, Granero R, Gudiol C, Jiménez-Murcia S, Karwautz A, Le Grange D, Menchón JM, Tchanturia K, Treasure J. COVID-19 and implications for eating disorders. *Eur Eat Disord Rev* 2020; 28: 239-245.
- 89) Ghanemi A, Yoshioka M, St-Amand J. Will an obesity pandemic replace the coronavirus disease-2019 (COVID-19) pandemic? *Med Hypotheses* 2020; 144: 110042.
- 90) Olszanecka-Glinianowicz M, Dudek D, Filipiak KJ, Krzystanek M, Markuszewski L, Ruchała M, Tomiak E. Letter to Editor. Treatment of overweight and obesity during and after a pandemic. Let's not wait for the development of complications - new guidelines for doctors. *Psychiatr Pol* 2020; 54: 1263-1268.
- 91) Huang R, Zhu L, Xue L, Liu L, Yan X, Wang J, Zhang B, Xu T, Ji F, Zhao Y, Cheng J, Wang Y, Shao H, Hong S, Cao Q, Li C, Zhao XA, Zou L, Sang D, Zhao H, Guan X, Chen X, Shan C, Xia J, Chen Y, Yan X, Wei J, Zhu C, Wu C. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multi-center study. *PLoS Negl Trop Dis* 2020; 14: e0008280.
- 92) Steinberg E, Wright E, Kushner B. In Young Adults with COVID-19, Obesity Is Associated with Adverse Outcomes. *West J Emerg Med* 2020; 21: 752-755.

- 93) Al-Sabah S, Al-Haddad M, Al-Youha S, Jamal M, Almazeedi S. COVID-19: Impact of obesity and diabetes on disease severity. *Clin Obes* 2020; 10: e12414.
- 94) Hajifathalian K, Kumar S, Newberry C, Shah S, Fortune B, Krisko T, Ortiz-Pujols S, Zhou XK, Dannenberg AJ, Kumar R, Sharaiha RZ. Obesity is Associated with Worse Outcomes in COVID-19: Analysis of Early Data from New York City. *Obesity (Silver Spring)* 2020; 28: 1606-1612.
- 95) Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, Southern WN, Mantzoros CS. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism* 2020; 108: 154262.
- 96) Hamer M, Gale CR, Kivimäki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: A community-based cohort study of adults in the United Kingdom. *PNAS* 2020; 117: 21011-21013.
- 97) Yang J, Ma Z, Lei Y. A meta-analysis of the association between obesity and COVID-19. *Epidemiol Infect* 2020; 149: e11.
- 98) 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* 2021; 93: 2662-2674.
- 99) Zhao X, Gang X, He G, Li Z, Lv Y, Han Q, Wang G. Obesity Increases the Severity and Mortality of Influenza and COVID-19: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)* 2020; 11: 595109.
- 100) Földi M, Farkas N, Kiss S, Zádori N, Váncsa S, Szakó L, Dembrovszky F, Solymár M, Bartalis E, Szakács Z, Hartmann P, Pár G, Eröss B, Molnár Z, Hegyi P, Szentesi A; KETLAK Study Group. Obesity is a risk factor for developing critical condition in COVID-19 patients: A systematic review and meta-analysis. *Obes Rev* 2020; 21: e13095.
- 101) Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 2020; 14: 395-403.
- 102) Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect* 2020; 81: e16-e25.
- 103) Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, Coupland CAC, Tan PS, Clift AK, Harrison D, Gould DW, Pavord ID, Hippisley-Cox J. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med* 2021; 1:2213-2600(21)00095-3.
- 104) Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, Quaderi S, Mandal S, Hurst JR. Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. *PLoS One* 2020; 15: e0233147.