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# Obesity: A critical risk factor in the COVID-19 pandemic

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**Summary**

Obesity is an emerging independent risk factor for susceptibility to and severity of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Previous viral pandemics have shown that obesity, particularly severe obesity (BMI > 40 kg/m<sup>2</sup>), is associated with increased risk of hospitalization, critical care admission and fatalities. In this narrative review, we examine emerging evidence of the influence of obesity on COVID-19, the challenges to clinical management from pulmonary, endocrine and immune dysfunctions in individuals with obesity and identify potential areas for further research. We recommend that people with severe obesity be deemed a vulnerable group for COVID-19; clinical trials of pharmacotherapeutics, immunotherapies and vaccination should prioritize inclusion of people with obesity.

**KEYWORDS**

coronavirus, immune dysfunction, obesity, SARS-CoV-2 | bariatric surgery

## 1 | INTRODUCTION

Obesity, a known risk factor for respiratory infection, is increasingly being recognized as a predisposing factor in the current coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).<sup>1</sup> This has important implications on global health as excess weight, usually represented by a raised body mass index (BMI), affects vast numbers of people worldwide: 39% of adults are

overweight (BMI ≥25.0 to 29.9 kg/m<sup>2</sup>) and 13% have clinical obesity (BMI ≥30.0 kg/m<sup>2</sup>) globally.<sup>2</sup> Western populations have markedly higher rates of obesity: 40% of adults have obesity and another 32% are overweight in the United States,<sup>3</sup> while in England 29% of adults have obesity and a further 36% are overweight.<sup>4</sup> The prevalence of obesity in men and women increases with age. In this narrative review, we explore the relationship between excess weight and response to infection with SARS-CoV-2 and the severity and complications of COVID-19, discuss the clinical and public health strategies for managing the risks, and identify research priorities.

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## 2 | COVID-19 PANDEMIC

From its first recognition in Wuhan City, Hubei Province in China in December 2019,<sup>5</sup> SARS-CoV-2 has spread globally. The novel coronavirus has similarities in its genetic sequence to SARS-CoV that caused the severe acute respiratory syndrome (SARS) pandemic in 2003.<sup>6</sup> They both have the spike (S) protein of coronaviruses. The S protein is primed by cellular serine protease TMPRSS2, facilitating binding with angiotensin-converting enzyme 2 (ACE2) receptor to gain cellular entry.<sup>6,7</sup> Compared to SARS-CoV, the novel SARS-CoV-2 has higher affinity for ACE2,<sup>8</sup> and it is thus more readily transmissible. Despite the relationship between SARS-CoV-2 and ACE2, currently there is no evidence to show that ACE-inhibitors or angiotensin receptor blockers contribute to infection.

The commonest presenting symptoms of COVID-19 have consistently been fever (98%) and dry cough (70%).<sup>9</sup> Respiratory manifestations of severe COVID-19 include pneumonia, pulmonary embolism and acute respiratory distress syndrome (ARDS). All age groups may be infected and median age of hospitalized cohorts varies from 47 to 63 years.<sup>9-11</sup> Infection is more common in men with reported prevalence of 58% to 68%.<sup>10,12,13</sup> In one intensive care unit (ICU) cohort from Italy, 82% were men.<sup>14</sup> The higher prevalence of men in hospitalized population needing critical care may also reflect difference in disease severity between the sexes.

The median age of death from the disease was 75 years.<sup>9</sup> Mortality rates were reported as 2.3% in Hubei Province; however, infection fatality rates were higher elsewhere at, for example, 26% in an Italian ICU.<sup>13,14</sup> Clinically, COVID-19 causes lymphocytopenia (up to 82% of patients), elevations of inflammatory markers including C-reactive protein (CRP), D-dimer, interleukins and tumour necrosis factor-alpha (TNF- $\alpha$ ).<sup>8,9</sup> It has been suggested that patients more likely to progress to critical disease have higher initial levels of inflammatory markers and D-dimer.<sup>15,16</sup> It is recognized that a sub-group of COVID-19 patients develop a hyper-inflammatory syndrome, or 'cytokine storm', with sustained excess production of cytokines and chemokines which may lead to ARDS and multi-organ failure. These patients require critical care and are less likely to survive.<sup>15,17</sup> Early indicators of the syndrome may include exceptionally high levels of interleukins, ferritin and D-dimer from the outset at hospital admission.<sup>18,19</sup> While obesity is associated with a chronic low-grade inflammatory state, whether this drives patients with obesity towards a potentially more extreme clinical course is uncertain.

Comorbidities are associated with severe COVID-19; while they were recorded in 24% to 51% of hospitalized patients,<sup>10,12,15</sup> they were noted in 68% to 72% of ICU patients.<sup>14,20</sup> The common comorbidities recorded in reports from China (and elsewhere) included hypertension, cardiovascular disease and diabetes mellitus,<sup>20</sup> all of which are known to be associated with obesity and indeed obesity itself is increasingly recognized as both a comorbidity and a risk factor.<sup>21</sup>

Many early reports of the current COVID-19 pandemic do not include anthropometric information; however, more recent reports have identified obesity as a predictor of hospitalization.<sup>16</sup> In a study from Lille in France, people with obesity were significantly over-represented among patients admitted to ICU with COVID-19 compared to non-SARS-CoV-2 respiratory disease in previous years

(47.5% vs 25.8%).<sup>22</sup> Furthermore, the need for invasive mechanical ventilation, a surrogate for the severity of SARS-CoV-2, increased with rising levels of obesity, reaching nearly 90% in patients with a BMI > 35 kg/m<sup>2</sup>. Similar associations of obesity and disease severity were observed in hospitalized COVID-19 patients in China and the United States.<sup>23-25</sup>

A systematic review and meta-analysis of 13 studies with a combined total of 3027 patients with SARS-CoV-2 infection found that male sex, age over 65 years, smoking, hypertension, diabetes, cardiovascular disease, and respiratory diseases were associated with worse disease while another meta-analysis of 14 studies found that obesity was also a predictor of mortality (Figure 1).<sup>26,27</sup> These findings were similar to those in a UK report of hospitalized COVID-19 patients.<sup>28</sup>

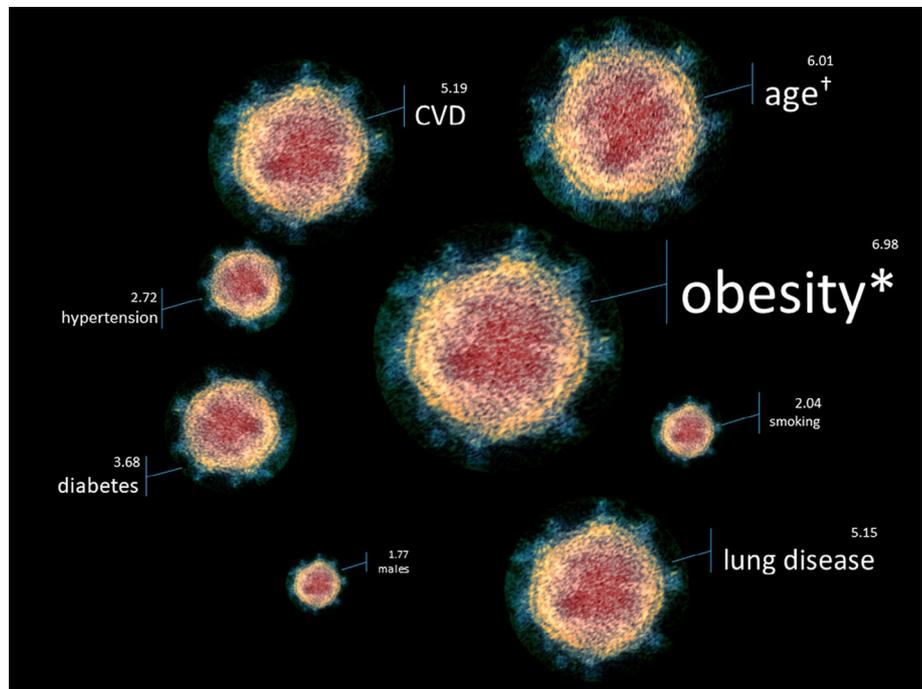
There is mounting concern of higher incidence of COVID-19 and worse outcomes in people from black, Asian and minority ethnic communities.<sup>29,30</sup> While socioeconomic, cultural, or lifestyle factors, genetic predisposition, or pathophysiological differences in susceptibility or response to infection have been mooted,<sup>29</sup> another factor may be the higher prevalence of metabolic disorders among ethnic minorities of normal weight.<sup>31,32</sup> Both 'normal weight obesity' and 'metabolically unhealthy normal weight' have been used to classify normal weight individuals with manifestations of metabolic syndrome such as insulin resistance, dyslipidaemia, and hypertension.<sup>33-35</sup> This cohort of patients are characterized by a metabolically unhealthy fat distribution with increased visceral adiposity but reduced lower-body fat mass.<sup>36,37</sup> Furthermore, elevated percentage body fat has been linked with increased cardiometabolic dysregulation and mortality, even among patients of normal weight.<sup>35</sup>

## 3 | OBESITY AND RESPIRATORY VIRUSES

Obesity is associated with infection and hospitalization due to respiratory viruses such as coronavirus, influenza, parainfluenza, metapneumovirus and rhinovirus.<sup>38,39</sup> It was acknowledged to be an independent risk factor in the 2009 H1N1 influenza pandemic.<sup>40,41</sup> Previous viral pandemics have shown that obesity, particularly severe obesity (BMI > 40 kg/m<sup>2</sup>), is associated with increased risk of hospitalization, ICU admission and fatalities,<sup>42-44</sup> and individuals with obesity have a greater than 6-fold increase in odds of hospitalization compared to normal-weight adults.<sup>38</sup> Emerging evidence indicates that obesity is also a risk factor for the current SARS-CoV-2 outbreak.

Obesity contributes to worse disease outcome in viral infections. Obesity has been found to be associated with increased frequency of both upper respiratory tract infections (adjusted OR 1.55) and lower respiratory tract infections (adjusted OR 2.02).<sup>45</sup> In a mouse model, when diet-induced obese (DIO) mice and lean mice were infected with mouse-adapted influenza virus, the DIO mice had greater mortality than the lean mice (42% vs 5.5%).<sup>46</sup> When two non-pandemic influenza seasons were examined, an association was found between BMI and disease severity. In the 2003-2004 and 2004-2005 influenza seasons, associations of obesity and severe disease were OR 1.14 and OR 1.24 respectively.<sup>41</sup> Indeed, it was noted during the H1N1

**FIGURE 1** Major determinants of critical illness in COVID-19. The size of each SARS-CoV-2 virion (electron micrograph; credit: NIAID, National Institutes of Health, USA) depicts odds ratio of developing critical vs non-critical COVID-19.<sup>26,27</sup> \*Odds ratio for advanced respiratory support in people with body mass index  $\geq 25$  kg/m<sup>2</sup>. †Age > 65 years



influenza pandemic in 2009 that, whereas there was no evidence that people with obesity had increased susceptibility to infection,<sup>47</sup> obesity was nevertheless a risk factor for more severe disease and increased pulmonary complications.<sup>41,44,48</sup> Mortality rates were also significantly higher, especially in those with severe obesity (BMI > 40 kg/m<sup>2</sup>).<sup>39,43</sup>

It is well recognized that in critically ill ICU patients admitted with any cause, patients with obesity have an increased risk of developing ARDS.<sup>49,50</sup> Unexpectedly, although these patients may have worse morbidity outcomes, their mortality rates are not increased. This 'obesity paradox' has been affirmed in meta-analyses but the mechanisms remain unclear.<sup>51-56</sup> Nonetheless, during the 2009 H1N1 pandemic, this paradox phenomenon was not observed in ICU patients with obesity infected with the virus.<sup>39,43</sup> It is likely that similar pictures will emerge in the current COVID-19 pandemic and patients with obesity lose the survival advantage when they contract the virus. Patients with obesity tend to have more comorbidities which may be a contributory factor to poorer outcomes. Furthermore, the mechanical effects of obesity on respiration (discussed further in the next section) may outweigh any potential protection from catabolic effects of severe disease that may accrue from excess energy stores. Another factor may be the dysregulated immune response in patients with obesity to viral infections, particularly impaired T-cell mediated immunity. This is discussed later in section entitled 'Obesity and Immune Function'.

#### 4 | OBESITY AND PULMONARY FUNCTION

Obesity affects respiratory function through a number of mechanisms (Figure 2), such as pulmonary restriction, ventilation-perfusion mismatch and respiratory muscle fatigue, which can lead to reductions in

ventilatory capacity and increases in the load placed upon it; furthermore, respiratory drive can be reduced. These complications increase the risk of obesity hypoventilation syndrome,<sup>57</sup> particularly in those with severe obesity. Obesity is also frequently associated with obstructive sleep apnoea syndrome.<sup>57</sup> It has been demonstrated that a 10% increase in weight is associated with a 32% increase in the apnoea-hypopnoea index and a 6-fold increase in the risk of moderate to severe obstructive sleep apnoea.<sup>58</sup> Central obesity and excess visceral fat adversely affect both chest wall and lung compliance due to accumulation of fat deposits within the thorax and in the abdominal cavity.<sup>59</sup> Movements of the diaphragm and chest wall are restricted by the thoracic wall and intra-abdominal fat mass resulting in reduced resting volume of the lung (functional residual capacity).<sup>59</sup> These changes in body mechanics and pulmonary function, coupled with a potentially dysfunctional immune system and increased likelihood of comorbidities in obesity, predispose patients with obesity to respiratory infections.

A previous study showed that intubation of individuals with obesity was more challenging than lean counterparts.<sup>60</sup> Additionally, the propensity towards atelectasis in patients with obesity makes managing critical respiratory support challenging in these patients.<sup>61</sup> It is accepted that in critical care prone-positioning improves air entry to posterior lung regions and drainage of airway secretions, improving gas exchange and survival in patients with ARDS.<sup>62</sup> Prone-positioning has been recommended in mechanically ventilated COVID-19 patients.<sup>63</sup> Patients with obesity benefit from this technique although the mandatory regular turning of a sedated patient with obesity can be physically demanding for ICU staff. In a single centre ICU study it was shown that prone-positioning in ARDS patients improved partial arterial oxygen pressure significantly more in patients with obesity than healthy-weight patients.<sup>64</sup> Additionally upper chest and pelvic



**FIGURE 2** Potential mechanisms that augment risk of critical illness and death from COVID-19 in people with obesity. There are a number of potential mechanisms by which obesity may influence adverse outcomes from COVID-19. These include chronic inflammation, impairment of respiratory function and pulmonary perfusion, practical considerations when managing obese patients in critical care settings, immune dysregulation, metabolic and vascular complications of obesity and relative reductions in key hormones. TNF- $\alpha$ , tumour necrosis factor alpha; FRC, functional residual capacity

supports are usually required in patients with obesity to avoid abdominal compression and the bed is frequently placed in the reverse Trendelenburg position to lessen transdiaphragmatic pressure and atelectasis.<sup>50</sup>

#### 4.1 | Obesity and pulmonary perfusion

Obesity and chronic inflammation are also closely related to endothelial dysfunction, which is both a contributor and consequence of pro-inflammatory pathway activation. Host infection of SARS-CoV-2 occurs through the ACE2 receptor, which is expressed in multiple organs including the lungs, heart, kidneys, as well as the endothelial cells.<sup>65</sup> SARS-CoV-2 has been shown to be capable of directly infecting engineered human blood vessel tissue cultures,<sup>66</sup> and this observation was subsequently extended to a patient series where diffuse endothelial inflammation, dysfunction and apoptosis were seen on post-mortem histology. In an autopsy study of the pulmonary pathobiology of COVID-19 compared to H1N1, there were three distinctive angiocentric features of COVID-19.<sup>67</sup> The first was severe endothelial injury associated with intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes; the second was widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries; the third was significant new vessel growth through a mechanism of intussusceptive angiogenesis in the lungs from patients with COVID-19. This provides a link between COVID-19 and the complications of organ ischaemia, inflammation and pro-thrombotic

state driven by systemic microcirculatory impairment, which is likely to be compounded by the pre-existing endothelial dysfunction associated with obesity and its related comorbidities (Figure 2).

## 5 | OBESITY AND THROMBOTIC RISK

Obesity is a known risk factor for thrombotic disorders such as venous thromboembolism (VTE) including deep vein thrombosis and pulmonary embolism, cardiovascular disease and stroke, and an independent predictor of myocardial infarction irrespective of sex, age, and ethnicity. Obesity-driven chronic inflammation and impaired fibrinolysis appear to be major effector mechanisms of thrombosis in obesity.<sup>68</sup> It is thought that the pro-inflammatory and hypofibrinolytic effects of obesity may be exacerbated by dysregulated expression and secretion of adipokines and microRNAs.

An early study from Wuhan reported that mortality from COVID-19 was associated with significantly higher levels of D-dimer and fibrin degradation product (FDP) and prolongation of prothrombin and activated partial thromboplastin times on admission compared to survivors<sup>69</sup>; 71.4% of non-survivors compared to 0.6% survivors had disseminated intravascular coagulation. The reported incidence of VTE in COVID-19 ranges up to 8% in general wards, up to 35% in the ICU setting, and up to 58% in consecutive autopsies in patients in whom VTE was not suspected before death (reviewed by Marietta et al).<sup>70</sup> Intriguingly, it has been speculated that in patients with severe/critical COVID-19 disease there develops a 'consumptive fibrinolysis' due to

overwhelming levels of fibrin and misfolded proteins/necrotic tissue in the lung, suggesting a clinical paradox where plasmin formation can be either deleterious or beneficial in COVID-19, but not at the same time.<sup>71</sup> In hospitalized patients with COVID-19, low molecular weight heparin (preferred) or unfractionated heparin at prophylactic doses for prevention of VTE is recommended by the World Health Organization<sup>72</sup> and several scientific societies (reviewed by Marietta et al).<sup>70</sup> There is also limited evidence of benefit from enhanced platelet inhibition treatment with aspirin, clopidogrel, tirofiban and the factor Xa inhibitor fondaparinux.<sup>73</sup>

## 6 | OBESITY AND IMMUNE FUNCTION

Obesity is associated with increased production of inflammatory cytokines such as TNF- $\alpha$ , interleukins and interferons that characterize chronic low-grade inflammation, which impair immune responses, both innate and adaptive. A hyperinflammatory response in which there are raised levels of interleukins and TNF- $\alpha$  has been associated with increased mortality from COVID-19.<sup>74</sup> The chronic inflammation in patients with obesity is speculated to be contributory to the observed increased mortality due to a potential enhancement of the inflammatory response to COVID-19 infection and induced disturbances in T-cell mediated immunity.<sup>75,76</sup> Indeed, obesity has been associated with increased activation of pro-inflammatory T-helper (Th-) 1 and Th-17 cells with reductions in anti-inflammatory Th-2 and regulatory T-cells.<sup>77,78</sup> An elegant study by Misumi et al demonstrated that not only were memory T cell quantities increased in obesity, their function was disrupted leading to tissue destruction following viral infections.<sup>79</sup> A more recent study of peripheral blood mononuclear cells showed enhancement in TNF- and Fas-induced T cell-apoptosis in patients with COVID-19.<sup>80</sup> The T-cell response is increasingly being postulated as being pivotal in reducing susceptibility to and adversity from SARS-CoV-2<sup>81-83</sup> and impaired T-cell immunity may be key to obesity-related detriment in relation to COVID-19.

Obesity is characterized by adipose tissue remodelling,<sup>84</sup> and pro-inflammatory alteration of the adipokine profile.<sup>85</sup> The resultant imbalance between pro- and anti-inflammatory adipokines have been implicated as key to obesity being a major risk factor for acute lung injury.<sup>85,86</sup> Leptin, a pro-inflammatory adipokine produced primarily by white adipocytes, is closely related to the immune system, playing a regulatory role in T-cell activation and cytokine production.<sup>87</sup> The impairment in host defence against pulmonary infections is thought to relate to leptin resistance resulting from prolonged hyperleptinaemia.<sup>88</sup> Indeed, leptin resistance in T cells, natural killer (NK) cells and peripheral blood monocytes have been demonstrated in obesity.<sup>89-92</sup>

Adiponectin has anti-inflammatory properties and exerts favourable effects on insulin sensitivity.<sup>65</sup> Reduced adiponectin levels have been observed among both patients of normal weight and obesity in the presence of cardiometabolic dysregulation.<sup>93</sup> Adiponectin functions as a regulator of macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 macrophages,<sup>94</sup> and low

levels in obesity have been associated with adverse outcomes in patients with emphysema, asthma, and respiratory failure in the critical care setting.<sup>95</sup> Adiponectin deficiency has also been demonstrated to increase lung inflammation and reduce clearance of apoptotic cells in animal models.<sup>96</sup> It is of note that adiponectin levels in metabolically healthy individuals with obesity (MHO) are higher than those with impaired metabolic health<sup>93</sup>; it is the latter group that is predisposed to increased risk of pneumonia and worse outcome in COVID-19.<sup>97</sup>

## 7 | OBESITY AND THE ENDOCRINE SYSTEM IN COVID-19

Adipose tissue is an active organ that plays an important role in several important physiological functions that are mediated through hormones and adipocytokines.<sup>98</sup> Obesity is associated with several endocrine alterations that arise as a result of changes in the hypothalamic-pituitary hormonal axes. These include hypogonadism, hypothyroidism and cortisol deficiency (Figure 2), which may have a role in mediating the adverse relationship between obesity and COVID-19 outcomes.

### 7.1 | Obesity and testosterone

Testosterone concentrations are lower in older men,<sup>99</sup> and in men with severe obesity of all ages.<sup>100</sup> While low testosterone is associated with reduced respiratory muscle activity and exercise capacity<sup>101</sup> and higher levels of pro-inflammatory cytokines,<sup>102</sup> testosterone replacement therapy improves peak oxygen consumption<sup>103</sup> and reduces cytokine levels.<sup>102</sup> Therefore, the hypothesis arises that low testosterone in ageing men with obesity may have a role in the cytokine storm of SARS-CoV-2 infection leading to more severe disease. It is not yet known, however, if testosterone is beneficial in the treatment of COVID-19 in men with obesity and low testosterone levels. Furthermore, a contrary hypothesis of testosterone-driven COVID-19 progression also exists.<sup>104</sup> This is based on androgen receptor activation of a protease that is crucial for COVID-19 viral spread.<sup>105</sup> It is thus postulated that it is the higher testosterone levels observed in men that leads to their higher mortality outcomes. More research is needed to elucidate the exact relationship between testosterone and COVID-19 before any definite conclusions can be drawn.

### 7.2 | Obesity and thyroid function

The hypothalamic-pituitary-thyroid hormone axis may be affected by both obesity and significant illness. Conversely, the treatment of thyroid dysfunction may also be associated with weight gain.<sup>106</sup> Obesity is associated with a rise in serum thyrotropin (thyroid stimulating hormone; TSH) level although thyroid hormones tend to remain stable or may even be mildly elevated.<sup>107</sup> In illness thyroid function tends to be

abnormal, typically leading to reduction in TSH and triiodothyronine (T3) levels in the initial phase. This dampening down of the hypothalamic-pituitary-thyroid pathway has historically been considered as an adaptive response to reduce metabolism and conserve energy. However, some experts have questioned this view as those with the lowest serum T3 levels have the worst outcomes.<sup>108</sup> The reduction in T3 levels seems to mirror the rise in inflammatory cytokines seen in acute illness.<sup>109</sup> Controversy continues as to whether thyroid hormone therapy has beneficial or detrimental effects in euthyroid individuals with obesity undergoing caloric deprivation and in euthyroid adult patients during non-thyroidal illnesses.<sup>110</sup> One randomized controlled trial of T3 therapy in patients with heart failure and low circulating T3 levels demonstrated a significant improvement in left ventricular ejection fraction and improvement in inflammatory markers.<sup>111</sup> There is no data, as yet, to suggest that abnormal thyroid function, particularly in people with obesity infected with SARS-CoV-2, is associated with adverse outcomes. Therefore, it remains to be seen if patients with obesity and COVID-19 infection and low serum T3 levels benefit from T3 supplementation.

### 7.3 | Obesity and the glucocorticoid axis

The hypothalamic-pituitary-adrenal axis, which is intimately involved in the regulation of energy metabolism and bodyweight,<sup>112</sup> may play an important role in the global rise in obesity. Hair cortisol levels, a novel non-invasive parameter reflecting mean cortisol levels over several months, are increased in people with obesity compared to normal-weight individuals.<sup>113,114</sup> The hypothalamic-pituitary-adrenal pathway may be affected by COVID-19 infection. Autopsy studies performed on patients who died from the SARS virus in 2003 showed degeneration and necrosis of the adrenal cortical cells. In fact the coronavirus causing SARS was first identified in the adrenal glands, hinting towards a direct cytopathic effect of the virus. Hence it is likely that cortisol dynamics may be altered in patients with SARS (and possibly in patients with COVID-19 too). One of the primary immune-invasive strategies employed by the SARS-CoV is to knock down the host's cortisol stress response.<sup>115</sup> Antibodies produced by the host to counteract the virus, in turn, would unknowingly destroy the host ACTH (adrenocorticotrophic hormone), thereby blunting the cortisol rise. This would imply that all patients with SARS might have had underlying relative cortisol insufficiency.<sup>116</sup> However, observational data on circulating cortisol levels in patients with COVID-19 are scarce. A recent cohort study reported higher levels of cortisol in hospitalized COVID-19 patients on admission compared to those without COVID-19.<sup>117</sup> Elevated cortisol level was associated with reduced survival and was a marker of disease severity. The results of ongoing trials of corticosteroid therapy in patients hospitalized with COVID-19 infection will be insightful. Indeed, an early report from the RECOVERY trial has shown that oral or intravenous dexamethasone 6 mg daily reduced deaths by one-third in ventilated patients (rate ratio 0.64) and by one fifth in other patients receiving oxygen only (RR 0.82).<sup>118</sup> However, dexamethasone treatment in this context is

likely to work via its anti-inflammatory and immunomodulatory actions rather than any possible effects on the pathophysiology of COVID-19.

## 8 | OBESITY AND MICRONUTRIENTS

The role of trace elements and vitamins in COVID-19 has drawn the attention of the scientific community and the lay public. A large body of data show that vitamins, including vitamins A, B6, B12, C, D, E, and folate, trace elements, including zinc, iron, selenium, magnesium, and copper, and omega-3 fatty acids play important and complementary roles in supporting the immune system.<sup>119</sup> Vitamin D deficiency, in particular, has been mooted as a potential contributor to susceptibility to COVID-19.<sup>120</sup> Prevalence of vitamin D deficiency is 35% greater in people with obesity compared to healthy-weight individuals and is associated with obesity irrespective of age, latitude, cut-offs to define vitamin D deficiency and the Human Development Index of the study location.<sup>121</sup> Rates of vitamin D deficiency are markedly high in people with severe obesity and potential bariatric surgical candidates in northern latitudes.<sup>122</sup> Further research into screening and treating vitamin D deficiency to reduce COVID-19 risk is warranted. While some small observational studies, which did not control for potential confounding factors such as BMI or underlying health issues, have reported that inadequately-treated vitamin D deficiency is associated with increased risk of COVID-19, a large-scale population study of UK Biobank participants reported that vitamin D was weakly associated with COVID-19 infection on univariable analysis, but not after adjustment for confounders.<sup>123</sup> A rapid review from Oxford found no clinical evidence related to vitamin D deficiency predisposing to COVID-19, nor evidence in favour of supplementation for preventing or treating COVID-19.<sup>124</sup> An evidence review from the National Institute for Health and Care Excellence concluded that there is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19.<sup>125</sup> However, all people should continue to follow public health advice for the general population on vitamin D supplementation,<sup>126</sup> to prevent vitamin D deficiency and maintain bone and muscle health during the COVID-19 pandemic, irrespective of any possible link with respiratory infection.

## 9 | OBESITY, DRUGS AND VACCINES

There remains a need to develop effective treatment and a vaccine for SARS-CoV-2. Obesity poses potential difficulties for both. It is often overlooked as a cause of suboptimal treatment in infectious diseases owing to its adverse influence on pharmacokinetic and pharmacodynamic properties of drugs, as well as their efficacy and safety.<sup>127</sup> Even as obesity becomes a global phenomenon, the effects obesity has on drug absorption, distribution, metabolism and clearance are not completely understood,<sup>128</sup> and dosing recommendations for patients with obesity are often not provided in pharmaceutical drug information sheets. Lower vaccine efficacy has been reported in

people with obesity following the H1N1 pandemic.<sup>38</sup> While there was no significant difference in antibody titres between people with obesity and healthy-weight individuals 1 month after H1N1 vaccination, people with obesity had a 4-fold or greater decline in antibody titres compared to healthy-weight individuals at 12 months post-vaccination.<sup>129</sup> Obesity is associated with T cell dysfunction and the impaired response means a proportion of individuals with obesity remains at risk of influenza despite vaccination.<sup>130</sup> A similar risk with a future COVID-19 vaccine would be concerning. Importantly, the typical participant in the recently published early phase trials of vaccines against SARS-CoV-2 was normal weight.<sup>131-133</sup> Although these trials have shown promising results, applying their findings to populations with high background prevalence of obesity – 40% in the United States, 29% in England and 13% globally – carries a degree of uncertainty which may hopefully be addressed in Phase 3 trials.

## 10 | BENEFITS OF WEIGHT LOSS

The benefits of weight-loss on complications of obesity, insulin resistance and systemic inflammation are well-documented, especially after bariatric surgery.<sup>134-136</sup> However, even short-term small amounts of weight-loss can show substantial metabolic benefits.<sup>137</sup> This is particularly important during the COVID-19 pandemic; it is essential that weight-loss is encouraged as a public health intervention, albeit even if only small changes are feasible. Healthcare professionals should discuss weight-loss goals and methods with patients with obesity; this can be done using virtual and telephonic consultations with the patient's own weighing scale as a reference. Patients should be encouraged to make lifestyle changes focused on nutritional modification, calorie restriction and augmentation of exercise; individualized approaches are likely to yield most benefit. Bariatric surgery should be considered where clinically appropriate as it leads to improvements in obesity-related metabolic comorbidities such as diabetes, hypertension, dyslipidaemia, insulin resistance and inflammation.<sup>136,138</sup> It slows the atherosclerotic process and reduces cardiovascular and all-cause mortality. Recent data have demonstrated regression of the microvascular complications of obesity and diabetes, including regeneration of small nerve fibres after bariatric surgery.<sup>138</sup> A recent consensus statement provides guidance on bariatric surgery during the COVID-19 pandemic.<sup>139</sup> With the current public awareness about the risks of death from COVID-19 in persons with obesity, there may be an added motivation for patients to partake in weight-loss programs. Conversely, this public awareness can provide a source of anxiety for these patients and therefore the benefits of any amount of weight-loss should be emphasized to patients to aid their general well-being.

## 11 | FUTURE RESEARCH DIRECTIONS

Our current understanding of obesity as an independent risk factor for severity of COVID-19 is borne out of observational studies.

Further research is necessary to better elucidate the cellular and molecular mechanisms that underlie this increased risk. Urgent research is also required into pharmacotherapeutics for COVID-19 in people with obesity to better understand efficacy and failure of antiviral drugs, immunotherapies and vaccines. Whether significant weight loss in people with obesity, particularly massive weight loss after bariatric surgery, influences outcomes of COVID-19 remains to be seen and needs further study. Ultimately, research into the biological, psychological, socio-cultural and economic drivers of obesity and its management are essential for building societal resilience to future pandemics.

## 12 | CONCLUSION

Obesity is a risk factor in viral pandemics and infected patients with obesity have a worse disease prognosis. COVID-19 is no exception and a report has just been published by Public Health England on the associations of excess weight with COVID-19.<sup>140</sup> During pandemics individuals with obesity should be included as one of the clinically vulnerable groups, especially those with morbid obesity (BMI > 40 kg/m<sup>2</sup>). Clinical trials of medicinal products should emphasize the inclusion of people with obesity to better understand the effects of obesity on pharmacokinetics. Further research into vaccination regimes is necessary to achieve and maintain better immune response in patients with obesity to subsequent virus exposure.

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### REFERENCES

1. Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev.* 2020;21(6):e13034. <https://doi.org/10.1111/obr.13034>.
2. Obesity and Overweight; 2020. Geneva: World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed May 3, 2020.
3. Fryar CD, Carroll MD, Ogden CL. *Prevalence of Overweight, Obesity, and Severe Obesity Among Adults Aged 20 and Over: United States,*

- 1960-1962 Through 2015-2016. Hyattsville, MD: NCHS Health E-Stats, CDC Stacks Public Health Publications; 2018. <https://stacks.cdc.gov/view/cdc/58670>. Accessed May 3, 2020.
4. Baker C. Obesity statistics. *Commons Research Briefing SN03336*. London: House of Commons Library; 2019 <https://commonslibrary.parliament.uk/research-briefings/sn03336/>. Accessed May 3, 2020.
  5. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395:470-473. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9).
  6. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270-273.
  7. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:1-10.
  8. Xie M, Chen Q. Insight into 2019 novel coronavirus – An updated interim review and lessons from SARS-CoV and MERS-CoV. *Int J Infect Dis*. 2020;94:119-124. <http://dx.doi.org/10.1016/j.ijid.2020.03.071>.
  9. Wang L, Wang Y, Ye D, Liu Q. A review of the 2019 novel coronavirus (COVID-19) based on current evidence. *Int J Antimicrob Agents*. 2020;55(6):105948. <https://doi.org/10.1016/j.ijantimicag.2020.105948>.
  10. Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5):2000547. <https://doi.org/10.1183/13993003.00547-2020>.
  11. Sorbello M, El-Boghdady K, Di Giacinto I, et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia*. 2020;75(6):724-732.
  12. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
  13. Adhikari SP, Meng S, Wu Y, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty*. 2020;9(1):29.
  14. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020;323(16):1574-1581.
  15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
  16. Petrilli CM, Jones S, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York city: prospective cohort study. *BMJ*. 2020;369:m1966. <https://doi.org/10.1136/bmj.m1966>.
  17. Herold T, Jurinovic V, Amreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol*. 2020;146(1):128-136. <http://dx.doi.org/10.1016/j.jaci.2020.05.008>.
  18. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. *China Intensive Care Med*. 2020;46(5):846-848.
  19. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062.
  20. Yang J, Zheng Y, Xi Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.
  21. Sattar N, McInnes IB, McMurray JJV. Obesity a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation*. 2020;142(1):4-6. <https://doi.org/10.1161/circulationaha.120.047659>.
  22. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)*. 2020;28(7):1195-1199. <https://doi.org/10.1002/oby.22831>.
  23. Huang R, Zhu L, Xue L, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multi-center study. *PLoS Neglected Tropical Diseases*. 2020;14 (5): e0008280. <http://dx.doi.org/10.1371/journal.pntd.0008280>.
  24. Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care*. 2020;43(7):1392-1398. <https://doi.org/10.2337/dc20-0576>.
  25. Kalligeros M, Shehadeh F, Mylona EK, et al. Association of obesity with disease severity among patients with COVID-19. *Obesity (Silver Spring)*. 2020;28(7):1200-1204. <https://doi.org/10.1002/oby.22859>.
  26. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-e25. <https://doi.org/10.1016/j.jinf.2020.04.021>.
  27. Huang R, Zhu L, Xue L, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multi-center study. *PLoS Negl Trop Dis*. 2020 May 8;14(5):e0008280. <http://dx.doi.org/10.1371/journal.pntd.0008280>.
  28. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985. <https://doi.org/10.1136/bmj.m1985>.
  29. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? *BMJ*. 2000;369:m1548.
  30. Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. *Lancet Respir Med*. 2020;8(6):547-548. [https://doi.org/10.1016/S2213-2600\(20\)30228-9](https://doi.org/10.1016/S2213-2600(20)30228-9).
  31. Gujral UP, Vittinghoff E, Mongraw-Chaffin M, et al. Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: a cross-sectional analysis of two cohort studies. *Ann Intern Med*. 2017;166(9):628-636. <https://doi.org/10.7326/M16-1895>.
  32. Kapoor N, Furler J, Paul TV, et al. Normal weight obesity: an under-recognized problem in individuals of South Asian descent. *Clin Ther*. 2019;41(8):1638-1642. <https://doi.org/10.1016/j.clinthera.2019.05.016>.
  33. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. *Prog Cardiovasc Dis*. 2014;56(4):426-433. <https://doi.org/10.1016/j.pcad.2013.10.003>.
  34. Franco LP, Morais CC, Cominetti C. Normal-weight obesity syndrome: diagnosis, prevalence, and clinical implications. *Nutr Rev*. 2016;74(9):558-570. <https://doi.org/10.1093/nutrit/nuw019>.
  35. Batsis JA, Sahakyan KR, Rodriguez-Escudero JP, Bartels SJ, Somers VK, Lopez-Jimenez F. Normal weight obesity and mortality in United States subjects  $\geq 60$  years of age (from the Third National Health and Nutrition Examination Survey). *Am J Cardiol*. 2013;112(10):1592-1598. <https://doi.org/10.1016/j.amjcard.2013.07.014>.
  36. Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. *Cell Metab*. 2017;26(2):292-300. <https://doi.org/10.1016/j.cmet.2017.07.008>.
  37. Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinol*. 2020;8(7):616-627.
  38. Moser JS, Galindo-Fraga A, Ortiz-Hernández AA, et al. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. *Influenza Other Respi Viruses*. 2019;13(1):3-9.
  39. Van Kerkhove MD, Vandemaële KAH, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med*. 2011;8(7):e1001053.

40. Almond MH, Edwards MR, Barclay WS, Johnston SL. Obesity and susceptibility to severe outcomes following respiratory viral infection. *Thorax*. 2013;68:684-686.
41. Cocoros NM, Lash TL, DeMaria A Jr, Klompas M. Obesity as a risk factor for severe influenza-like illness. *Influenza Other Respi Viruses*. 2014;8(1):25-32.
42. Louie JK, Acosta M, Samuel MC, et al. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza a (H1N1). *Clin Infect Dis*. 2011;52(3):301-312.
43. Fezeu L, Julia C, Henegar A, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. *Obes Rev*. 2011;12(8):653-659.
44. Fuhrman C, Bonmarin I, Bitar D, et al. Adult intensive-care patients with 2009 pandemic influenza A (H1N1) infection. *Epidemiol Infect*. 2011;139:1202-1209.
45. Maccioni L, Weber S, Elgizouli M, et al. Obesity and risk of respiratory tract infections: results of an infection-diary based cohort study. *BMC Public Health*. 2018;18(1):271.
46. Smith AG, Sheridan PA, Harp JB, et al. Diet-induced obese mice have increased mortality and altered immune responses when infected with influenza virus. *J Nutr*. 2007;137:1236-1243.
47. Murphy R, Fragaszy EB, Hayward AC, Warren-Gash C. Investigating obesity as a risk factor for influenza-like illness during the 2009 H1N1 influenza pandemic using the Health Survey for England. *Influenza Other Respi Viruses*. 2017;11:66-73.
48. Rello J, Rodriguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by influenza A (H1N1)v in Spain. *Crit Care*. 2009;13(5):R148.
49. Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax*. 2010;65(1):44-50.
50. De Jong A, Verzilli D, Jaber S. ARDS in obese patients: specificities and management. *Crit Care*. 2019;23(1):74.
51. Akinnusi ME, Pineda LA, El Solh AA. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. *Crit Care Med*. 2008;36(1):151-158.
52. Martino JL, Stapleton RD, Wang M, et al. Extreme obesity and outcomes in critically ill patients. *Chest*. 2011;140(5):1198-1206.
53. O'Brien JM Jr, Philips GS, Ali NA, Aberegg SK, Marsh CB, Lemeshow S. The association between body mass index, processes of care, and outcomes from mechanical ventilation: a prospective cohort study. *Crit Care Med*. 2012;40(5):1456-1463.
54. Wardell S, Wall A, Bryce R, Gjevrev JA, Laframboise K, Reid JK. The association between obesity and outcomes in critically ill patients. *Can Respir J*. 2015;22(1):23-30.
55. Tafelski S, Yi H, Ismael F, Krannich A, Spies C, Nachtigall I. Obesity in critically ill patients is associated with increased need of mechanical ventilation but not with mortality. *J Infect Public Health*. 2016;9(5):577-585.
56. Zhi G, Xin W, Ying W, Guohong X, Shuying L. "Obesity paradox" in acute respiratory distress syndrome: a systematic review and meta-analysis. *PLoS One*. 2016;11(9):e0163677.
57. Malhotra A, Hillman D. Obesity and the lung: 3. Obesity, respiration and intensive care. *Thorax*. 2008;63(10):925-931.
58. Peppard PE, Young T, Barnett JH, Palta M, Hagen EW, Hla KM. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284:3015-3021.
59. Peters U, Dixon AE. The effect of obesity on lung function. *Expert Rev Respir Med*. 2018;12(9):755-767.
60. Shailaja S, Nichelle SM, Shetty AK, Hegde BR. Comparing ease of intubation in obese and lean patients using intubation difficulty scale. *Anesth Essays Res*. 2014;8(2):168-174. <https://doi.org/10.4103/0259-1162.134493>.
61. Schetz M, De Jong A, Deane AM, et al. Obesity in the critically ill: a narrative review. *Intensive Care Med*. 2019;45:757-769.
62. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168.
63. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med*. 2020;8:506-517.
64. De Jong A, Molinari N, Sebbane M, et al. Feasibility and effectiveness of prone position in morbidly obese patients with ARDS: a case-control clinical study. *Chest*. 2013;143:1554-1561.
65. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020;12(1):8. <https://doi.org/10.1038/s41368-020-0074-x>.
66. Monteil VKH, Prado P, Hagelkrüys A, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*. 2020;181(4):905-913.e7. <https://doi.org/10.1016/j.cell.2020.04.004>. Accessed April 24, 2020.
67. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120-128. <https://doi.org/10.1056/NEJMoa2015432>.
68. Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. *Curr Opin Hematol*. 2013;20(5):437-444. <https://doi.org/10.1097/MOH.0b013e3283634443>.
69. 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(4):844-847. <https://doi.org/10.1111/jth.14768>.
70. Marietta M, Coluccio V, Luppi M. COVID-19, coagulopathy and venous thromboembolism: more questions than answers. *Intern Emerg Med*. 2020;1-13. <https://doi.org/10.1007/s11739-020-02432-x>. [Epub ahead of print].
71. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: a plasmin paradox. *J Thromb Haemost*. 2020. <https://doi.org/10.1111/jth.14960>. [Epub ahead of print].
72. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. Geneva: World Health Organization. 2020; <https://apps.who.int/iris/handle/10665/331446>. Accessed May 3, 2020.
73. Viecca M, Radovanovic D, Forleo GB, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. *Pharmacol Res*. 2020;158:104950. <https://doi.org/10.1016/j.phrs.2020.104950>.
74. Cardone M, Yano M, Rosenberg AS, Puig M. Lessons learned to date on COVID-19 hyperinflammatory syndrome: considerations for interventions to mitigate SARS-CoV-2 viral infection and detrimental hyperinflammation. *Front Immunol*. 2020;11:1131.
75. Chiappetta S, Sharma AM, Bottino V, et al. COVID-19 and the role of chronic inflammation in patients with obesity. *Int J Obes (Lond)*. 2020;44:1790-1792.
76. Frydrych LM, Bian G, O'Lone DE, Ward PA, Delano MJ. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. *J Leukoc Biol*. 2018;104:525-534.
77. Zhou H, Liu F. Regulation, communication, and functional roles of adipose tissue-resident CD4+ T cells in the control of metabolic homeostasis. *Front Immunol*. 2018;9:1961.
78. Liu R, Nikolajczyk BS. Tissue immune cells fuel obesity-associated inflammation in adipose tissue and beyond. *Front Immunol*. 2019;10:1587.
79. Misumi I, Starmer J, Uchimura T, Beck MA, Magnuson T, Whitmire JK. Obesity expands a distinct population of T cells in adipose tissue and increases vulnerability to infection. *Cell Rep*. 2019;27(2):514-524.e5.

80. Zhu L, Yang P, Zhao Y, et al. Single-cell sequencing of peripheral blood mononuclear cells reveals distinct immune response landscapes of COVID-19 and influenza patients. *Immunity*. 2020;51074-7613(20)30316-2. <https://doi.org/10.1016/j.immuni.2020.07.009>. [Epub ahead of print].
81. Juno JA, Tan H, Lee WS, et al. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. *Nat Med*. 2020 Jul 13. <https://doi.org/10.1038/s41591-020-0995-0>. [Epub ahead of print].
82. Le Bert N, Tan AT, Kunasegaran K, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature*. 2020 Jul 15. <https://doi.org/10.1038/s41586-020-2550-z>. [Epub ahead of print].
83. Altmann DM, Boyton RJ. SARS-CoV-2 T cell immunity: specificity, function, durability, and role in protection. *Sci Immunol*. 2020;5(49):eabd6160. <https://doi.org/10.1126/sciimmunol.abd6160>.
84. Heinonen S, Saarinen L, Naukkarinen J, et al. Adipocyte morphology and implications for metabolic derangements in acquired obesity. *Int J Obes (Lond)*. 2014;38(11):1423-1431.
85. de Oliveira LV, Mafra D. Adipokines in obesity. *Clin Chim Acta*. 2013;419:87-94.
86. Stapleton RD, Dixon AE, Parsons PE, Ware LB, Suratt BT, NHLBI Acute Respiratory Distress Syndrome Network. The association between BMI and plasma cytokine levels in patients with acute lung injury. *Chest*. 2010;138(3):568-577.
87. Gajic O, Dabbagh O, Park PK, et al. (USCIITG-LIPS). Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011;183(4):462-470.
88. Oral EA, Javor ED, Ding L, et al. Leptin replacement therapy modulates circulating lymphocyte subsets and cytokine responsiveness in severe lipodystrophy. *J Clin Endocrinol Metab*. 2006;91(2):621-628.
89. Mancuso P. Obesity and respiratory infections: does excess adiposity weigh down host defense. *Pulm Pharmacol Ther*. 2013;26(4):412-419.
90. Tsiotra PC, Pappa V, Raptis SA, Tsigos C. Expression of the long and short leptin receptor isoforms in peripheral blood mononuclear cells: implications for leptin's actions. *Metabolism*. 2000;49(12):1537-1541.
91. Papatheanassoglou E, El-Haschimi K, Li XC, Matarese G, Strom T, Mantzoros C. Leptin receptor expression and signaling in lymphocytes: kinetics during lymphocyte activation, role in lymphocyte survival, and response to high fat diet in mice. *J Immunol*. 2006;176(12):7745-7752.
92. Nave H, Mueller G, Siegmund B, et al. Resistance of Janus kinase-2 dependent leptin signaling in natural killer (NK) cells: a novel mechanism of NK cell dysfunction in diet-induced obesity. *Endocrinology*. 2008;149(7):3370-3378.
93. Ahl S, Guenther M, Zhao S, et al. Adiponectin levels differentiate metabolically healthy vs unhealthy among obese and nonobese white individuals. *J Clin Endocrinol Metab*. 2015;100(11):4172-4180. <https://doi.org/10.1210/jc.2015-2765>.
94. Ohashi K, Parker JL, Ouchi N, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J Biol Chem*. 2010;285(9):6153-6160.
95. Walkey AJ, Rice TW, Konter J, et al. Plasma adiponectin and mortality in critically ill subjects with acute respiratory failure. *Crit Care Med*. 2010;38(12):2329-2334.
96. Summer R, Little FF, Ouchi N, et al. Alveolar macrophage activation and an emphysema-like phenotype in adiponectin-deficient mice. *Am J Physiol Lung Cell Mol Physiol*. 2008;294(6):L1035-L1042.
97. Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. *Nat Rev Endocrinol*. 2020;16(7):341-342. <https://doi.org/10.1038/s41574-020-0364-6>.
98. Stern JH, Rutkowski JM, Scherer PE. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell Metab*. 2016;23(5):770-784. <https://doi.org/10.1016/j.cmet.2016.04.011>.
99. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744.
100. Ho JH, Adam S, Azmi S, et al. Male sexual dysfunction in obesity: the role of sex hormones and small fibre neuropathy. *PLoS One*. 2019;14(9):e0221992.
101. Montano LM, Espinoza J, Flores-Soto E, Chavez J, Perusquia M. Androgens are bronchoactive drugs that act by relaxing airway smooth muscle and preventing bronchospasm. *J Endocrinol*. 2014;222(1):1-13. <https://doi.org/10.1530/JOE-14-0074>.
102. Mohamad NV, Wong SK, Hasan WNW, et al. The relationship between circulating testosterone and inflammatory cytokines in men. *Aging Male*. 2019;22(2):129-140. <https://doi.org/10.1080/13685538.2018.1482487>.
103. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and Baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol*. 2009;54(10):919-927. <https://doi.org/10.1016/j.jacc.2009.04.078>.
104. Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. *J Am Acad Dermatol*. 2020;83(1):308-309. <https://doi.org/10.1016/j.jaad.2020.04.032>.
105. Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *EMBO J*. 2020;39(10):e105114. <https://doi.org/10.15252/emj.20105114>.
106. Kyriacou A, Kyriacou A, Makris KC, Syed AA, Perros P. Weight gain following treatment of hyperthyroidism – a forgotten tale. *Clin Obes*. 2019;9(5):e12328. <https://doi.org/10.1111/cob.12328>.
107. Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid obesity. *Thyroid*. 2006;16(1):73-78. <https://doi.org/10.1089/thy.2006.16.73>.
108. Iervasi G, Molinaro S, Landi P, et al. Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med*. 2007;167(14):1526-1532. <https://doi.org/10.1001/archinte.167.14.1526>.
109. Friberg L, Werner S, Eggertsen G, Ahnve S. Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina? *Arch Intern Med*. 2002;162(12):1388-1394. <https://doi.org/10.1001/archinte.162.12.1388>.
110. Kaptein EM, Beale E, Chan LS. Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. *J Clin Endocrinol Metab*. 2009;94(10):3663-3675. <https://doi.org/10.1210/jc.2009-0899>.
111. Amin A, Chitsazan M, Taghavi S, Ardeshiri M. Effects of triiodothyronine replacement therapy in patients with chronic stable heart failure and low-triiodothyronine syndrome: a randomized, double-blind, placebo-controlled study. *ESC Heart Fail*. 2015;2(1):5-11. <https://doi.org/10.1002/ehf2.12025>.
112. Syed AA, Weaver JU. Glucocorticoid sensitivity: the hypothalamic-pituitary-adrenal-tissue axis. *Obes Res*. 2005;13(7):1131-1133. <https://doi.org/10.1038/oby.2005.132>.
113. Wester VL, Staufenbiel SM, Veldhorst MAB, et al. Long-term cortisol levels measured in scalp hair of obese patients. *Obesity (Silver Spring)*. 2014;22(9):1956-1958. <https://doi.org/10.1002/oby.20795>.
114. Jackson SE, Kirschbaum C, Steptoe A. Hair cortisol and adiposity in a population-based sample of 2,527 men and women aged 54 to

- 87 years. *Obesity (Silver Spring)*. 2017;25(3):539-544. <https://doi.org/10.1002/oby.21733>.
115. Pal R. COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. *Endocrine*. 2020;68(2):251-252. <https://doi.org/10.1007/s12020-020-02325-1>.
  116. Wheatland R. Molecular mimicry of ACTH in SARS – implications for corticosteroid treatment and prophylaxis. *Med Hypotheses*. 2004; 63(5):855-862. <https://doi.org/10.1016/j.mehy.2004.04.009>.
  117. Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(8):659–660. [https://doi.org/10.1016/S2213-8587\(20\)30216-3](https://doi.org/10.1016/S2213-8587(20)30216-3).
  118. The RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. *N Eng J Med*. 2020 Jul 17;NEJMoa2021436. <https://doi.org/10.1056/NEJMoa2021436>. [Epub ahead of print].
  119. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients*. 2020;12(4):1181. <https://doi.org/10.3390/nu12041181>.
  120. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12(4):988. <https://doi.org/10.3390/nu12040988>.
  121. 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(4):341-349. <https://doi.org/10.1111/obr.12239>.
  122. Fox A, Slater C, Ahmed B, et al. Vitamin D status after gastric bypass or sleeve gastrectomy over 4 years of follow-up. *Obes Surg*. 2020;30(4):1473-1481. <https://doi.org/10.1007/s11695-019-04318-0>.
  123. Hastie CE, Mackay DF, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr*. 2020;14(4):561-565. <https://doi.org/10.1016/j.dsx.2020.04.050>.
  124. Lee J, Van Hecke O, Roberts N. Vitamin D: A rapid review of the evidence for treatment or prevention in COVID-19. Oxford: Centre for Evidence-Based Medicine, The University of Oxford. 2020. <https://www.cebm.net/covid-19/vitamin-d-a-rapid-review-of-the-evidence-for-treatment-or-prevention-in-covid-19/> Accessed June 1, 2020.
  125. Covid 19 rapid evidence summary: vitamin D for covid-19 evidence summary. London: National Institute for Health and Care Excellence. 2020.; <https://www.nice.org.uk/advice/es28/evidence>. Accessed July 1, 2020.
  126. SACN *vitamin D and health report*. London: Scientific Advisory Committee on Nutrition. 2016; <https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report>. Accessed May 3, 2020.
  127. Syed AA, Soran H, Adam S. Obesity and Covid-19: the unseen risks. *BMJ*. 2020;370:m2823. <https://doi.org/10.1136/bmj.m2823>.
  128. Morrish GA, Green B, Pai MP. The effects of obesity on drug pharmacokinetics in humans. *Expert Opin Drug Metab Toxicol*. 2011;7(6): 697-706.
  129. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes (Lond)*. 2012;36(8):1072-1077.
  130. Green WD, Beck MA. Obesity impairs the adaptive immune response to influenza virus. *Ann Am Thorac Soc*. 2017;14(suppl 5):S406-S409.
  131. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet*. 2020;396(10249):467–478. [https://doi.org/10.1016/S0140-6736\(20\)31604-4](https://doi.org/10.1016/S0140-6736(20)31604-4).
  132. Zhu FC, Li YH, Guan XH, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet*. 2020;395(10240):1845-1854.
  133. Jackson LA, Anderson EJ, Roupheal NG, et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. *N Engl J Med*. 2020 Jul 14;NEJMoa2022483. <https://doi.org/10.1056/NEJMoa2022483>. [Epub ahead of print].
  134. Yadav R, Hama S, Liu Y, et al. Effect of Roux-en-Y bariatric surgery on lipoproteins, insulin resistance, and systemic and vascular inflammation in obesity and diabetes. *Front Immunol*. 2017;8:1512.
  135. Adam S, Liu Y, Siahmansur T, et al. Bariatric surgery as a model to explore the basis and consequences of the Reaven hypothesis: small, dense low-density lipoprotein and interleukin-6. *Diab Vasc Dis Res*. 2019;16(2):144-152. <https://doi.org/10.1177/1479164119826479>.
  136. Ammori BJ, Skarulis MC, Soran H, Syed AA, Eledrisi M, Malik RA. Medical and surgical management of obesity and diabetes: what's new? *Diabet Med*. 2020;37(2):203-210. <https://doi.org/10.1111/dme.14215>.
  137. Magkos F, Fraterrigo G, Yoshino J, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab*. 2016;23(4): 591-601.
  138. Iqbal Z, Adam S, Ho JH, et al. Metabolic and cardiovascular outcomes of bariatric surgery. *Curr Opin Lipidol*. 2020;31(4):246-256.
  139. Rubino F, Cohen RV, Mingrone G, et al. Bariatric and metabolic surgery during and after the COVID-19 pandemic: DSS recommendations for management of surgical candidates and postoperative patients and prioritisation of access to surgery. *Lancet Diabetes Endocrinol*. 2020;8(7):640–648.
  140. Excess weight and COVID-19: insights from new evidence. London: Public Health England. 2020. <https://www.gov.uk/government/publications/excess-weight-and-covid-19-insights-from-new-evidence>. Accessed July 24, 2020.

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