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benefit from ECMO, understanding that these modified referral criteria are not absolute but part of a dynamic shared decision-making process between the referring team and the ECMO service.

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## Potential pathophysiology of COVID-19 in patients with obesity. Comment on *Br J Anaesth* 2020; 125: e262–e263

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Editor—We read with great interest the correspondence of Memtsoudis and colleagues,<sup>1</sup> which reported an over-prevalence of obesity amongst both critically ill coronavirus disease 2019 (COVID-19) patients with respiratory failure admitted to the ICU and severely ill patients not admitted to the ICU. The authors suggested that obstructive sleep apnoea-associated baseline inflammation and generation of intrathoracic shear forces could explain the co-occurrence of obesity and severe-to-critical COVID-19 disease. We commend the authors for their novel contribution to the evolving literature on COVID-19 and its potential risk factors and pathophysiology. We wish to further propose several pathophysiological pathways that may explain the disproportionate incidence of adverse outcomes amongst obese COVID-19 patients.

Preliminary studies suggest a strong association between obesity and COVID-19 mortality and morbidity. An unpublished observational cohort study of 16 749 COVID-19 patients in the UK found that obese patients were 37% more likely to die

in-hospital than non-obese patients after adjusting for comorbidities and patient characteristics (preprint data available from <https://www.medrxiv.org/content/10.1101/2020.04.23.20076042v1>). Amongst a cohort of 383 COVID-19 patients in Shenzhen, China, patients identified as obese had a 142% higher risk of developing severe pneumonia compared with non-obese patients.<sup>2</sup> The Intensive Care National Audit & Research Centre report on COVID-19 in critical care showed that the distribution of BMI of COVID-19 patients matched that of the general population, suggesting that obesity is likely not linked to severe COVID-19 infection requiring an ICU admission.<sup>3</sup> However, the report does support evidence of an increased risk of death amongst obese patients admitted to the ICU. Obesity should at least be viewed as a potential risk factor for severe COVID-19 manifestations or worse outcomes, and clinicians and scientists should gain a better understanding of the possible mechanistic role obesity plays in the pathogenesis of COVID-19.<sup>4,5</sup>

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters human cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor.<sup>6</sup> This receptor is

expressed in heart, lungs, kidneys, and intestines, thereby providing a multimodal entry point for the virus to infiltrate the body. Preliminary unpublished data indicate that ACE-2 receptor concentrations are higher in adipose tissue in comparison with lung tissue, suggesting that adipose tissue might be vulnerable to SARS-CoV-2 infection (preprint data available from <https://www.preprints.org/manuscript/202002.0315/v1>). This presents a risk for adverse outcomes for obese patients with more adipose tissue and a greater number of ACE-2 receptors in comparison with their non-obese counterparts.

Alterations of adipose tissue distribution and function linked to obesity have been shown to promote production of pro-inflammatory cytokines and induce chronic systemic inflammation.<sup>7</sup> Increased production and release of cytokines further exacerbates activation of kinase receptors, triggering a positive feedback loop of inflammation and metabolic dysfunction. Amongst obese patients with COVID-19, this heightened inflammatory response may put them at greater risk for a cytokine storm, an over-response of the immune system characterised by uncontrolled release and attack of cytokines on the body's own tissues and organs. Although obesity-specific clinical data are lacking, general findings provide evidence supporting the cytokine storm concept with COVID-19 non-survivors having significantly higher concentrations of interleukin-6, a pro-inflammatory cytokine that regulates homeostasis and inflammation, compared with survivors.<sup>8</sup> Research will need to explore these mechanisms in the context of the obesity paradox, the epidemiologically observed inverse relationship between obesity and mortality amongst select medical and surgical populations (interestingly, with surgery being a pro-inflammatory event).<sup>9</sup>

Furthermore, it is well documented that elevated concentrations of inflammatory biomarkers amongst obese patients are linked to increased risk of co-morbidities, including cardiovascular disease, diabetes mellitus, metabolic syndrome, and liver disease.<sup>7</sup> The presence of these co-morbidities in COVID-19 patients has been shown to be associated with greater vulnerability to multi-organ injuries.<sup>10</sup> Ultimately, many patients die from complications that stem from these underlying illnesses, providing yet another reason for clinicians to be hyper vigilant when treating and monitoring obese patients with COVID-19.

As research surrounding COVID-19 continues to evolve, it is crucial to consider obesity as a potential risk factor for adverse outcomes. A better understanding of the pathophysiological contributors linking obesity with severe-to-critical COVID-19 disease will not only help inform

medical management of obese patients, but also aid in the development of successful therapeutics to prevent and treat COVID-19.

## Declarations of interest

The authors declare that they have no conflicts of interest.

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## Videolaryngoscopy for tracheal intubation in patients with COVID-19

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