

# Metabolic health and lifestyle medicine should be a cornerstone of future pandemic preparedness

The recent impact of SARS-CoV-2 and coronavirus disease 2019 (COVID-19) has shown major differences in infrastructure and approach across healthcare systems worldwide. One thing we can already be certain of is that governments and policy makers worldwide will place a greater focus on pandemic preparedness in the future. However, as well as ensuring that robust pipelines for rapid test, highly effective treatment or vaccine, and personal protective equipment (PPE) production are in place, we must address underlying resilience and susceptibility of our populations to infectious disease. Although the true spread and case fatality rate of SARS-CoV-2 may not be known for several months or even years, what is becoming increasingly clear is the significant degree to which underlying conditions associated with suboptimal metabolic health appear to be associated with poor outcomes in those with COVID-19.<sup>1-4</sup> Considering the nature of these underlying conditions such as obesity and hypertension, lifestyle-based approaches are likely to be one of our best tools in order to address ongoing and future disease burden during pandemics.

Based on the largest available studies at time of writing, the comorbidities particularly associated with hospitalization and poor outcome in patients with COVID-19 are age, obesity, hypertension, and diabetes. For instance, one study in New York City found that, of 5700 patients hospitalized with COVID-19, 57%, 42%, and 34% had hypertension, obesity, and diabetes, respectively.<sup>1</sup> Of 72 314 cases from the Chinese Center for Disease Control and Prevention, reported case fatality rate was elevated in those with comorbid conditions: at least 10% for cardiovascular diseases, 7% for diabetes, and 6% for hypertension.<sup>2</sup> Importantly, however, the diabetes diagnoses associated with increased risk have not routinely been separated by type (1 or 2) or duration, and this is a key area of future research. As outlined below, with metabolic derangement (eg, systemic insulin resistance) and hyperglycemia potentially underlying changes in the immune system seen in the comorbid conditions associated with worse COVID-19 outcome, it is possible that the well-controlled type 1 diabetic is not at increased risk. In studies of COVID-19 patients requiring invasive mechanical ventilation in Italy and New York City, the latter as a preprint at time of writing, both age and obesity were significant contributors to risk, with the mechanical disadvantage of ventilation in obese patients a potential contributor.<sup>3,4</sup> In the United Kingdom, the

Office of National Statistics (ONS) reported that the most common comorbid condition in COVID-19 deaths was ischemic heart disease,<sup>5</sup> which is also tightly associated with obesity, metabolic syndrome, and glycemic control.<sup>6-9</sup> Similarly, a report from the Intensive Care National Audit and Research Centre (ICNARC) on 8 May 2020 stated that of the first 8250 critically ill COVID-19 cases in the United Kingdom (64% of whom required mechanical ventilation within 24 h of admission), 73% were overweight or obese, which was significantly greater than the 60% of critically ill historical controls admitted for viral pneumonia ( $P < .001$ , Chi-squared test by authors).<sup>10</sup>

A major driver of morbidity and mortality in those at risk appears to be a dysregulated immune response characterized by lymphopenia and an associated "cytokine" storm.<sup>11-14</sup> This cytokine storm is typically associated markedly higher levels of cytokines such as IL-6, IL-10, and TNF- $\alpha$ , as well as elevated lactate dehydrogenase (LDH) and C-reactive protein,<sup>11,14</sup> which may reflect systemic injury responses as well as both direct (eg, myocarditis) and indirect injury to the heart<sup>15,16</sup> and lungs.<sup>17</sup> As we learn more, it seems likely that the COVID-19 cytokine storm is at least partly rooted in the immune dysregulation seen as a result of metabolic disease, a phenomenon explored in the burgeoning field of "immunometabolism."<sup>18</sup> These changes include a shift toward greater innate immune responses, relative lymphopenia, and a decrease in the balance of the T-helper (Th) system of cytokines resulting in reduced Th1-type cytokines and increased Th2-type cytokines.<sup>19</sup> These changes are associated both the with ongoing disease process as well as periods of acute hyperglycaemia.<sup>19-21</sup> Though the Th1/Th2 classification is oversimplified, and cytokines from both branches are increased in COVID-19, it has been hypothesized that relative increases in the Th2 response contribute in inhibition of inflammatory resolution in severe COVID-19.<sup>22</sup> Hyperactivation of the Th2 system is thought to underlie the increase in mortality seen in mice who received a prototype vaccine for the related SARS-CoV-1 virus and were then exposed to a viral challenge.<sup>23</sup> The preclinical literature has also documented the course of the immune response to viral challenge in rodents with diet-induced obesity, with influenza A as the model infection.<sup>24</sup> At baseline, obese mice have higher levels of pro-inflammatory cytokines in the lungs, but they display as slower initial immune response that results in a higher overall viral

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load and increased inflammatory response later on in the course of the infection.<sup>24</sup> This potentially explains the anecdotal reports of COVID-19 progression occurring in two phases, with an initial brief resolution of certain symptoms followed by a later significant deterioration.

Another critical aspect of immune overactivation in severe COVID-19 appears to be involvement of the NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome, one of many inflammasomes that make up the innate immune system.<sup>25</sup> Tonic NLRP3 activation increases in the elderly and is also associated with the progression and severity of obesity and other metabolic diseases.<sup>22</sup> Activation of NLRP3 during the immune response drives a necrotic-type cell death known as pyroptosis, one hallmark of which is the release of intracellular LDH.<sup>26</sup> As increased LDH is seen in severe COVID-19, this has led many to suggest that NLRP3 overactivation and pyroptosis, particularly in the respiratory tissues, is a significant contributor to COVID-19 morbidity.<sup>17</sup> Overactivation of the NLRP3 pathway may also partly explain why males appear to be at greater risk for poor COVID-19 outcomes<sup>1,27,28</sup>; in older adults, a greater activation of the innate immune system, including the nucleotide-binding oligomerization domain (NOD) pathway of which NLRP3 is a subset, is seen in males compared to females.<sup>29</sup>

Though the diseases associated with worse outcome are based on specific diagnostic criteria, it is likely that these immunometabolic changes lie along a continuum as health changes over time. Considering that recent estimates in the United States suggest that less than 20% of adults have optimal metabolic health,<sup>30</sup> a sliding scale exists that could still place the majority of adults at some degree of increased risk of susceptibility to certain infectious diseases. More broadly, the comorbidities associated with increased risk of severe COVID-19 can also all be characterized as having the presence of low-grade chronic inflammation,<sup>31-34</sup> as well as the presence of many of the hallmarks of aging,<sup>35</sup> which together are pathognomonic for the process of "inflammaging."<sup>36,37</sup> Indeed, a group of researchers with significant experience in the field of aging and biomarkers of biological age have released a preprint proposing that COVID-19 is an emergent disease of aging.<sup>38</sup> Previous studies of patients with the related SARS-CoV-1 and MERS (Middle East Respiratory Syndrome) coronaviruses also suggest that in addition to age, similar comorbidities to those that predispose to worse outcomes in COVID-19 played a role in mortality risk.<sup>39-42</sup> During the unrelated Influenza A (H1N1) pandemic, both obesity and hypertension were also identified as risk factors for poor outcome.<sup>43,44</sup> Both preclinical models and clinical data from the H1N1 pandemic also suggest that diabetes, particularly when associated with hyperglycemia and glycemic variability, is associated with worse outcomes after infection with influenza.<sup>45,46</sup> Glycemic variability has similarly been found to be associated with outcomes in type 2 diabetics with COVID-19.<sup>47</sup> This suggests that regardless of the virus type, taking steps to improve population metabolic and immune health will play a crucial role in reducing the impact of future pandemics. Though they are clearly important in the current SARS-CoV-2 pandemic, in the context of long-term population health, the diseases associated with inflammaging and poor metabolic health should become a key focus as

we prepare for future pandemics, which are most likely to be due to a strain of influenza.<sup>48</sup>

A ray of hope for those hoping to improve health and reduce risk at the population level is the fact that the majority of at-risk comorbidities are thought to be largely driven by lifestyle factors, with lifestyle-based interventions such as lifestyle medicine having a rapidly expanding evidence base to support their use as the cornerstone of disease treatment, prevention, and reversal.<sup>49</sup> Even age, traditionally thought to be an unmodifiable risk factor for disease and mortality, may be partially modifiable, with biological age and immune age superseding chronological age as predictors of outcome.<sup>50-52</sup> Increased relative biological age, which can be inferred from a number of potential biomarkers, is tightly linked to lifestyle factors such as smoking, being sedentary, excessive alcohol intake, and a poor-quality diet.<sup>51-54</sup>

Regardless whether the exact underlying mechanisms are currently understood, it is clear that the tenets of lifestyle medicine have extraordinary power to improve the health of the population, both overall as well as in the face of unknown future pandemics. For instance, a wide variety of dietary approaches have been shown to be effective in providing long-term weight loss, reductions in blood pressure, improved glycemic control, and even reversal of type 2 diabetes. These include the dietary approaches to stop hypertension (DASH) and Mediterranean diets.<sup>55,56</sup> More severe disease may benefit from more restrictive approaches for a short period, including low-fat whole food plant-based diets, low-carbohydrate ketogenic diets, and severe caloric restriction.<sup>57-59</sup> Time-restricted eating may also be beneficial by increasing the fasting window and spontaneously improving diet quality and reducing caloric intake.<sup>60</sup> Importantly, if long-term improvements in weight and metabolic health are the goal, any and all of these dietary tools should remain in our toolkit based on the disease and individual patient, avoiding tacit ideological support of any single approach. In addition to larger dietary changes, targeted approaches to nutrient status may also be beneficial, with two reports (with one only available as a conference abstract) suggesting at least of 90% acute respiratory distress syndrome (ARDS) cases have Vitamin D deficiency.<sup>61,62</sup> Multiple recent preprints have also suggested vitamin D deficiency/insufficiency being associated with worse outcomes in COVID-19, with the greatest benefit seemingly being associated with vitamin D levels above 30 ng/mL (75 nmol/L).<sup>63-66</sup> Although randomized controlled trials of vitamin D supplementation in those who are deficient do seem to reduce the incidence of acute respiratory tract infections,<sup>67</sup> supplementation with vitamin D in critically ill patients at high risk of mortality does not appear to be beneficial after admission to intensive care.<sup>68</sup> An increased prevalence of vitamin D deficiency may partly explain the higher COVID-19 risk seen in BAME (Black, Asian, and Minority Ethnic) populations, who are at greater risk of Vitamin D deficiency in northern latitudes as well as being at greater risk of metabolic disease.<sup>69-71</sup> In the United Kingdom, this apparent increase in COVID-19 risk in BAME populations, as well as the apparent overrepresentation of those from BAME backgrounds in the death toll of the UK healthcare workers, has resulted in significant and much-needed funding from the National Institute for Health Research (NIHR) and the UK Research and Innovation (UKRI) for

research examining the associations between ethnicity and COVID-19 outcome.<sup>72</sup> As information on the demographics associated with poor COVID-19 outcomes will only continue to increase and evolve, platforms such as OpenSAFELY and the Oxford rapid COVID-19 Evidence Service will remain crucial to ongoing data collection and understanding of those at greater risk, and potential reasons why.<sup>73,74</sup>

Beyond diet, regular movement is associated with significant improvements in glycemic control, often independent of weight loss. Importantly, this does not need to be a daunting task. Coined by Francois et al in 2014,<sup>75</sup> small regular movement or exercise “snacks” (eg, 2-6 min of simple movement every 30-60 min or before meals) are associated with improved glycemic control, including when compared to energy-matched long single training sessions.<sup>76</sup> Simple walking is also associated with decreased mortality that plateaus around 10 000 steps per day.<sup>77</sup> Beyond that, both resistance training (and resulting improvements in strength and muscle mass) and aerobic exercise are associated with reduced risk of obesity, hypertension, metabolic disease, and survival after critical illness.<sup>78-82</sup> Lifestyle medicine also has significant scope to improve sleep quantity and quality, both of which are associated with immune function and overall mortality.<sup>83-86</sup> Initiatives such as group consultations and social prescribing can even help to tackle loneliness and social isolation, which are associated with both altered inflammatory processes and increased mortality.<sup>87-89</sup> The majority of lifestyle medicine interventions can also be implemented and tracked using simple telemedicine and digital health solutions. These have become increasingly prevalent in the modern healthcare system, with a further increase due to social distancing during COVID-19, and are likely to become a cornerstone of future health care as a result, particularly for vulnerable populations.

As the SARS-CoV-2 pandemic curve appears to be flattening in many countries, the priority is to ensure that developing nations are supported in their response to the first wave, whereas surveillance and a heightened test, track, and trace strategy anticipate and mitigate further waves. There will be an increased interest in planning for future pandemics to reduce the likelihood of healthcare systems becoming overwhelmed with patients such that care needs to be rationed,<sup>90</sup> with the attendant risk of accentuating inequality in access to adequate healthcare.<sup>91</sup> Although improving essential infrastructure will be an important aspect of this planning, proactively improving population health will also be crucial in order to minimize the future burden on health care during a pandemic. Lifestyle medicine is poised to be at the forefront of these efforts and should be increasingly promoted as part of healthcare policy in order to improve the resiliency and health of the population in an unknowable future.

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#### CONFLICT OF INTEREST

TRW is a director of the British Society of Lifestyle Medicine.

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