The role of the exposome in promoting resilience or susceptibility after SARS-CoV-2 infection

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To the Editor:

One of the more perplexing aspects of the recent SARS-CoV-2 pandemic is the high level of variability among patients in terms of disease severity. It is currently unclear why some patients remain largely asymptomatic, while others require intensive care. A key factor in determining variations in disease severity may be the exposome, or measure of all exposures across an individual's lifetime (environmental toxins, pharmacological treatments, lifestyle, diet, etc.) (Fig. 1). Sequence similarities between SARS-CoV-2, the infectious agent behind the Coronavirus Disease 2019 (COVID-19) pandemic, and other coronaviruses indicate that SARS-CoV-2 spike protein binds to human angiotensin converting enzyme 2 (ACE2) as the virus receptor for entry [1]. ACE2 belongs to the ACE family of dipeptidyl carboxydipeptidases and is expressed in epithelial cells of the lungs, intestine, kidney, brain, and blood vessels [1–3]. Given the ubiquitous distribution of ACE2 throughout the host, increases in ACE2 receptor expression may potentially result in the proliferation of SARS-CoV-2 to multiple organ systems.

Exposure to environmental toxins as well as lifestyle choices can affect ACE2 expression, and may possibly increase the severity of infection. For example, exposure to ultrafine particulate matter from air pollution (PM 2.5) has previously been shown to increase the expression of ACE2 [4]. In line with these findings, a recent report indicates that higher levels of air pollution may be a contributing factor to the increased fatality rate among COVID-19 patients in northern Italy [5]. Dietary/lifestyle factors may also play a role in determining resilience or susceptibility to severe outcomes after SARS-CoV-2 infection. High fat diet has previously been shown to increase ACE2 mRNA expression in adipose tissue as well as the kidney and liver [6]. Furthermore, a recent meta-analysis found that diabetes was associated with more severe outcomes in COVID-19 patients [7]. These findings might also suggest that racial and ethnic differences in rates of metabolic/cardiovascular disorders could contribute to gene × environment interactions in determining COVID-19 susceptibility.

Interestingly, nicotine has been shown to decrease the expression of ACE2 in neurons and glia [8]. While the damage to lung tissue caused by smoking would likely exacerbate COVID-19 pathology, nicotine consumption by other methods (i.e. oral lozenge or transdermal patch) could potentially confer some resilience against neurological complications. The ACE inhibitors and angiotensin II type-I receptor blockers (ABRs) losartan and olmesartan have been found to significantly increase ACE2 expression in humans and animal models [9]. Ibuprofen, a frequently administered non-steroidal anti-inflammatory drug (NSAID), has also been shown to increase ACE2 [10]. The upregulation of ACE2 by drugs such as ibuprofen alone or in combination with ARBs or ACE inhibitors may thus exacerbate SARS-CoV-2 infection. In fact, preliminary reports from physicians in France have indicated that administration of NSAIDs was associated with more severe outcomes in patients infected with SARS-CoV-2.

Thus, it is possible that multiple independent variables may affect ACE2 expression and thereby confer resilience or susceptibility towards severe life-threatening conditions after SARS-Cov-2 infection. A crucial step forward in understanding disease variability in COVID-19 patients will be the cross-referencing of patient medical history (prescription drug use) with blood glucose levels, air pollution index in city of origin, history of nicotine consumption, and

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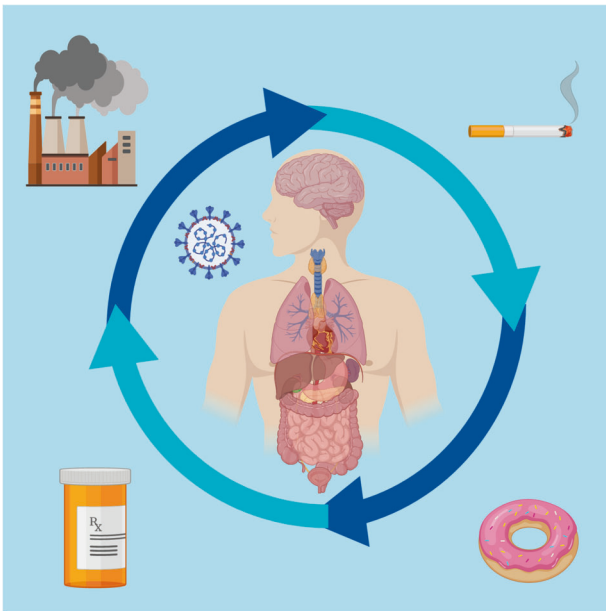
Fig. 1 Environmental and lifestyle factors and SARS-CoV-2 susceptibility. ACE2 is readily distributed throughout a number of organs as well as the nasal mucosa and can be modulated by pharmacological, toxicological, and dietary factors.

any additional variables which are found to affect ACE2 expression.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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