Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

The Forrest Gump approach to preventing severe COVID-19 – reverse the predisposing pro-inflammatory state with exercise

Dear Editor,

Why do only a small proportion of those infected with SARS-CoV-2 get severe disease? Most infections are pauci- or asymptomatic [1]. Studies show that the vast majority of those who get severe disease have predisposing conditions such as hypertension, obesity, cardiovascular disease, diabetes or older age [2–5]. For example, in New York, of the 5700 COVID-19 patients sick enough to need hospitalization, 57% had high blood pressure, 42% were obese and 34% had diabetes [2]. However, only a small set of chronic diseases predispose to severe disease. Diseases like asthma and HIV appear not to Refs. [2,5,6]. Why should hypertension and cardiovascular disease be such prominent risk factors for severe disease in a viral infection? Increasing evidence suggests that the reason why only certain chronic diseases predispose to severe disease is that they are associated with a pro-inflammatory state and an imbalance between the pro-inflammatory angiotensin converting enzyme-1 (ACE1) and anti-inflammatory ACE2 axes in particular [7,8]. The chronic diseases associated with COVID-19 are typified by a dominance of the ACE1 axis which promotes vasoconstriction as well as inflammatory, oxidative and fibrotic tissue damage [7,8]. A sedentary, excess-calorie-lifestyle results in the same proinflammatory ACE1 bias [9]. So does aging without staying fit [10].

This low-grade tissue inflammation may be critical in determining who gets severe COVID-19 [7,8]. As shown on the right side of Fig. 1, an unfit, overweight individual with a high blood pressure is likely to have an overactive ACE1 and an underactive ACE2 axis [7,8]. This generates a proinflammatory state in their lungs [8]. SARS-CoV-2 infection in this setting may precipitate an excessive inflammatory reaction. Part of the reason the inflammatory response is so excessive and poorly targeted may be due to two features of SARS-CoV-2 infection. Firstly, the virus uses ACE2 as its cellular receptor and in so doing dramatically reduces the expression of the anti-inflammatory ACE2 [8]. Secondly, a number of viral proteins inhibit the host's type I and III interferon response which is critical for directing an antiviral immune response [11]. The resulting exuberant inflammation fills the alveoli in fluid (which is one of the key clinicopathological feature of severe COVID-19) before the immune system has a chance to mount an effective immune response to clear the virus [8]. The fit healthy individual on the left has a balanced ACE1/2 system with sufficient ACE2 and no tissue inflammation at baseline. Following infection, the virus depletes ACE2, but this is from a high baseline, and sufficient ACE2 remains to ensure that the inflammatory response is proportionate. The immune cells are not overwhelmed by non-specific inflammation and despite an insufficient interferon response are still able to mount an sufficient response to effectively eliminate the virus [8,11].

1. The ACE-1 bias and excess inflammation can be reversed by exercise/diet

Whilst this is an over-simplification of a complex process it goes some way to explaining the association between severe COVID-19 and age, obesity, and hypertension. As one ages, becomes more obese or hypertensive one's ACE axis is biased in the ACE1 direction which then predisposes one to severe COVID-19 [7,8,10]. Other pro-inflammatory pathways are also activated and likely also play a role [10]. These changes are however not inevitable with aging or irreversible. A large number of studies in humans and other animals have shown that aerobic exercise can fairly rapidly reverse this bias, regardless of one's age, sex or abdominal girth [12,13]. Whilst the initial reversal of this bias occurs within minutes to hours of exercise, more profound reversal requires sustaining a regular program of exercise [12–14]. Exercise has also consistently been shown to be an effective way to reduce blood pressure in hypertensives [15]. A healthy, tailored diet can also play an important complementary role. As an example, randomized controlled trials have shown that certain diets can lead to remission of diabetes in up to 50% of participants [16,17].

2. Testing the exercise/diet hypothesis

If this theory is correct, then regular exercise and a healthy diet would not reduce one's risk of getting infected with SARS-CoV-2, but they would reduce one's risk of getting severe disease. We must acknowledge that randomized clinical trials in high risk populations would need to be conducted before we can conclude that exercise and diet would have this protective effect. Unfortunately, no such trials are currently registered on www.clinicaltrials.gov. As an alternative, the protective-effect-of-exercise/diet could be tested in animal models of severe COVID-19 [18].

In the absence of these studies it is worth recalling the good evidence for a broad array of other health benefits from exercise. One study for example found that every hour of running prolongs one's life by 7 h [14]. If exercise protects against severe COVID-19 too, then this would be the cherry on the cake. The advice "run, Forrest, run!" saved the handicapped Forrest Gump from nasty bullies, cured his physical disability and paved the way for a new healthy lifestyle. In this time of widespread COVID-19-induced anxiety and sense-of-helplessness, advising people to exercise regularly will likewise accomplish more than preventing severe COVID-19.

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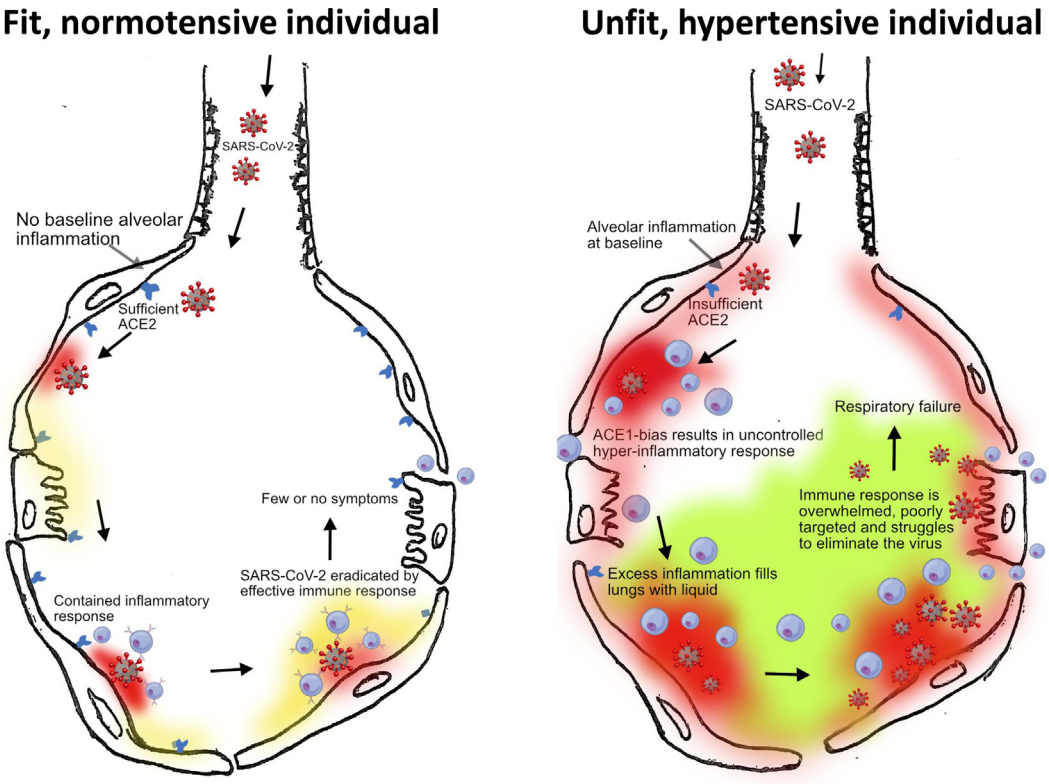

Fig. 1. Schematic representation of hypothesized link between being physically unfit/normotensive and the risk of severe COVID-19, contrasting SARS-CoV-2 infection in the alveolus of a fit, normotensive individual with balanced ACE1/2 axes (left) with an unfit, hypertensive individual with an ACE1-biased proinflammatory alveolus (right). Inflammation is represented by red and the pulmonary exudative fluid characteristic of severe COVID-19 is depicted by yellow-green fluid.

At a macro level, a number of authors have concluded that the current COVID-19 pandemic was ultimately caused by excessive human consumption that has resulted in extensive habitat destruction and spillover of SARS-CoV-2 into humans [19–21]. This is mirrored at a micro level by an imbalance between excessive consumption, large ecological footprints and insufficient exercise [20,22]. This imbalance extends to the marked contemporary inequalities in wealth and opportunities between individuals and populations [22,23]. These insights suggest that dealing with the current pandemic and preventing future pandemics and other health disasters will ultimately require rebalancing each of these levels [20,21,23]. Each of us could start this process by donning our running shoes more regularly.

Conflict of interest

The author states he has no conflict of interest.

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