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Cardiovascular and immunological implications of social distancing in the context of COVID-19

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Genesis 2:18 cites: *'It is not good for man to be alone'*, and 'No man is an island' by John Donne states: *'No man is an island entire of itself; every man is a piece of the continent, a part of the main'*. These popular cultural references highlight how social interactions are vital for our emotional and psychological well-being. In current times, it is appreciated that social interactions are pivotal for both our mental and physical health.[1] Over the last decade, studies have explored how loneliness, a perception of being isolated, and social isolation, the number of social contacts one has, impacts the cardiovascular and immune systems. The COVID-19 pandemic has made it essential to social distance by use of worldwide lockdowns, dramatically changing social interactions. Whilst social distancing minimizes the spread of COVID-19, such social isolation has the potential to affect the cardiovascular and immune systems.

Limited social interactions, such as in lockdown, will affect the body at three levels, physiological, psychological, and behavioural, and increase traditional risk factors and thus risk of cardiovascular disease (CVD) itself.[2] For example, such people have an increased likelihood of depression, having a poor diet, being sedentary, and having increased blood pressure.[2] These effects are liable to be most pronounced in those from poorer socioeconomic backgrounds, who are more likely to lose jobs and less likely to have gardens in which to exercise. Changes in health behaviour are reversible and may improve when lockdown measures are eased, e.g. exercising in groups. However, loneliness, a potential consequence of social distancing, is an independent risk factor for CVD.[3] This effect is most clear over prolonged periods of loneliness; thus, the consequences of social distancing on the cardiovascular system are most likely to be dependent on how long such measures remain in place.

The closest model of social distancing is social isolation (*Figure 1*). At the cellular and molecular level, several hypotheses have been proposed, with differences depending on the pathophysiological context in which experimental social isolation has been tested.[4,5] *In vivo*, multiple systems including the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, the immune system, and stress hormones work together towards a concerted response to social isolation.[4,6] *In vitro*, epigenetic changes might account for the effects of social isolation on a given tissue or cell.[7]

Socially isolated individuals have a higher vascular resistance in response to stressful stimuli, despite emotional reactions to stress similar to the control group suggesting an intrinsic response.[8] In support of this hypothesis, an *in vitro* study examining vascular relaxation induced by acetylcholine in phenylephrine-contracted aorta rings from socially isolated prairie voles showed a significant reduction in relaxation compared with paired control animals.[9] It was also demonstrated that acetylcholine caused a contractile response rather than a relaxation in socially isolated animals, even in the absence of phenylephrine pre-contraction.[9] Such increases in vascular contraction might partially contribute to the increased blood pressure associated with few social interactions, suggesting that increased blood pressure might be seen during social distancing.[2] This points to the existence of possible novel pathways influencing vascular contractility that are specifically controlled by social interactions. It is undeniable that these studies have provided sufficient evidence to support a significant effect of social isolation on homeostatic biological responses such as the control of vascular reactivity.

Does social distancing affect the immune system? Studies in socially isolated mice, primates, and other species have shown an up-regulation of antimicrobial inflammatory response and a parallel down-regulation of antiviral genes as well as higher overall levels of inflammation.[10,11] Of note, high levels of inflammation are a driver for CVD. Social isolation was linked to down-regulation of Type I and II interferons and an impaired response to infection by simian immunodeficiency virus.[10,11] The unique change in the gene fingerprint of immune cells has been named 'conserved transcriptional response to adversity' (CTRA) and can be induced by social isolation including divorce, low socioeconomic status, bereavement, and post-traumatic stress disorders.[4,11] The intrinsic difference in the nature of these conditions should highlight that the emotional rather than physical separation might be the key element triggering CTRA. As the period of time in lockdown and social distancing increases, distress and loneliness will increase; thus, it is likely that the aforementioned changes in the immune system would become more pronounced over time.

A study that more closely reflects lockdown involved six healthy men living in confinement for 520 days to simulate a mission to Mars.[12] An *ex vivo* stimulation with Epstein–Barr virus (EBV) showed a heightened

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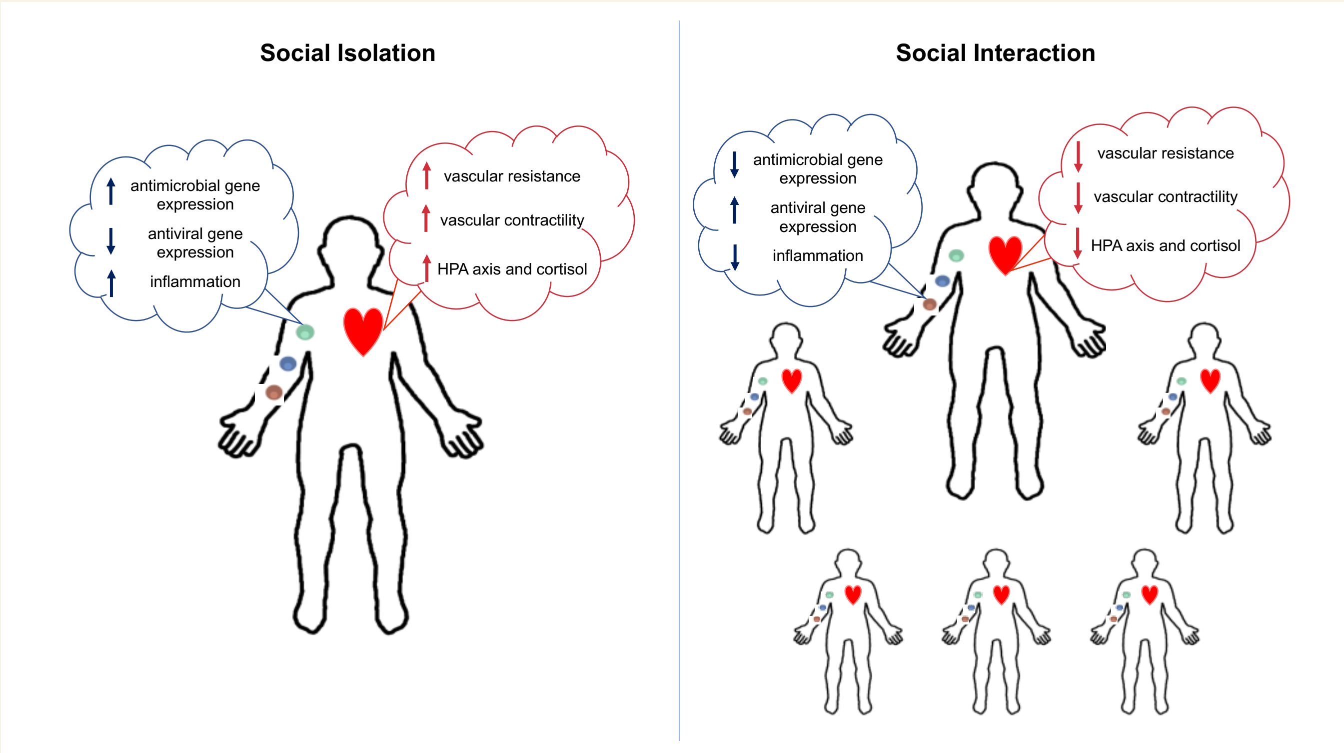

Figure 1 How might social distancing affect the cardiovascular and immune systems? Social distancing by its very nature is socially isolating. In individuals who are socially isolated, there is evidence to suggest they have increased vascular resistance and contraction as well as increased cortisol and HPA axis activity. High levels of social isolation normalize vascular resistance, contraction, cortisol, and HPA axis sensitivity. Social isolation has been shown to increase inflammation and gene expression of antimicrobial signalling at the expense of the antiviral response. This is the polar opposite of what is seen in those individuals with high social interaction.

antiviral response. The study authors specifically commented: 'we did not observe reactivation of latent EBV virus [in the astronauts], whereas strongly heightened antiviral immune responses have been found against viral infection simulation, and during the isolation period EBV loads in saliva were largely negative, showing an interesting contrast to the baseline'.[12]

During the period of lockdown and social distancing, it is likely that people have increasingly turned to technology to keep in touch with friends, family, and colleagues. COVID-19 lockdowns have being associated with increased loneliness and distress, particularly for young woman and those isolating alone.[13] Technology is particularly beneficial to the elderly in reducing loneliness, with some suggesting that high levels of technology usage led to overall better health.[14] In contrast, in the general population, high levels of social media use led to increased loneliness, and physical in-person social interactions were needed to reduce loneliness.[15] This suggests that using technology during lockdown could help mitigate the negative effects of loneliness on the body in the elderly whilst having little to no effect on the general population.

It is clear that social distancing measures such as lockdown during the COVID-19 pandemic will have subsequent effects on the body including the immune and cardiovascular systems, the extent of which will be dependent on the duration of such measures. The take-home message of these investigations is that social interaction is an integral part of a wide range of conditions that influence cardiovascular and immunological homeostasis. An appreciation of different aspects of lifestyle and living conditions should be the basis for future therapies, and the efficacy of these enhanced with drug-based therapies.

Conflict of interest: none declared.

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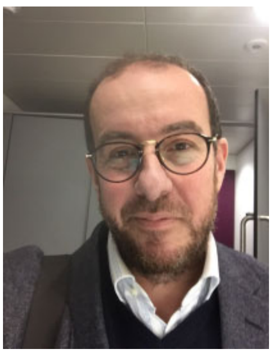

Biography: Fulvio D'Acquisto is a Professor of Immunology and Director of the Health Science Centre at the University of Roehampton in London, UK. He has been the lead scientist and inventor for three patents and two licences, and has authored more than 100 publications in translational research. His current research interest is the investigation of the link between emotions, immunity, and inflammation—an area of research that he christened 'Affective Immunology' (http://www.affectiveimmunology.com). The overall aim of this new field of studies is to demonstrate the therapeutic potential of emotion-affecting immunomodulatory therapies and to foster new studies in this field. His hope and ambition are that research in this field will constitute an example of 'paradigm shift' in translational research where 'body and mind' are together taken into consideration to achieve a better and patient-tailored treatment.

Biography: Dr Alice Hamilton is a postdoctoral research assistant at the Department of Cellular Medicine at the University of Dundee. Her current research is focused on the impact of NRF2 on liver fibrogenesis and the resolution of fibrogenesis. She successfully completed her British Heart Foundation-funded PhD from Queen Mary University of London in 2020. The focus of her doctoral work was investigating the effect of social isolation on the immune system in both the acute, sepsis, and chronic, atherosclerosis, settings.