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Letter to the Editor

Response to Plat and Mensink

We thank Plat and Mensink for their interest in our letter[1]. They highlight that we focussed on the importance of ensuring nutritional adequacy in older people because of the immune impairments that occur with ageing, which are collectively referred to as immunosenescence[2,3]. These age-related changes are exaggerated by frailty[4], by insufficient intake of key micronutrients[5] and, possibly, by gut dysbiosis[6,7], each of which occurs in many older people. Immunosenescence can result in poorer responses to some vaccines in older people[8,9] and to increased susceptibility to infection[9]. The context of our letter[1] was the possibility of poorer responses to 'COVID-19 vaccines' in older people[10,11]. Ageing is also associated with heightened low-grade inflammation, a state that is termed inflammageing[12]. Of course, many factors other than ageing influence both the immune response and low-grade inflammation, and Plat and Mensink highlight one of those, obesity. People living with obesity can show immune impairments[13,14], have increased susceptibility to some infections[15] and have poorer outcomes following some vaccinations[16], perhaps including COVID-19 vaccines[17]. Therefore, we fully agree with Plat and Mensink that a focus on weight management and on nutritional adequacy in those living with overweight and obesity is also important in the context of vaccination programmes.

Plat and Mensink go on to highlight the role of cholesterol in determining immune responses. There are different aspects to this interaction. Firstly, blood lipoproteins are able to influence immune function[18], and therefore, strategies that modify lipoprotein concentrations are likely to have some impact on immunity and, perhaps, infection. In support of this is the observation that plant stanol esters increased antibody titres against hepatitis A vaccination especially in those living with overweight or obesity[19]. Secondly, many viruses, including SARS-CoV-2, use cholesterol-rich regions of membranes to facilitate entry into cells[20]. Thus, strategies that modify cell-membrane cholesterol content or that disrupt cholesterol-rich regions of the membrane may affect viral infection. In addition to their blood cholesterol lowering effect, statins disrupt cholesterol-rich regions of the membrane[20], and it has been argued that statins may be effective in preventing viral entry into cells[21]. In this regard, it has been reported that statin use prior to hospital admission due to COVID-19 was associated with reduced risk of severe disease and faster time to recovery[22]. Furthermore, in-hospital use of statins in those with COVID-19 reduced the risk of mortality[23]. These benefits might relate to effects of statins on blood cholesterol or on viral entry into cells. However, statins are pleiotropic, and therefore, the clinical benefits seen in COVID-19 may involve other actions of statins. For example, statins are anti-inflammatory[24], and hyperinflammation is a major predictor of poor outcome in those with COVID-19[25,26]. Furthermore, some statins interact with PUFA metabolism to promote the production of highly potent *n*-3 fatty acid-derived mediators that resolve inflammation[27]. These secondary actions of statins indicate that not all 'cholesterol lowering' strategies would have the same effect on immunity, inflammation, infection and the course of infectious disease. Nevertheless, we fully concur with Plat and Mensink that multiple approaches need to be tested to identify effective strategies to support immunity, promote vaccination responses and reduce risk and severity of infection especially in vulnerable sub-groups of the population.

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