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.

with a lower risk of hospitalisation for COVID-19 and risk of SARS-CoV-2 infection.[3]

Although we do not question the validity of the results presented by Bovijn and colleagues, we think that the molecular nature of all variants should be discussed and related to the complex biology of IL-6. Specifically, we disagree with their notion that genetic IL-6R variants mimic therapeutic inhibition of IL-6R signalling. For example, the variant rs2228145 increases sIL-6R serum concentrations in individuals who are heterozygous or homozygous for this allele, owing to enhanced proteolytic cleavage of IL-6R and consequently reduced membrane bound IL-6R.[4] Importantly, all IL-6R variants retain their biological activity and can bind IL-6. This is a completely different scenario in patients treated with tocilizumab, in which IL-6 signalling via both membrane-bound and soluble IL-6R variants is blocked. In our opinion, the more probable explanation is that increased sIL-6R in combination with endogenous soluble gp130 acts as a buffer that neutralises IL-6[5] and that this mechanism accounts for the reduced risks of hospitalisation for COVID-19 and other inflammatory diseases.

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*Christoph Garbers, Stefan Rose-John
christoph.garbers@med.ovgu.de

Department of Pathology, Otto-von-Guericke-University Magdeburg, Medical Faculty, Magdeburg, Germany (CG); Institute of Biochemistry, Kiel University, Kiel, Germany (SR-J)

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Authors' reply

We thank Christoph Garbers and Stefan Rose-John for their interest in our Correspondence[1] on genetic variants in the gene encoding the interleukin (IL)-6 receptor (*IL6R*) mimicking pharmacological IL-6 receptor inhibition. Garbers and Rose-John propose an interpretation of our genetic findings that posits that the genetic instrument acts as a buffer for IL-6. We see this as a complementary interpretation to that in which the genetic instrument mimics therapeutic inhibition of the IL-6 receptor.

The precise mechanism by which a drug modulates a therapeutic target, and by which a genetic variant influences the same target, might not be identical. However, this does not necessarily obviate the use of such genetic instruments to make deductions about the probable efficacy of modifying a therapeutic target, especially if a drug and genetic variant exhibit similar associations with target-associated molecular pathways. The concordant effects of *IL6R* genetic variants and pharmacological IL-6 receptor inhibition on multiple biomarkers (eg, fibrinogen, C-reactive protein, IL-6, and soluble IL-6R[2]) and disease (eg, rheumatoid arthritis) argue for phenotypic consistency between the genetic instrument and therapeutic effect. Furthermore, the rs2228145 missense variant has been shown to impede membrane-bound IL-6 receptor signalling,[3] and the effect on disease outcomes (including potentially COVID-19) might therefore be mediated via this mechanism (in addition to, or in lieu of, the IL-6 buffering mechanism proposed by Garbers and Rose-John).

Mendelian randomisation studies of drug targets are subject to various caveats (including the mechanistic considerations highlighted in the foregoing text), and results from such studies should not be interpreted as representing definitive evidence of drug efficacy or safety. Rather, such genetic investigations provide evidence for (or against) therapeutic hypotheses, in which the acid test ultimately remains evidence of efficacy derived from well-designed randomised, controlled trials. As we noted in our original Correspondence,[1] our results provide evidence for the potential efficacy of IL-6 receptor inhibition (and possibly the role of IL-6 signalling more broadly) in COVID-19, which should be further evaluated in adequately powered randomised, controlled trials.

A further dimension must be considered in the context of drug-target Mendelian randomisation applied to an emerging infectious disease such as COVID-19. In contrast to coronary heart disease, for example, where data from large-scale genome-wide association study consortia are already established, the same is not the case for COVID-19. Effect estimates might therefore not be stable to the addition of newer data that become available. To this end, following our original publication,[1] the COVID-19 Host Genetics Initiative released an updated dataset including a larger number of cases and controls. We updated our analyses using these newly released data and found that our results remained largely unchanged (appendix p 1). Notably, we found that the association of the IL-6 receptor genetic instrument with the most severe COVID-19 phenotype (COVID-19 requiring respiratory support or leading to death) was strengthened with an increased number of cases from 536 to 4336 (OR 0·94 scaled to a 0·1 SD lower C-reactive protein, [95% CI, 0·90–0·98], p=0·005, by use of the updated data, *vs* 0·98,

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See **Online** for appendix

[95% CI, 0·88–1·10], p=0·78 by use of the original data). Findings from randomised, controlled trials of tocilizumab have shown conflicting results,[4] which might suggest that IL-6 receptor inhibition does not provide therapeutic benefit in all patients with COVID-19. Ongoing randomised, controlled trials, such as the RECOVERY trial,[5] will be crucial in providing further evidence.

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*Jonas Bovijn, Cecilia M Lindgren†, Michael V Holmes†
jbovijn@well.ox.ac.uk

†These authors contributed equally to this work.

Big Data Institute at the Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, OX3 7FZ, UK (JB, CML), Medical Research Council Population Health Research Unit (MRC PHRU), Nuffield Department of Population Health, University of Oxford, Oxford, OX3 7LF, UK (MVH).

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