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# Comment on Sobczyk, M.K.; Gaunt, T.R. The Effect of Circulating Zinc, Selenium, Copper and Vitamin $K_1$ on COVID-19 Outcomes: A Mendelian Randomization Study. *Nutrients* 2022, *14*, 233

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Sobczyk and Gaunt genetically predicted circulating zinc, selenium, copper, and vitamin $K_1$ levels—instead of directly measuring nutrients in blood—and hypothesized that these levels would associate with SARS-CoV-2 infection and COVID-19 severity [1]. We have concerns about their conclusions regarding vitamin K in COVID-19. Major study limitations were that the genetic instruments had not demonstrated reliable association with the measured exposure (plasma vitamin $K_1$) and that the authors used the same genome-wide association study for instrument discovery and effect estimation. Moreover, even direct quantification of blood vitamin $K_1$ concentrations is not a valid method for quantifying vitamin $K_1$ status, since this assessment only reflects a snapshot of recent vitamin $K_1$ intake, is sensitive to triglyceride concentrations, and gives little information about the vitamin $K_1$ utilization in tissue.

There are also differences between vitamins $K_1$ and $K_2$ in half-life time, tissue distribution, and bioavailability [2]. Vitamin $K_2$ has a much longer half-life and may, therefore, be important particularly during acute illness, where vitamin K reserves are being used and become less available in peripheral tissues. Consumption of vitamin $K_2$ is usually too low to accurately quantify their plasma concentration. Due to these factors, most experts in the field advocate measuring levels of inactive circulating vitamin-K-dependent proteins to assess the combined deficiency of vitamins $K_1$ and $K_2$. In our studies, we used *PIVKA-II* and *dp-ucMGP* as measures of hepatic and extrahepatic vitamin K status, respectively [3–5]. Particularly extrahepatic vitamin K status is severely compromised in COVID-19, and high dp-ucMGP levels are associated with increased mortality [4,5].

Another debatable assumption made by Sobczyk and Gaunt is that the baseline vitamin K status—at the moment of SARS-CoV-2 contraction—is a predictive factor for the disease course of subsequently developing COVID-19 [1]. An alternative explanation for the poor vitamin K status in COVID-19 patients is high vitamin K expenditure during the disease. Interestingly, observations in individuals using vitamin K antagonists as anticoagulant drugs support our theory that it is mainly increased vitamin K utilization during the infection, rather than poor baseline vitamin K status, that is responsible for the extrahepatic vitamin K deficiency we found in our studies [6,7].

Given that Sobczyk and Gaunt may not have accurately predicted overall extrahepatic vitamin K status, and that they estimated pre-COVID rather than vitamin K levels during

the infection, we are of the opinion that their genetic data analysis is interesting but cannot be used to decide whether vitamin K supplementation has a role in COVID-19.

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**Conflicts of Interest:** R.J. discloses the application of a patent on vitamin K in COVID-19. R.J., J.W., and A.L. have a scientific collaboration with Kappa Bioscience AS, a manufacturer of vitamin $K_2$ (MK-7). C.V. declares no competing interest.

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