Dear Editor,

We would like to call attention to a possible sex-specific association between vitamin D deficiency and COVID-19 mortality in the older population, and thus potential implications for the vitamin D research pipeline.

The COVID-19 disease pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to wreak havoc across the globe with a still uncertain outcome. At the time of writing, over 972,220 confirmed COVID-19-related deaths have been reported worldwide, the bulk of those deaths coming from older people, especially those over 80 years [1].

Emerging global data show sex disparities in COVID-19 mortality, infected men facing a higher risk to die of SARS-CoV-2 infection than women. This has led to a call to an in-depth analysis of sex-disaggregated data [2] and emphasized the need to understand the precise drivers and mechanisms of sex disparity in COVID-19 fatality which still remains poorly understood, especially in the understudied very old-aged population.

In the research efforts to identify drivers/risk factors for COVID-19 mortality, the role of vitamin D has received attracted interest, especially given its potent modulatory action on the immune system and on the renin–angiotensin system (RAS), particularly the angiotensin-converting enzyme2 (ACE2), the main host cell receptor of SARS-CoV-2 [3, 4]. However, studies failed to explicitly address the effect of sex on the associations between vitamin D and COVID-19 outcomes.

With this in view, we assessed the sex-specific association between vitamin D deficiency and in-hospital mortality in an extension of the COVIDage study, a retrospective cohort conducted among Caucasian older COVID-19 patients hospitalized in our geriatric wards between March and April 2020 [5]. A total of 160 older inpatients (mean age 85.9 ± 6.6 years; 95 women/65 men) with COVID-19 (i.e., positive SARS-CoV-2 swab or clinical/radiological diagnosis of COVID-19) and available serum level of 25-hydroxyvitamin D (25[OH]D) during acute disease were included in our analysis. Among them, 34% (32/95) of women and 42% (27/65) of men had vitamin D deficiency (i.e., 25[OH]D < 50 nmol/L), without significant sex difference (**p** = 0.312). Forty patients (25%; 25/65 men and 15/95 women) died during hospitalization. The in-hospital mortality risk was significantly higher in men than women (odds ratio: 3.10; 95% confidence interval (CI) 1.81–5.29; **p** < 0.001). In sex-stratified Cox’s proportional hazard models for survival analysis, severe vitamin D deficiency was independently associated with in-hospital mortality risk in men, in the univariate (crude hazard ratio (HR): 2.80; 95%CI 1.25–6.28; **p** = 0.012) (Fig. 1) and multivariate models (adjusted HR for model with age, comorbidities, C-reactive protein level, and frailty status: 2.47; 95%CI 1.02–5.97; **p** = 0.044). No association was found in women in either the univariate or the multivariate models (all **p** values >0.521).

These findings suggest that vitamin D research pipeline should integrate appropriate sex-specific analyses, from fundamental to clinical research. Especially they should inform...
the design and interpretation of awaited interventional trials evaluating the therapeutic potential of vitamin D supplementation in older COVID-19 patients. The mechanisms behind the sex-differential association, such as the implication of vitamin D deficiency on the X-chromosome linked RAS activity, remain to be fully elucidated [4].

**Funding**  No funding sources.

**Data availability**  Selected data are available from the corresponding author on reasonable request.

**Compliance with ethical standards**

**Conflicts of interest**  None.

**Ethical approval**  The COVIDage study was approved by the State of Geneva’s Ethics Committee (protocol 2019–01288).

**Informed consent**  Informed consent was not required for this retrospective study and all details that might disclose the identity of the subjects under study was omitted or anonymized.

**References**

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