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Response to Rossato et al.

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Dear Editor:

We thank Rossato et al. for their interest in our study and applaud their efforts to assess sex differences in coronavirus disease 2019 (COVID-19)-related mortality.[1] We agree with the authors that sex- and gender-related differences with regard to COVID-19 became apparent during the pandemic. For example, although our study shows no sex difference in COVID-19 diagnoses and testing in the general population, we do demonstrate that female health care workers have significantly lower odds of being tested and diagnosed with COVID-19 than male health care workers.[2] However, as the authors rightfully note, age is an important modifier in the association between sex and health outcomes.[3]

Therefore, we build further upon the analyses conducted by Rossato et al. by assessing sex differences in hospitalization rates due to COVID-19 in the Dutch Lifelines COVID-19 Cohort Study.[4–6] As data collection proceeded, we included 20 consecutive measurements collected between March 2020 and March 2021, in contrast to our previous study in which we included 13 consecutive measurements up to August 2020.[2] In total, 76,422 participants of the general population completed 774,826 questionnaires about their mental and physical health during the COVID-19 pandemic. During this time, the alpha variant (B.1.1.7) was predominant in the Netherlands and by the end of March 2021 a minority of participants were fully vaccinated (5.2%).

The majority of the COVID-19-positive participants in our study was female ($n = 2{,}149$ female; 66.2%). However, previous studies show that male participants are more frequently hospitalized than female participants.[7,8] Similarly, in our study, 41 women (1.9% of COVID-19-positive women) and 54 men (4.8% of COVID-19-positive men) were hospitalized due to COVID-19 ($\chi^2 = 22.0$; Df = 1; $p < 0.001$). The mean age of hospitalized women was 55.8 (standard deviation [SD] = 12.0) years, compared with 59.0 (SD = 10.7) years in men. This difference is not statistically significant ($t_{(92)} = 1.06$; $p = 0.29$). Bivariate logistic regression analysis shows that women have lower odds than men for hospitalization due to COVID-19 (odds ratio [OR] = 0.38; 95% confidence interval [CI] = 0.24–0.58).

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Multiple logistic regression analysis, in which we adjusted for participants' age and the presence of chronic disease, shows that sex (OR = 0.44; 95% CI = 0.29–0.68), age (OR = 1.05; 95% CI = 1.03–1.08), and the presence of chronic disease (OR = 1.85; 95% CI = 1.14–3.02) are all significantly associated with hospitalization due to COVID-19. Sex-by-age and sex-by-chronic disease interaction terms were not statistically significant (OR = 1.01; 95% CI = 0.96–1.06 and OR = 0.77; 95% CI = 0.29–2.05, respectively). This indicates that the association between age and hospitalization, as well as the association between the presence of a chronic disease and hospitalization due to COVID-19 do not differ between women and men.

The lower odds of female hospitalization due to COVID-19 are most likely attributable to both sex- and gender-related factors. Women's innate and humoral immune responses, as well as their ability to balance inflammation and tissue damage, appear to be stronger than men's.[7,9] These immunological sex differences may result in more effective clearing of infection in women and a potentially accelerated recovery after infection.[10] In addition, higher age-adjusted rates of pre-existing somatic comorbidities are reported in male COVID-19 patients, including cardiovascular disease, which associate with a poor COVID-19 prognosis.[11–13]

In addition to sex-specific factors, gender-related factors may also associate with the course of SARS-CoV-2 infection. For example, men are generally more likely to display poor health-related behaviors that worsen a COVID-19 prognosis, such as smoking and poor diet.[14,15] The aforementioned sex-related factors may interact with gender-specific factors and thus synergistically influence the prognosis of COVID-19. Notably, sex- and gender-based differences regarding hospitalization due to COVID-19 may differ between cultures and location. In general, our findings regarding a female preponderance in COVID-19 diagnoses, but a poor male prognosis of COVID-19 are in line with those of Rossato et al. However, further research could focus on sex- and gender-based differences in physical consequences (*e.g.*, post-COVID-19 condition) and sociocultural consequences (*e.g.*, loss of productivity) due to COVID-19 and the pandemic in general.

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