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COVID-19

Sex differences in the mortality rate for coronavirus disease 2019 compared to other causes of death: an analysis of population-wide data from 63 countries

Pascal Geldsetzer[1,2] · Trasias Mukama[3,4,5] · Nadine Kamel Jawad[6] · Tim Riffe[7,8,9] · Angela Rogers[10] · Nikkil Sudharsanan[3,11]

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Abstract

Men are more likely than women to die due to coronavirus disease 2019 (COVID-19). An open question is whether these sex differences reflect men's generally poorer health and lower life expectancy compared to women of similar ages or if men face a unique COVID-19 disadvantage. Using age-specific data on COVID-19 mortality as well as cause-specific and all-cause mortality for 63 countries, we compared the sex difference in COVID-19 mortality to sex differences in all-cause mortality and mortality from other common causes of death to determine the magnitude of the excess male mortality disadvantage for COVID-19. We found that sex differences in the age-standardized COVID-19 mortality rate were substantially larger than for the age-standardized all-cause mortality rate and mortality rate for most other common causes of death. The excess male mortality disadvantage for COVID-19 was especially large in the oldest age groups. Our findings suggest that the causal pathways that link male sex to a higher mortality from a SARS-CoV-2 infection may be specific to SARS-CoV-2, rather than shared with the pathways responsible for the shorter life expectancy among men or sex differences for other common causes of death. Understanding these causal chains could assist in the development of therapeutics and preventive measures for COVID-19 and, possibly, other coronavirus diseases.

Keywords COVID-19 · SARS-CoV-2 · Sex · Gender · Mortality

Introduction

Males have a higher risk of death from coronavirus disease 2019 (COVID-19) than females [1–6]. This difference has been observed for both the case fatality rate (CFR; i.e., deaths among those diagnosed with a SARS-CoV-2 infection) and infection fatality rate (IFR; i.e., deaths among all those who were infected with SARS-CoV-2) [1]. This higher risk of death from COVID-19 in males has been highlighted both in the academic literature and the media [7–9].

✉ Pascal Geldsetzer
pgeldsetzer@stanford.edu

1 Division of Primary Care and Population Health, Department of Medicine, Stanford University, 1265 Welch Road, Stanford, CA 94305, USA

2 Chan Zuckerberg Biohub, San Francisco, CA, USA

3 Heidelberg Institute of Global Health, Heidelberg University, Heidelberg, Germany

4 Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

5 Department of Disease Control and Environmental Health, School of Public Health, College of Health Sciences, Makerere University, Kampala, Uganda

6 Stanford University School of Medicine, Stanford, CA, USA

7 Laboratory of Population Health, Max Planck Institute for Demographic Research, Rostock, Germany

8 Department of Sociology and Social Work, OPIK, University of the Basque Country, Leioa, Spain

9 Ikerbasque, Basque Foundation for Science, Bilbao, Spain

10 Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

11 TUM Department of Sport and Health Sciences, Technical University of Munich, Munich, Germany

Understanding why these disparities by sex exist has become an active area of research. However, given that the risk of death from COVID-19 is strongly related to age and other risk factors for all-cause mortality [6], and thus one's expected remaining life expectancy [6], it is unclear whether the observed sex differences in the COVID-19 fatality rate are simply a reflection of men's shorter life expectancy [10], which is at least in part due to their poorer health status at any given age. This study aimed to determine if sex differences in COVID-19 mortality are larger when compared to the all-cause mortality rate, mortality rates for other common causes of death, and—given SARS-CoV-2's common respiratory manifestations—other respiratory causes of death, including respiratory infections. This information is important, as it begins to elucidate whether the higher COVID-19 mortality risk among males reflects the survival advantage among females compared to males, and is, thus, likely a result of the biological, behavioral, and social pathways that cause this survival advantage as opposed to causal pathways that are specific to COVID-19. Understanding these causal pathways could help in the development of therapeutics and preventive measures for COVID-19 and possibly other coronavirus diseases.

Methods

Data sources

COVID-19 mortality data

We extracted country-level data on COVID-19 deaths from the COVerAGE-DB database for countries for which age- and sex-disaggregated data were available with a reference date as near as possible to 9 February 2021 (as of 1 March 2022) and which had at least 50 recorded COVID-19 deaths as of this reference date [11]. We chose this cut-off date because coverage of COVID-19 vaccination, for which uptake likely differed by sex over time in different countries, was minimal in most countries until that date [12]. Age- and sex-disaggregated data were available for 63 countries: Afghanistan, Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Cameroon, Canada, Chad, Chile, Colombia, Cuba, Czechia, Denmark, Dominican Republic, Ecuador, Eswatini, France, Germany, Greece, Honduras, Hungary, India, Iraq, Israel, Italy, Japan, Jordan, Kenya, Latvia, Lithuania, Malawi, Mexico, Moldova, Nepal, Netherlands, Nigeria, North Macedonia, Norway, Oman, Pakistan, Panama, Paraguay, Peru, Philippines, Portugal, Qatar, Romania, Slovakia, Slovenia, South Korea, Spain, Switzerland, Togo, Turkey, Ukraine, United Arab Emirates, United Kingdom, Uruguay, and the United States of America (USA). The disaggregation by age in COVerAGE-DB was by ten-year age groups.

General mortality data

For the 63 countries for which sex- and age-disaggregated COVID-19 mortality data were available, we obtained age- and sex-disaggregated data on all-cause mortality and total population size from the Human Mortality Database (HMD) [13]. We extracted the latest available population and deaths count data for each country (as of 1 March 2022). Population and deaths count data were available for 32 countries from the HMD: Australia, Belgium, Canada, Chile, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Slovenia, South Korea, Spain, Switzerland, Ukraine, United Kingdom, and USA. For countries not in the HMD, we obtained the standard projections of populations and deaths data for the 2015–2020 period from the 2019 revision of the United Nation's World Population Prospects (WPP) [10]. Data on population size and deaths were available for one-year age groups in the HMD and for five-year age categories in the WPP. To be consistent with COVerAGE-DB, we aggregated data from both the HMD and WPP into ten-year age groups, and combined data for age groups older than 80 into one category (80 +).

Cause-specific mortality data

We also obtained the latest available mortality data for specific causes of deaths from the WHO mortality database for 50 out of our 63 countries [14]. The 13 countries for which cause-specific death data were not available were Afghanistan, Cameroon, Chad, Czechia, Eswatini, Georgia, India, Kenya, Malawi, Nepal, Nigeria, Pakistan, and Togo. Causes of death were classified according to the 10th revision of the International Classification of Diseases (ICD-10) [15]. We obtained data for the top six causes of death groups globally (according to the WHO mortality database [13]), which were circulatory diseases, cancer, chronic respiratory diseases, respiratory infections and tuberculosis, diabetes, and neurologic disorders. To compare COVID-19 mortality differences by sex with differences observed for other respiratory causes of deaths, we further categorized respiratory causes into six groups: acute upper respiratory infections, influenza, pneumonia, other acute lower respiratory infections, other diseases of the upper respiratory tract, and chronic lower respiratory diseases. The ICD-10 codes used to define the six major causes of mortality and the respiratory causes of death are presented in Table S2.

Statistical analyses

We calculated age-standardized mortality rates separately by country for men and women for COVID-19-specific, cause-specific, and all-cause mortality. Separately for men and women, we first estimated COVID-19, cause-specific, and all-cause mortality rates for each age group by dividing the total number of deaths due to each cause (or all deaths for all-cause) by the mid-year population in that age group. We then standardized each rate using the overall age distribution of each country so that sex differences in mortality were not skewed by sex differences in the age distribution within countries.

Rate ratios for the sex differences in COVID-19 mortality were calculated for each country by dividing the age-standardized COVID-19-specific mortality rate in men by the age-standardized COVID-19-specific mortality rate in women. Similarly, sex differences in all-cause mortality were examined using the rate ratios obtained by dividing the age-standardized all-cause mortality rate in men by the age-standardized all-cause mortality rate in women. We calculated excess mortality disadvantage—the difference between the male-to-female mortality rate ratio from COVID-19 and that from all causes—by dividing the two ratios. We also present the relative difference in these rate ratios of mortality by age group (0–39, 40–49, 50–59, 60–69, 70–79, and 80 + years), major causes of mortality (circulatory diseases, cancer, chronic respiratory diseases, respiratory infections and tuberculosis, diabetes, and neurologic disorders), and common respiratory causes of death.

Lastly, instead of using age standardization, we calculated remaining life expectancy-adjusted mortality rates for men and women. The rationale for this robustness check is that remaining life expectancy may be a better measure of biological age than calendar age, since men and women at similar chronological ages often have different remaining life expectancies. To estimate remaining life expectancy-adjusted rates, we first obtained data on remaining life expectancy by age from the HMD and WPP. Specifically, for the latest year (in HMD) and period (in the WPP) for which data were available as of 09 February 2021, we obtained the remaining life expectancy at each single year of age separately for each country and sex. We then created 5-year groups for remaining life expectancy (0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–50, and 50 + years) and matched these to each age by sex and country (e.g., for each age in the mortality data, we noted which remaining life expectancy group this age belonged to). Lastly, we estimated standardized mortality rates, where rather than set a common age-distribution for men and women, we instead set a common distribution of individuals across remaining life expectancy groups. This results in a standardized rate that has the interpretation of "what would the mortality rates for men and women be if they had the same population distribution of years of life expectancy remaining?". All analyses were implemented in R version 4.1.2 [16].

We estimated confidence intervals around each of the ratios following the procedures recommended by Flanders [17] and Breslow and Day [18]. To do this, we first used the Delta method to estimate the standard error of each ratio. To construct confidence intervals, we used the observation that the natural log of rate ratios, rather than the ratios themselves, are approximately normally distributed and estimated the confidence interval first on the ln scale as log(estimates) ± 1.96(Standard error) and then exponentiated these bounds to convert them back to the ratio scale [18].

Data and materials availability

All the data used in the study are publicly available. COVID-19 mortality data are available from the COVerAGE-DB (https://osf.io/mpwjq/). Data on population size by age and sex are available from the HMD (www.mortality.org) and the United Nation's WPP (https://www.who.int/healthinfo/mortality_data/en/). All statistical code to reproduce our analyses is available publicly at https://osf.io/d54ws/.

Results

Age- and sex-disaggregated data on COVID-19 deaths were available for 63 countries (Table 1). Chad, Cuba, and Togo had less than 100 recorded deaths from COVID-19. The number of deaths by sex for each of the six major groups of causes of deaths examined in this analysis are shown in Table S1.

Sex differences in COVID-19 compared to all-cause mortality

Figure 1 presents the age-standardized male-to-female rate ratios of mortality from COVID-19 and all causes. Point estimates greater than one in Fig. 1 indicate that men had a higher rate of death than women. The same information but depicted as a scatterplot and as the relative difference in the rate ratio are shown in Figs. S1 and S2, respectively. We found that in most countries, the male disadvantage for COVID-19 mortality was substantially larger than their all-cause mortality disadvantage. This result was robust to standardization by remaining life expectancy (Fig. S3).

Rate ratios for the sex differences in COVID-19 and all-cause mortality were calculated for each country by

Table 1 Population, all-cause deaths, and COVID-19 cases and deaths by sex and country

Country	Period/year[†]	Population (000 s)		All-cause deaths (000 s)		Date[*]	COVID-19 deaths	
		Female	Male	Female	Male		Female	Male
Afghanistan	2015–2020	18,952	19,976	215.8	262.4	29/11/2020	385	1145
Argentina	2015–2020	23,147	22,049	182.0	199.9	09/02/2021	22,498	30,499
Australia	2018	12,599	12,400	76.2	82.3	08/02/2021	469	440
Austria	2019	4512	4368	42.6	40.8	09/02/2021	3,929	4232
Belgium	2020	5809	5650	64.7	62.2	09/02/2021	11,078	10,688
Bosnia and Herzegovina	2015–2020	1674	1607	18.5	19.7	31/12/2020	1609	2829
Brazil	2015–2020	108,124	104,436	700.5	898.2	09/02/2021	104,077	137,178
Bulgaria	2017	3640	3436	53.0	56.8	09/02/2021	3626	5697
Cameroon	2015–2020	13,269	13,277	201.7	229.9	09/09/2020	113	212
Canada	2019	18,882	18,642	138.5	145.6	19/02/2021	10,939	10,296
Chad	2015–2020	8226	8200	162.1	186.8	21/10/2020	22	70
Chile	2017	8952	8601	50.6	55.8	09/02/2021	8354	11,193
Colombia	2015–2020	25,898	24,985	151.5	182.5	09/02/2021	23,494	41,240
Cuba	2015–2020	5703	5623	51.6	57.1	24/05/2020	30	52
Czechia	2019	5414	5259	55.0	57.3	09/02/2021	–	18,061
Denmark	2020	2931	2901	26.7	28.0	09/02/2021	1024	1220
Dominican Republic	2015–2020	5430	5418	38.1	51.5	17/08/2020	509	980
Ecuador	2015–2020	8819	8,824	48.6	62.4	31/07/2020	3590	7025
Eswatini	2015–2020	590	570	7.0	8.6	30/12/2020	79	105
France	2018	33,440	31,336	300.0	296.6	09/02/2021	23,753	32,887
Georgia	2015–2020	2088	1901	26.1	27.9	31/12/2020	–	1458
Germany	2017	41,885	40,770	474.5	457.8	09/02/2021	35,747	37,524
Greece	2019	5511	5212	61.9	63.1	09/02/2021	2483	3534
Honduras	2015–2020	4956	4949	25.9	30.7	22/04/2021	697	984
Hungary	2020	5079	4673	72.3	68.7	09/02/2021	6553	6696
India	2015–2020	662,903	717,101	6,175.7	7,114.3	02/10/2020	30,988	69,887
Iraq	2015–2020	19,865	20,358	133.3	162.4	24/05/2020	50	110
Israel	2016	4309	4237	22.3	21.9	17/02/2021	2325	3,145
Italy	2018	30,731	29,142	328.7	300.7	10/02/2021	40,471	51,867
Japan	2020	63,397	60,026	665.9	706.8	09/02/2021	2419	3587
Jordan	2015–2020	5037	5166	24.0	29.0	09/02/2021	1565	2830
Kenya	2015–2020	27,053	26,719	222.6	275.3	31/08/2020	70	210
Latvia	2019	1031	883	14.7	13.0	31/12/2020	332	368
Lithuania	2020	1486	1309	22.2	21.3	31/12/2020	1077	1189
Malawi	2015–2020	9696	9434	98.5	122.0	27/12/2020	44	144
Mexico	2015–2020	65,861	63,071	411.2	502.7	09/02/2021	73,319	124,373
Moldova	2015–2020	2102	1932	23.3	26.9	09/02/2021	1738	1835
Nepal	2015–2020	15,788	13,348	120.1	129.0	26/01/2021	524	1226
Netherlands	2019	8730	8615	77.5	74.4	07/02/2021	6,767	7990
Nigeria	2015–2020	101,670	104,470	1,823.8	2,084.3	07/02/2021	353	912
North Macedonia	2015–2020	1041	1042	11.0	11.8	31/12/2020	1009	1801
Norway	2020	2667	2713	20.6	20.0	09/02/2021	275	308
Oman	2015–2020	1736	3370	5.4	10.0	31/12/2020	422	1078
Pakistan	2015–2020	107,220	113,672	1,303.2	1,592.8	02/06/2020	436	1251
Panama	2015–2020	2155	2160	11.4	15.6	04/07/2020	242	478
Paraguay	2015–2020	3508	3624	23.0	27.9	09/02/2021	1435	2072
Peru	2015–2020	16,593	16,379	96.8	127.6	09/02/2021	39,633	71,504
Philippines	2015–2020	54,552	55,029	335.3	484.3	09/02/2021	5185	7863

Table 1 (continued)

Country	Period/year†	Population (000 s)		All-cause deaths (000 s)		Date*	COVID-19 deaths	
		Female	Male	Female	Male		Female	Male
Portugal	2020	5439	4860	62.0	61.4	09/02/2021	7062	7656
Qatar	2015–2020	716	2165	1.2	3.3	31/12/2020	35	177
Romania	2015–2020	9884	9354	130.7	135.6	10/06/2020	550	808
Slovakia	2019	2791	2663	25.8	27.4	09/02/2021	3,179	3679
Slovenia	2019	1043	1045	10.5	10.1	09/02/2021	2,116	1890
South Korea	2018	25,703	25,607	137.6	161.2	28/06/2020	130	152
Spain	2020	24,152	23,213	243.7	248.7	09/02/2021	31,741	38,088
Switzerland	2020	4353	4286	38.6	37.6	09/02/2021	4158	4803
Togo	2015–2020	4159	4119	53.6	60.6	09/02/2021	23	57
Turkey	2015–2020	42,703	41,636	237.2	286.7	26/10/2020	3744	6,056
Ukraine	2013	24,367	20,940	337.7	324.7	09/02/2021	10,898	12,221
United Arab Emirates	2015–2020	3054	6836	4.7	13.7	31/12/2020	112	555
United Kingdom	2018	33,645	32,787	311.6	304.4	12/02/2021	37,540	40,351
Uruguay	2015–2020	1795	1678	17.5	17.8	18/01/2021	140	170
USA	2019	166,263	161,347	1,381	1,473.8	06/02/2021	229,075	276,356

*Reference date for cumulative sex-specific COVID-19 death data.

†Year for which population and death data are available in the HMD. Population and mortality projections for the 2015–2020 period from the UN's World Population Prospects (WPP) were used for countries not in the HMD.

dividing the age-standardized mortality rate in males by the age-standardized mortality rate in females. Horizontal lines depict 95% confidence intervals.

Sex differences in COVID-19 compared to all-cause mortality by age group

We found the largest excess male disadvantage in COVID-19 mortality for the group aged 80 years and older (Fig. 2). Among younger age groups, especially those aged less than 50 years, the direction and magnitude of the difference between the male COVID-19 disadvantage and the male disadvantage for all-cause mortality varied greatly by country. These patterns were similar when using remaining-life expectancy-adjusted rates.

The relative difference in the rate ratio was calculated by dividing (separately among each age group shown) the male-to-female rate ratio for the COVID-19-specific mortality rate by the male-to-female rate ratio for the all-cause mortality rate. Horizontal lines depict 95% confidence intervals.

Sex differences in COVID-19 compared to other major causes of mortality

Comparing the male disadvantage for COVID-19 to their disadvantage in mortality from several major causes of mortality (circulatory diseases, cancer, chronic respiratory diseases, respiratory infections and tuberculosis, diabetes, and neurologic disorders), we found that in most countries the relative sex differences for COVID-19 were larger than for each of the other common causes of death (Figs. 3 and S4). However, this was not true for chronic respiratory conditions for which countries were spread approximately equally across the vertical dashed line drawn at one, which indicates that the relative sex difference for COVID-19 mortality was approximately the same as for chronic respiratory diseases. Implementing the same analysis as in Fig. 3 for each common respiratory cause of death (the ICD-10 codes used for categorization are shown in Table S2) revealed that the similar male disadvantage in mortality for chronic respiratory conditions as for COVID-19 is largely driven by a high male disadvantage in mortality from bronchitis and emphysema (the most common condition grouped under "chronic lower respiratory diseases"; Fig. S5).

Discussion

Across 63 countries, the size of the male COVID-19 mortality disadvantage tends to be substantially larger than the general male mortality disadvantage and the male disadvantage in several major causes of death. Thus, the higher probability of succumbing to a SARS-CoV-2 infection among men compared to women does not appear to be fully explained by the fact that across ages men generally have poorer health and a lower remaining life expectancy. This observation suggests that the causal pathways that link male sex to a shorter life expectancy may not fully explain the

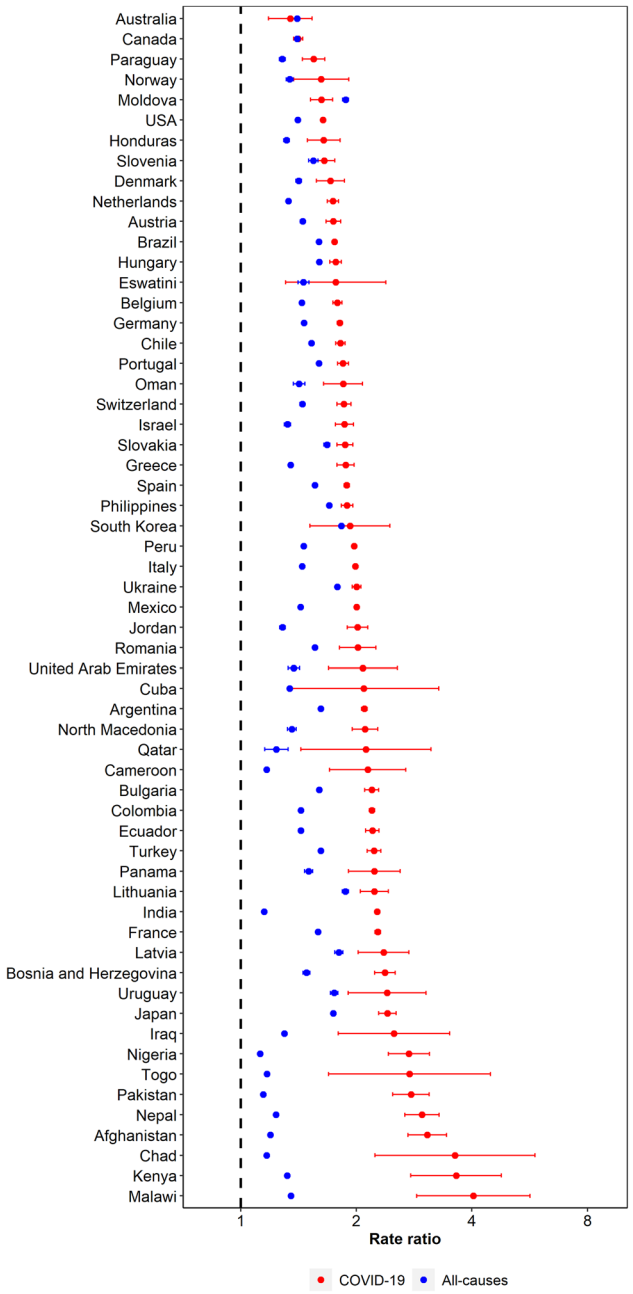

Fig. 1 Male-to-female rate ratios of mortality from COVID-19 and all causes

unusually high male disadvantage in COVID-19 mortality. Our findings, therefore, lend support to hypotheses that posit that the causal pathways that link male sex to a higher mortality from a SARS-CoV-2 infection may be specific to SARS-CoV-2 rather than shared with the pathways responsible for the shorter life expectancy among men than women or the causal pathways for sex differences for other common causes of death.

We do find that the male COVID-19 mortality disadvantage is similar to the size of the male disadvantage in mortality from chronic respiratory diseases. This might suggest that the sex differences in COVID-19 mortality exist due to a causal pathway that is shared by both COVID-19 and chronic respiratory disease. However, our analysis shows that the high male disadvantage for chronic respiratory disease is driven by a stark male mortality disadvantage for bronchitis and emphysema, which in turn is likely explained by the higher prevalence of smoking (especially in the past) among men than women [19–21]. Although smoking could be a part of the causal pathway that explains the male mortality disadvantage for COVID-19, it likely is not the main pathway because smoking has been found to not be as strong a risk factor for the combined outcome of SARS-CoV-2 infection and COVID-19 mortality as some other common risk factors, such as diabetes and obesity [6, 22].

There are several other potential reasons for the higher COVID-19 mortality rate among men. Some studies cite a higher rate of comorbidities, such as diabetes and heart disease, as the reason for the higher COVID-19 fatality rate among men [4, 20, 23–25]. While we cannot directly test this hypothesis, we find that across countries the male COVID-19 mortality disadvantage is substantially larger than their disadvantage for circulatory diseases and diabetes. This suggests that differences in cardiovascular comorbidities may not be a driving factor behind the sex differences in COVID-19 mortality. Other studies suggest that biological factors may explain these disparities. For example, men have a higher expression of the angiotensin-converting enzyme 2 receptor, which is used by SARS-CoV-2 to enter the host cell [3, 26, 27]. Other possible biological factors relate to immunological differences between males and females [28–31]. Ultimately, a combination of biological, behavioral, and social pathways may be responsible for the high male disadvantage in COVID-19 mortality. Elucidating these causal chains is an important research area given that it may assist in the development of therapeutics and preventive measures for COVID-19 and future outbreaks of coronavirus diseases.

This study has several limitations. First and foremost, this study can only provide suggestive evidence as to whether or not the causal pathways underlying the male disadvantage for COVID-19 mortality are shared with those underlying the all-cause mortality disadvantage for men. Second, our mortality rate calculations for COVID-19 use the total population (by sex) as the denominator. Thus, the assumption underlying the validity of our calculation is that there are no substantial differences in the probability of being infected with SARS-CoV-2 between males and females. To date, evidence from seroprevalence studies suggests that this assumption is reasonable [32, 33]. An alternative approach is to use the number of identified cases of SARS-CoV-2 infections as the denominator (i.e., calculating the case fatality rate). This approach, however, assumes that the degree of underdetection of SARS-CoV-2 infections is the same among men

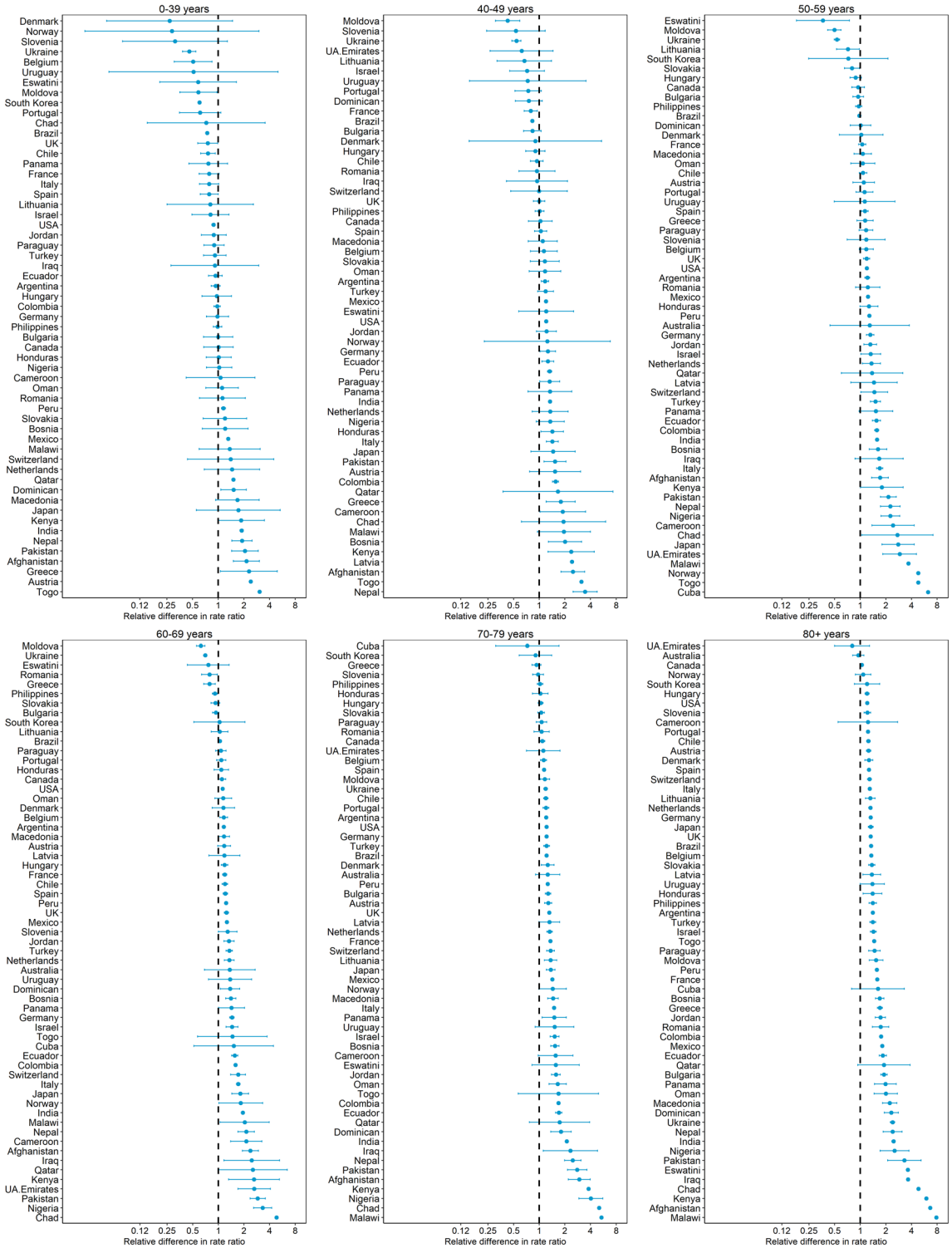

Fig. 2 Relative difference between the male-to-female rate ratios of COVID-19-specific and all-cause mortality, by age group

as among women. This assumption would, for example, be violated if males are more likely to develop symptoms from a SARS-CoV-2 infection than females and are, therefore, more likely to seek out a COVID-19 test, or if men have better access to testing than women. Although both choices for the denominator (total population or number of cases)

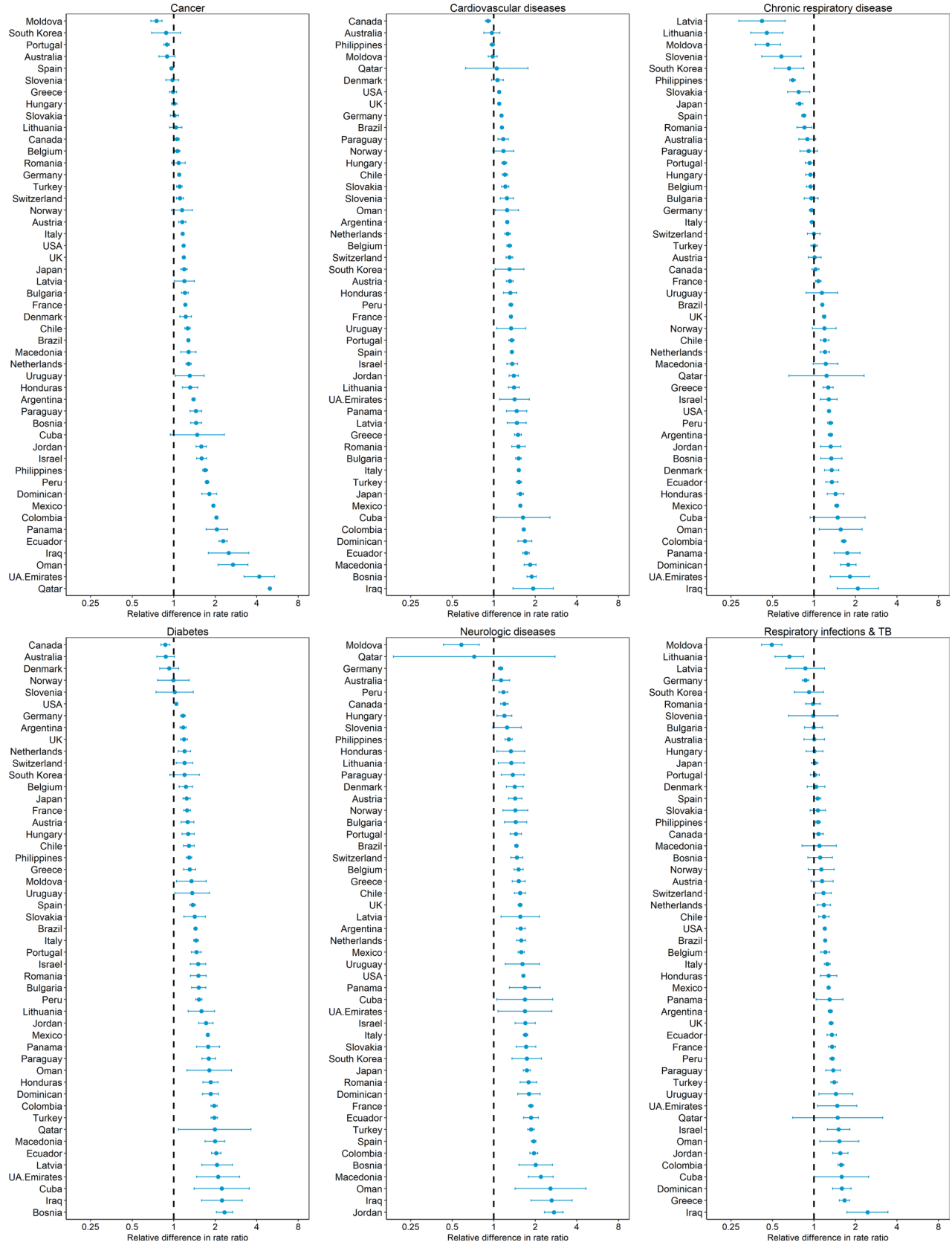

Fig. 3 Relative difference between the male-to-female rate ratios of COVID-19-specific mortality and six major causes of mortality. Respiratory infections and tuberculosis refers to ICD-10 codes J00-J22 and A15-A19. Horizontal lines depict 95% confidence intervals

rely on untestable assumptions, our analyses in which we use the number of cases instead of the total population as denominator found that the choice of denominator does not substantially change our conclusions.

This study indicates that the causal pathways that link male sex to a higher mortality from a SARS-CoV-2 infection may not be shared with the causal pathways for sex differences in all-cause mortality or other common causes of death. Instead, our analysis suggests that the male mortality disadvantage from COVID-19 may be due to sex-specific pathways of SARS-CoV-2 infections. Understanding these SARS-CoV-2-specific pathways could help with the design and development of both preventive measures and therapeutics for COVID-19 and potentially other coronavirus diseases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-022-00866-5.

Author contributions PG: conceptualization, methodology, writing—original draft preparation; TM: methodology, data analysis, writing—reviewing and editing; NJ: methodology, writing—original draft preparation; TR: conceptualization, methodology, data analysis. Writing—reviewing and editing; AR: methodology, writing—reviewing and editing; NS: conceptualization, methodology, writing—reviewing and editing.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study received a determination of not-human subjects research from the institutional review board of the Heidelberg University Hospital.

Consent to participate Not applicable.

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