The age pattern of the male-to-female ratio in mortality from COVID-19 mirrors that of cardiovascular disease in the general population

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ABSTRACT

Males are at a higher risk of dying from COVID-19 than females. Older age and cardiovascular disease are also associated with COVID-19 mortality. To better understand how age and sex interact in contributing to COVID-19 mortality, we stratified the male-to-female (sex) ratios in mortality by age group. We then compared the age-stratified sex ratios with those of cardiovascular mortality and cancer mortality in the general population. Data were obtained from official government sources in the US and five European countries: Italy, Spain, France, Germany, and the Netherlands. The sex ratio of deaths from COVID-19 exceeded one throughout adult life, increasing up to a peak in midlife, and declining markedly in later life. This pattern was also observed for the sex ratio of deaths from cardiovascular disease, but not cancer, in the general populations of the US and European countries. Therefore, the sex ratios of deaths from COVID-19 and from cardiovascular disease share similar patterns across the adult life course. The underlying mechanisms are poorly understood and warrant further investigation.

INTRODUCTION

More males than females die from COVID-19, the disease caused by SARS-CoV-2. This was first observed in China, where 64% of COVID-19 deaths occurred in males [1]. As the epidemic spread worldwide, other countries similarly observed a higher percentage of deaths from COVID-19 in males [1]. The higher number of deaths among males is consistent with mortality patterns observed in several major viral epidemics/pandemics of the 20th and 21st centuries, including the Western African Ebola virus epidemic (2013-2016) [2] and the H1N1 Spanish Flu pandemic of 1918 [3]. Adult men also have an overall higher

mortality rate than adult women from seasonal influenza based on data in the US between 1997-2007, with some variation depending on age group and underlying conditions [4].

In contrast, COVID-19 mortality by age differs from other viral pandemics. More than 80% of COVID-19 deaths in the US and European countries have occurred in adults older than 65 years [5], with very few deaths in young children [6]. Seasonal influenza causes relatively more pediatric deaths, especially in infants under the age of six months [7], in addition to a disproportionate number of deaths in older adults over the age of 65 years [8]. Several major viral pandemics of the 20th and

21st centuries have also shown different age-based mortality patterns from COVID-19. For instance, in the Spanish Flu of 1918 a large proportion of deaths were in young adults [9], and in the 2009 H1N1 influenza pandemic a large proportion occurred in children and adults under 60 years [10]. Therefore, COVID-19 mortality trends are consistent with sex-based, but not with age-based patterns seen in many other viral pandemics.

In searching for explanations for the distinctive pattern of deaths in COVID-19, we first examined variation by age group in the male-to-female (sex) ratio of mortality in data from the US and five European countries. Given that cardiovascular disease (CVD) has been strongly associated with increased risk of mortality in COVID-19 [11], we next examined variation in the sex ratio of CVD mortality by age group in the same countries. As CVD and cancer are the two major age-related disease categories that largely determine survival of adults in middle-and-high income societies [12], we further examined variation by age in the sex ratio of cancer mortality. Here we report our findings and offer potential explanations regarding their meaning.

RESULTS

Stratified by age, and adjusted for population at risk in each age group (Supplementary Figure 1, Supplementary Table 2), the sex ratios for COVID-19 deaths among adults in the US and five European countries (Italy, Spain, France, Germany, and the Netherlands) showed similar overall patterns, initially rising to a peak in midlife and then falling (Figure 1). Specifically, the sex ratio of mortality peaked between the ages of 35-44 years in the US and 60-69 years in the European countries, and then progressively declined at older ages without dropping below one.

We next examined the sex ratio of CVD mortality by age in these countries (Figure 2, Supplementary Figure 2). The sex ratio for CVD mortality initially rose to a peak in midlife and then declined, in both the US and Europe. For ages younger than 70 years, the sex ratio for CVD mortality in Europe was higher than in the US.

As cancer is the other leading cause of adult mortality in the US and Europe [13], we also examined the sex ratio for cancer mortality by age (Figure 3, Supplementary Figures 3, 4). The sex ratio for cancer mortality increased after midlife with no evidence of decline thereafter.

When the sex ratios of mortality by age for COVID-19, CVD and cancer were overlaid, the COVID-19 profile mirrored that of CVD, although, the sex ratio

for CVD was much higher in Europe than the US for ages younger than 70 years (Figure 4). The profile of the sex ratio by age for cancer mortality, however, clearly differed from the ratios for COVID-19 and for CVD.

DISCUSSION

General considerations

Our key findings are as follows: (i) for all age groups, the death rate from COVID-19 was higher in males than females; (ii) the sex mortality ratio for COVID-19 rose to a peak in midlife and then narrowed with increasing age; and (iii) the sex mortality ratio for COVID-19 by age mirrored that for CVD but not cancer. Since the COVID-19 data were not linked to population databases with individual-level health information, we could not specifically examine the potential contribution of CVD to the age pattern of the sex mortality ratio from COVID-19. We propose, nonetheless, based on data displayed in Figure 4, that the sex ratio for COVID-19 mortality, particularly for adults older than 60 years, might partially reflect the mechanisms that drive the age pattern of the sex mortality ratio for CVD in the general population.

What then might be these mechanisms? The underlying biological reasons are likely multifactorial and complex. We review several potential explanations: pre-existing cardiovascular risk factors, sex hormones, and X chromosome mosaicism.

Cardiovascular risk factors

Early available clinical data suggest that patients who become critically ill from COVID-19 are more likely to have pre-existing CVD risk factors such as hypertension and diabetes than patients who experience a milder disease course [14, 15]. Certain CVD risk factors also show different prevalence rates among males and females. For example, hypertension rates are higher in males than in females under the age of 60, but are not significantly different at ages 60 and over [16]. Males also have higher rates of both diagnosed and undiagnosed cases of diabetes, and typically develop atherosclerotic disease earlier than females [17]. These patterns for hypertension and atherosclerotic disease, which occur at higher rates in younger males and at more equal rates at older ages, share similarities with the sex ratios observed for COVID-19 and CVD mortality, and may partially explain the age pattern of the sex ratio in COVID-19 mortality. Though suggestive by our findings, definitive studies are needed to establish direct links between CVD risk factors and COVID-19 mortality.

Sex hormones: estrogens and androgens

Endogenous estrogens have been associated with a protective effect against CVD in premenopausal women [18], while predisposing women to certain cancers [19].

Higher estrogen [20] and progesterone [21] levels in premenopausal women might also modulate immune responses and attenuate the severity of COVID-19. In this regard, data from the US show a decline in the sex ratio of COVID-19 mortality after ages 45-54 years,
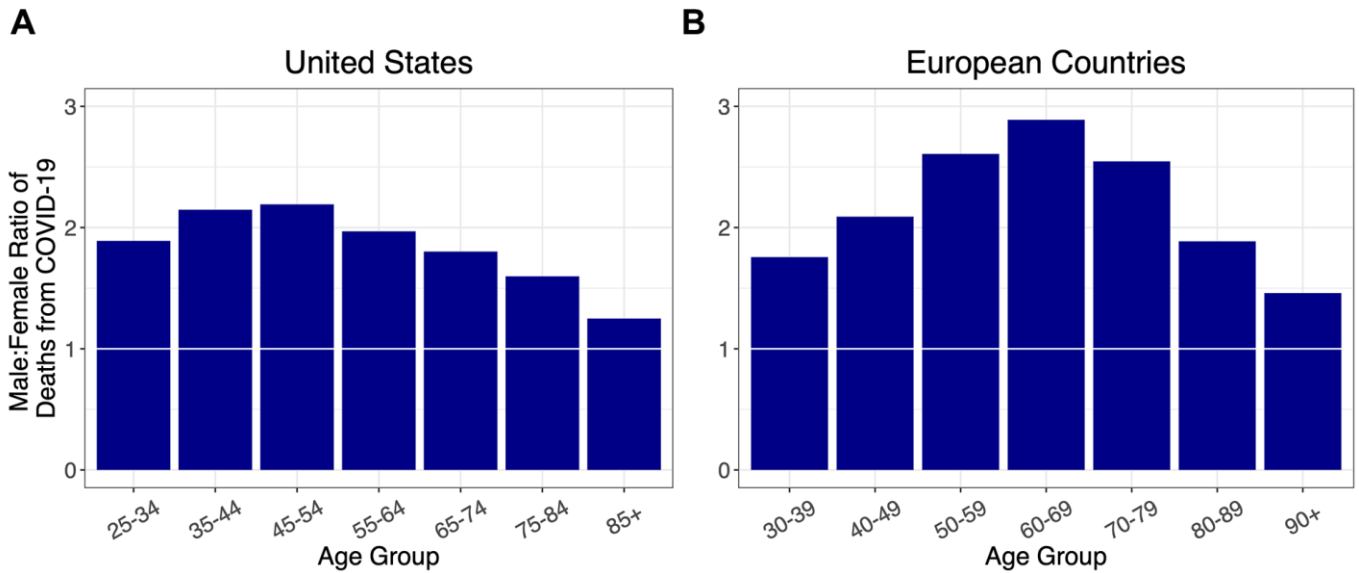

Figure 1. Ratios of male to female deaths from COVID-19 (adjusted for population sex distribution) for (**A**) the US, and (**B**) combined ratios for five European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white markers.
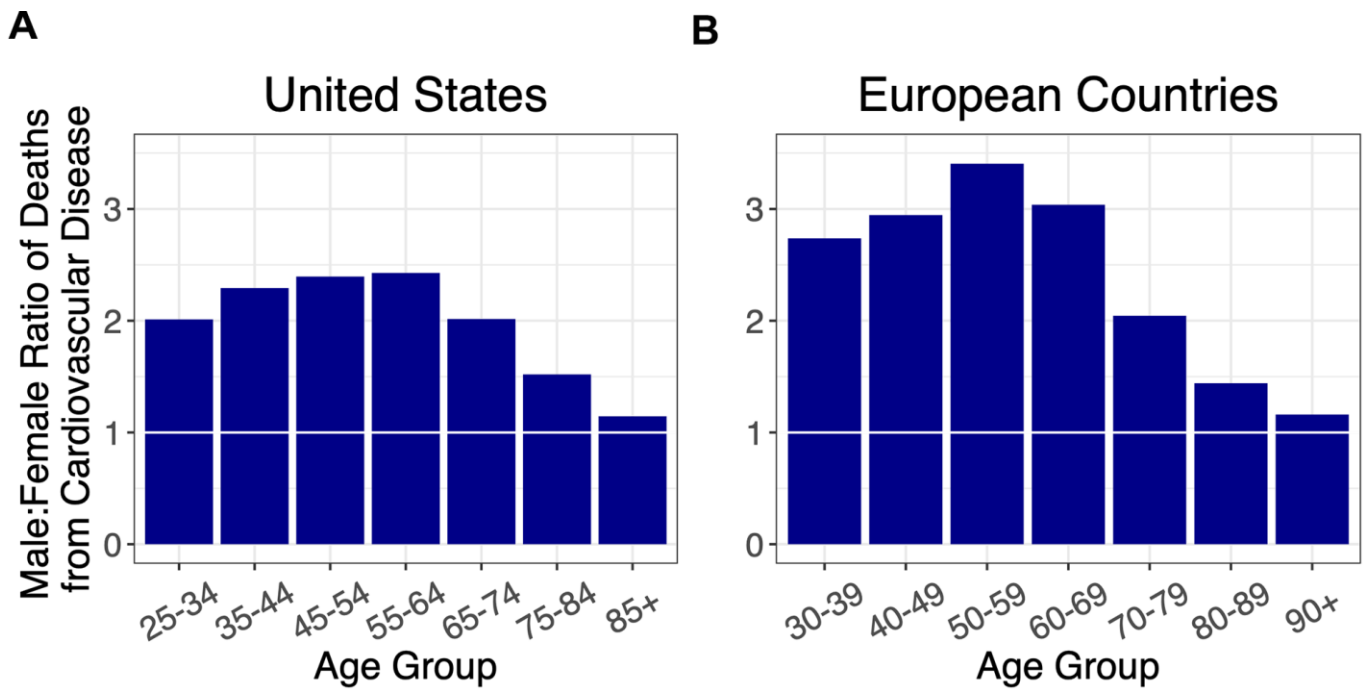

Figure 2. Ratios of male to female deaths from cardiovascular disease (adjusted for population sex distribution) for (**A**) the US, and (**B**) combined ratios for the European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white horizontal lines.

which coincides with the average age that women undergo menopause [22]. However, the data from the European countries show a drop in the sex ratio of COVID-19 mortality starting in the 60-69-year age group- later than the average age of menopause. Clinical trials are currently investigating whether estrogen or progesterone treatment can alleviate COVID-19 symptoms, which may provide more clarity to the role of ovarian hormones in COVID-19 pathogenesis (https://www.clinicaltrials.gov/ identifiers NCT04359329, NCT04365127).

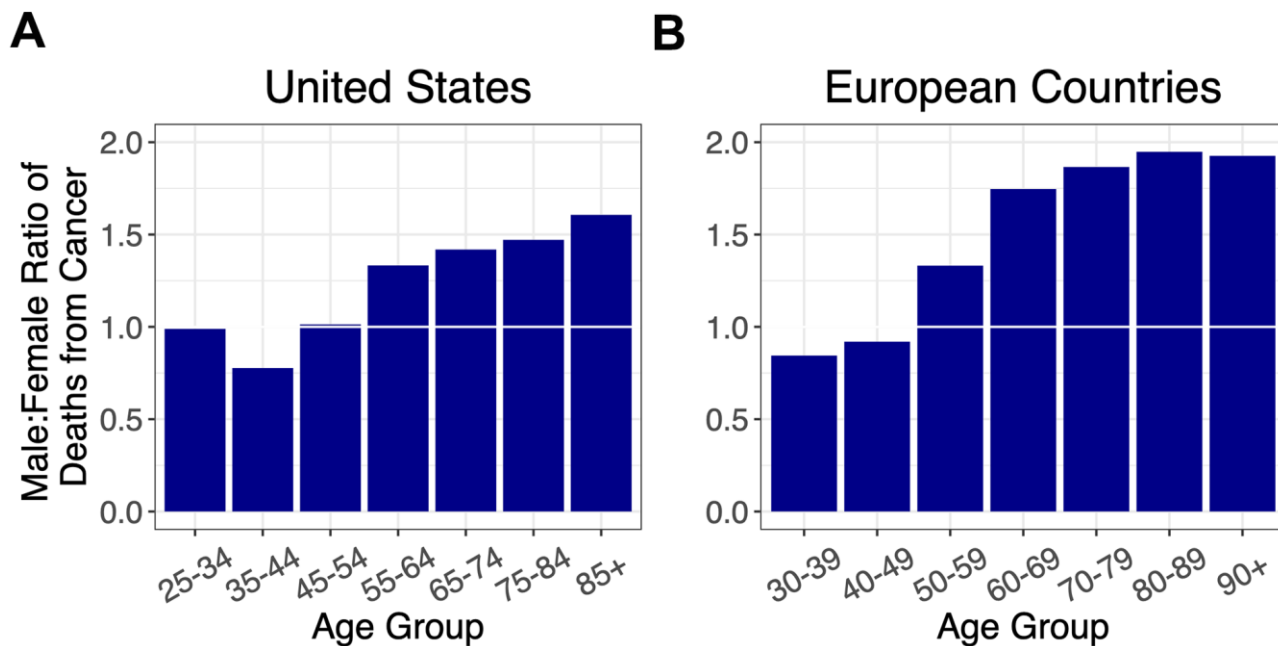Androgen increases the expression of *TMPRSS2* [23], a gene encoding Type II Transmembrane Serine Protease

Figure 3. Ratios of male to female deaths from cancer (adjusted for population sex distribution) for (**A**) the US, and (**B**) combined ratios for the European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white horizontal lines.
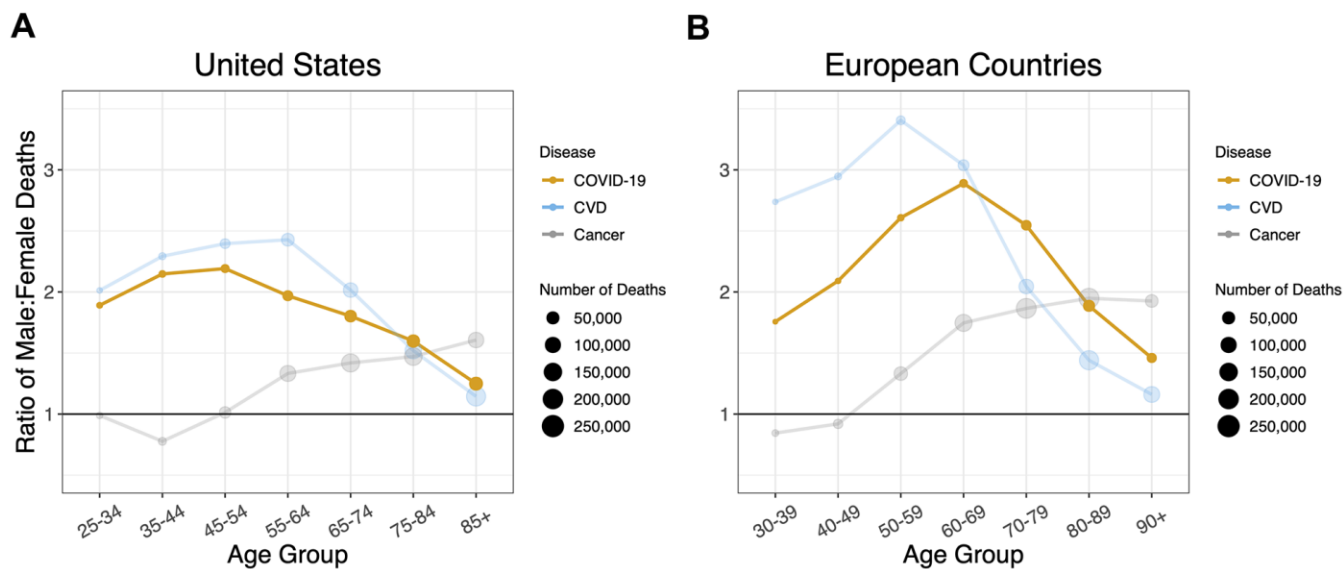

Figure 4. Sex ratios by age group in deaths for COVID-19, cardiovascular disease, and cancer in (**A**) the US and (**B**) the European Countries. A 1:1 ratio is indicated by black horizontal lines. Ratios are adjusted for sex distribution in the population at different age groups.

(TMPRSS2) which activates the SARS-CoV-2 spike protein, facilitating SARS-CoV-2 entry into cells [24]. A recent study suggests that androgen-deprivation therapies lowers the risk of SARS-CoV-2 infection [25]. Since testosterone level decreases with age, a higher level of the hormone in young and middle age men may upregulate *TMPRSS2* and thus contribute to the higher sex ratio for COVID-19 mortality before the sixth decade. That said, the knowledge of the effect of testosterone replacement therapy on the cardiovascular system is incomplete [26].

X chromosome mosaicism

The two X chromosomes provide an advantage related to X-linked recessive diseases and other potentially deleterious mutations on the X chromosome. Random inactivation *in utero* of one X chromosome in each somatic cell engenders mosaicism that provides females with somatic cell diversity and the potential for selection of cells with an X chromosome harboring advantageous variant genes [27]. X chromosome mosaicism might be particularly advantageous for surviving infectious disease, since the X chromosome harbors a number of genes engaged in immune function [28] – therefore having two copies of these genes confers additional immunological diversity in women [29]. In addition, *ACE2*, the gene encoding angiotensin-converting enzyme 2, the cellular receptor for SARS-CoV-2 is on the X chromosome [30]. *ACE2* variants might play a role in left ventricular hypertrophy that is often the outcome of hypertension [31], which tracks with age [32]. Some of these variants might also influence CVD [33], but no association of *ACE2* polymorphisms with COVID-19 was observed thus far [34, 35].

Limitations

Limitations to this study include: (a) potential differences in reporting COVID-19 deaths between the countries analyzed; (b) the lack of linked individual-level health and social databases; and (c) no information on the sex ratio of survival rates among people who acquired COVID-19. The latter would require, at a minimum, COVID-19 infection rates by age and sex in the general population (including asymptomatic infections) in order to determine whether there are sex- and age-based differences in survival from it.

Additionally, the study does not account for nuanced differences in the overall similar patterns for COVID-19 and CVD in the United States versus Europe. The peak sex ratio for COVID-19 occurs at an earlier age in the United States than Europe, and the sex ratio for CVD mortality is higher for Europe than the United States until the older age groups. Finally, we could not rule out that the lower sex ratios in COVID-19 and CVD for the oldest age groups were partly due to selection, in that males who survive to an exceptionally old age are "escapers" who hardly represent the general population of older males; in contrast, females who survive to such an old age might be "delayers" who largely represent the general population of older females [36, 37].

CONCLUSIONS

Our analyses show similar trends in the sex ratio by age of mortality from COVID-19 and from CVD. We propose that these findings might be due to some shared underlying biological mechanisms. Individual-level data are essential to examine potential shared mechanisms and to establish the potential contribution of CVD to the age patterning of the sex ratio of mortality in COVID-19. We suggest that this line of research should be pursued and might uncover some of the causal mechanisms underlying COVID-19 mortality.

MATERIALS AND METHODS

We focused our analysis on the US, Italy, Spain, France, Germany, and the Netherlands because of (a) availability of their sex- and age-disaggregated mortality data from COVID-19, (b) data stratification into age group bins of 10 years or less, and (c) a high number of cumulative deaths from COVID-19 (sources are shown in Supplementary Table 1). COVID-19 mortality data were retrieved from national databases including the US Centers for Disease Control, the Italian National Institute of Health, the French Institute for Demographic Studies, the Spanish Ministry of Health, the German Federal Ministry of Health, and the Dutch Ministry for Health, Welfare and Sport. The data were retrieved on October 14th, 2020 and reflect the cumulative COVID-19 deaths in each country from the beginning of the pandemic up to dates between May 22nd – October 13th 2020 (see Supplementary Tables 1, 2 for details). (Note that after May 22nd, the Spanish Ministry of Health stopped providing sex- and age-disaggregated data on COVID-19 deaths [38].) In the US, data were included for age groups 25 years and older, and stratified into 10-year bins. For the European Countries, data were included for age groups 30 years and above and stratified into 10-year bins, and deaths were combined across the five countries by age group and sex. Age groups below 25 years were excluded from the analysis due to the smaller number of cases. The population at risk in each age group was retrieved from populationpyramid.net, a website that aggregates data from the United Nations Department of Economic and Social Affairs, Population Division.

For the analysis of mortality from CVD and cancer, data were extracted from the World Health Organization Mortality Database (https://www.who.int/healthinfo/mortality_data/en/), which collects national data on deaths from civil registries. The Database contains number of deaths by country, year, sex, age group and cause of death, and population size by country, year, sex and age group. The causes of death are categorized by International Classification of Disease (ICD)-10 codes. CVD deaths principally included deaths from coronary heart disease (ICD-10 codes I20-I25) or stroke (I60-I69) [39]. Cancer death data included deaths from all neoplasms (C00-C97, D00-D48) (Supplementary Table 3). The non-sex-biased cancers (Supplementary Figure 4) included those indicated by ICD-10 codes C00-C49, C64-D04, D09-D23, D30-D38, and D41-D48. Data was extracted for France (2014), Germany (2015), Italy (2015), Netherlands (2016), Spain (2015), and the US (2015), with the year of the most recent data available indicated in parentheses (Supplementary Tables 4–6). Population adjustment was done using population data from the same years as the mortality data. These population data were also extracted from the World Health Organization Mortality Database.

Plots and data visualizations were created using the ggplot2 package in R (https://ggplot2.tidyverse.org).

AUTHOR CONTRIBUTIONS

I.N., L.V., E.S. and A.A. provided substantial contributions to the design of the study. I.N. and A.A. wrote the first draft of the manuscript. All coauthors provided substantial contributions to the analysis and interpretation of data, critically reviewed the manuscript for important intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work presented.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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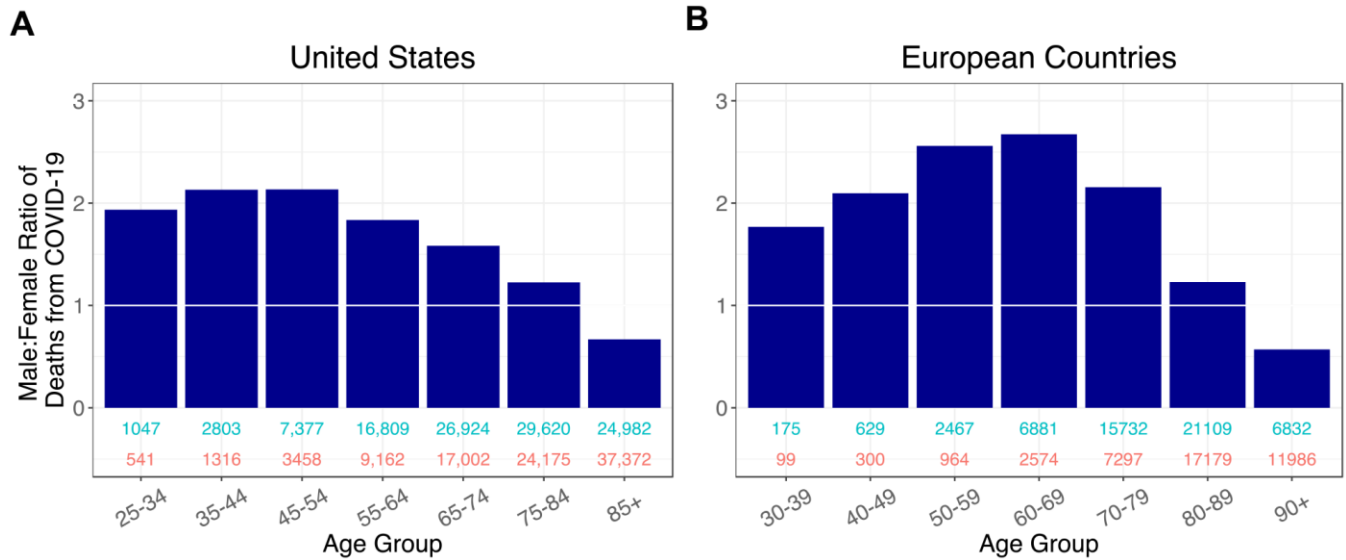
Supplementary Figure 1. Ratios of male to female deaths from COVID-19 (raw data) for the (**A**) United States, and (**B**) combined ratios for five European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white markers. Numbers below plots indicate number of male deaths (turquoise) and female deaths (orange).
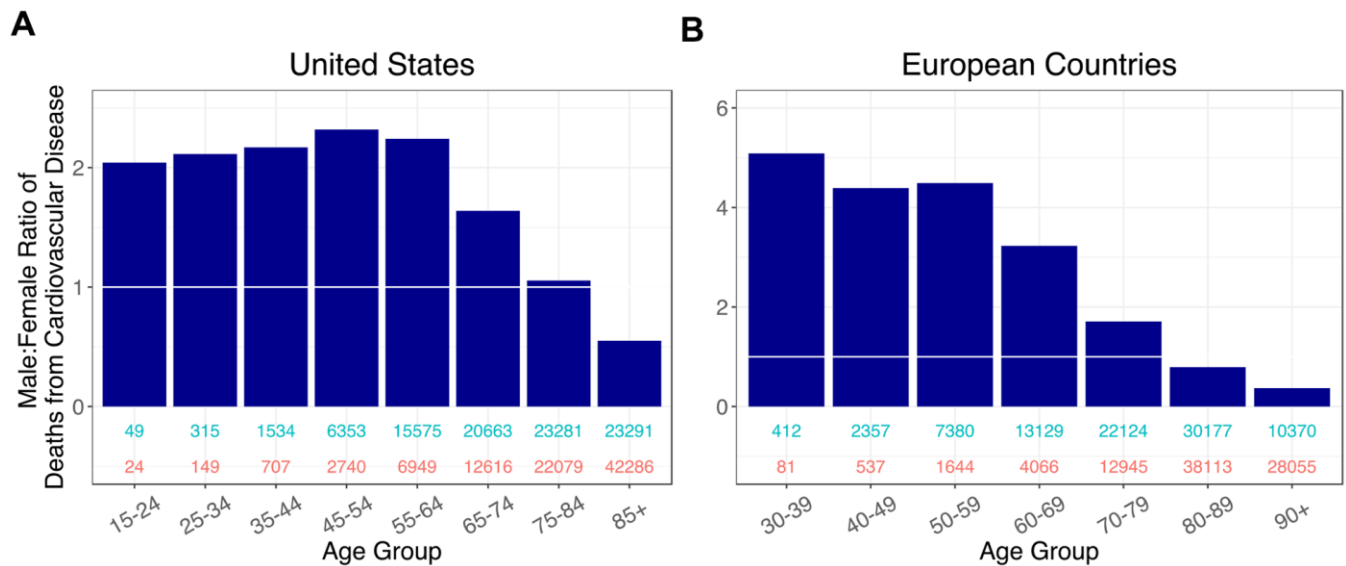
Supplementary Figure 2. Ratios of male to female deaths from cardiovascular disease (raw data) for the (**A**) United States, and (**B**) combined ratios for five European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white markers. Numbers below plots indicate number of male deaths (turquoise) and female deaths (orange). Note that y-axes have different scales.
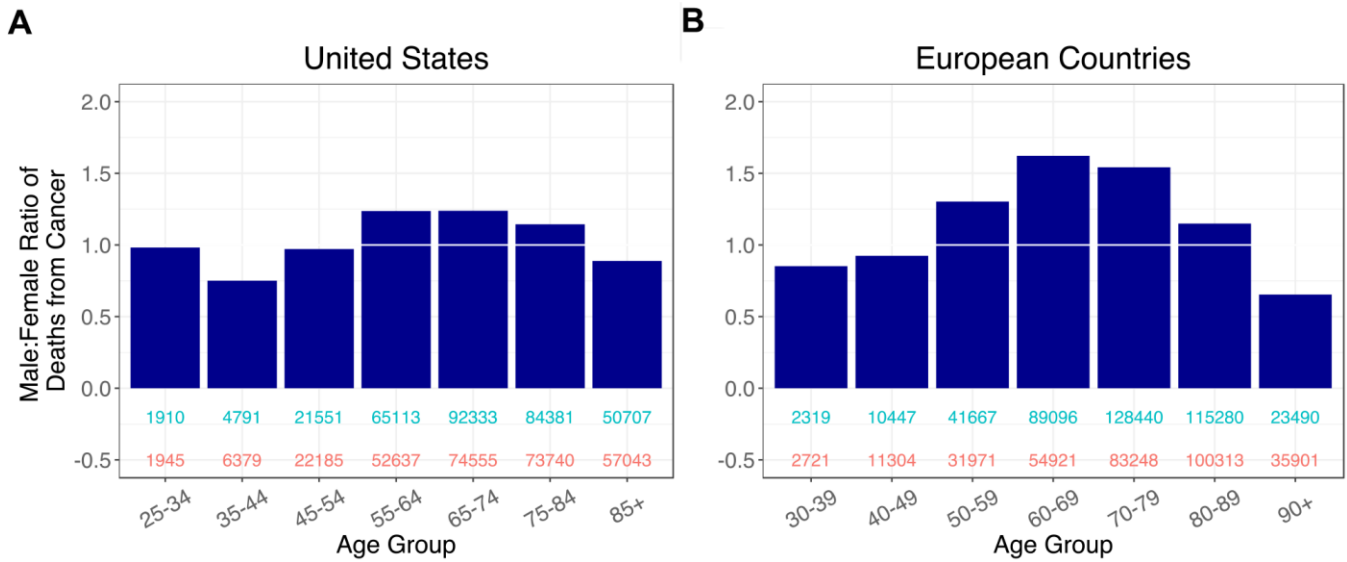
Supplementary Figure 3. Ratios of male to female deaths from cancer (raw data) for the (**A**) United States, and (**B**) combined ratios for five European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white markers. Numbers below plots indicate number of male deaths (turquoise) and female deaths (orange).
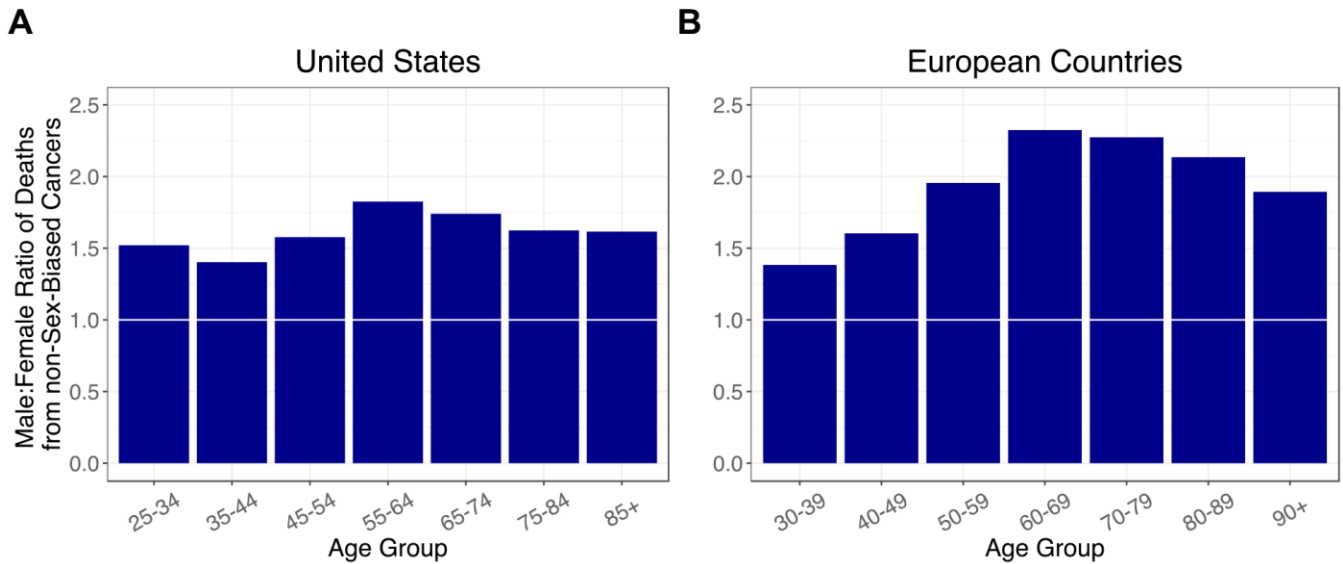
Supplementary Figure 4. Ratios of male to female deaths from non-sex-biased cancers (adjusted for population sex distribution) for the (**A**) United States, and (**B**) combined ratios for five European countries: Italy, France, Spain, Germany, and the Netherlands. A 1:1 ratio is indicated by white markers.

Supplementary Tables

Please browse Full Text version to see the data of Supplementary Table 3.

Supplementary Table 1. Sources for COVID-19 deaths data.

Country	Website	Date updated	Date accessed
United States	https://data.cdc.gov/	Oct 10 2020	Oct 14 2020
Italy	https://www.epicentro.iss.it/	Oct 4 2020	Oct 14 2020
France	https://dc-covid.site.ined.fr/	Oct 8 2020	Oct 14 2020
Spain	https://www.mscbs.gob.es/	May 22 2020	Oct 14 2020
Germany	https://www.rki.de/	Oct 13 2020	Oct 14 2020
Netherlands	https://www.rivm.nl/	Oct 13 2020	Oct 14 2020

Supplementary Table 2. Raw data for COVID-19 deaths stratified by age and sex.

	Age group	Male	Female		Age group	Males	Females		Age group	Male	Female
United States	0-4	22	15	**Italy**	0-9	1	3	**France**	0-9	2	1
	5-14	24	13		10-19	0	0		10-19	2	2
	15-24	230	144		20-29	12	3		20-29	18	9
	25-34	1047	541		30-39	46	24		30-39	61	42
	35-44	2803	1316		40-49	229	89		40-49	178	94
	45-54	7377	3458		50-59	959	302		50-59	667	324
	55-64	16809	9162		60-69	2742	864		60-69	1803	751
	65-74	26924	17002		70-79	6505	2892		70-79	3321	1506
	75-84	29620	24175		80-89	8047	6677		80-89	4600	3415
	85+	24982	37372		90+	2101	4511		90+	1989	2741
	Age group	Male	Female		Age group	Males	Females		Age group	Male	Female
Spain	0-9	1	1	**Germany**	0-9	0	1	**Netherlands**	0-9	0	0
	10-19	3	2		10-19	1	0		10-19	1	0
	20-29	15	9		20-29	8	3		20-29	3	0
	30-39	42	21		30-39	18	8		30-39	8	4
	40-49	140	77		40-49	60	24		40-49	22	16
	50-59	467	192		50-59	265	96		50-59	109	50
	60-69	1283	539		60-69	691	244		60-69	362	176
	70-79	3326	1564		70-79	1467	708		70-79	1113	627
	80-89	4655	3792		80-89	2226	2006		80-89	1581	1289
	90+	1681	2723		90+	617	1185		90+	444	826

Supplementary Table 3. International classification of diseases (ICD)-10 codes for causes of death. Causes of death marked with an 'X' in column 2 were not included in the analysis of non-sex-biased cancers.

Supplementary Table 4. Raw data for cardiovascular disease deaths stratified by age and sex.

Country	Year	Sex	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
Netherlands	2016	F	1	0	4	15	92	248	600	1523	3953	2715
Netherlands	2016	M	0	1	9	26	150	524	1371	2414	3410	1091
Germany	2015	F	7	11	33	86	488	1654	4004	15749	41202	30116
Germany	2015	M	6	8	52	247	1473	5720	11281	27166	35472	10437
Italy	2015	F	11	6	23	73	278	828	2300	8775	32644	28310
Italy	2015	M	10	11	39	207	954	2698	6127	13858	26324	11478
Spain	2015	F	1	2	10	66	245	583	1288	4087	14197	10084
Spain	2015	M	5	10	30	160	780	2286	4011	7396	12333	4629
France	2014	F	9	7	17	55	298	710	1449	3778	13798	11762
France	2014	M	11	6	31	175	790	2181	4417	6500	12377	5088
Country	**Year**	**Sex**	**0-4**	**5-14**	**15-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
United States of America	2015	F	63	45	112	515	2069	7714	18751	32406	58308	119546
United States of America	2015	M	86	51	187	1029	4585	17712	42256	57005	68928	75730

Supplementary Table 5. Raw data for cancer deaths (all) stratified by age and sex.

Country	Year	Sex	30-39	40-49	50-59	60-69	70-79	80-89	90+
Netherlands	2016	M	115	607	2178	5986	8205	6844	1324
Netherlands	2016	F	201	698	2452	4802	5789	5700	1893
Germany	2015	M	592	2960	13167	26374	45208	32306	5315
Germany	2015	F	723	3191	10623	18174	32371	31501	10438
Italy	2015	M	541	2302	7636	19063	32100	31181	6175
Italy	2015	F	613	2707	6776	12629	20792	26554	9083
Spain	2015	M	468	1885	7476	14435	19171	19631	4339
Spain	2015	F	483	1972	4891	6883	9573	14533	5120
France	2014	M	603	2693	11210	23238	23756	25318	6337
France	2014	F	701	2736	7229	12433	14723	22025	9367
Country	**Year**	**Sex**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
United States of America	2015	M	1910	4791	21551	65113	92333	84381	50707
United States of America	2015	F	1945	6379	22185	52637	74555	73740	57043

Supplementary Table 6. Raw data for cancer deaths (excluding sex-biased cancers) stratified by age and sex.

Country	Year	Sex	30-39	40-49	50-59	60-69	70-79	80-89	90+
Netherlands	2016	M	111	597	2106	5575	7294	5686	1042
Netherlands	2016	F	117	415	1684	3651	4567	4560	1455
Germany	2015	M	563	2895	12726	24698	40057	26589	3906
Germany	2015	F	425	1814	7037	13125	23680	23879	7973
Italy	2015	M	520	2254	7475	18327	29942	27450	4929
Italy	2015	F	370	1480	4328	9010	15972	21157	7176
Spain	2015	M	449	1853	7334	13858	17676	16814	3345
Spain	2015	F	278	1094	3326	4914	7335	11435	4036
France	2014	M	576	2659	11009	22242	21735	21342	4744
France	2014	F	400	1563	4864	8524	10504	16682	7284
Country	**Year**	**Sex**	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**85+**
United States of America	2015	M	1800	4686	21006	62199	85570	74508	40933
United States of America	2015	F	1192	3456	13893	36710	56325	58977	45779