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Sex and age differences in COVID-19 mortality in Europe

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Summary
Aim To examine the magnitude of sex differences in survival from the coronavirus disease 2019 (COVID-19) in Europe across age groups and regions. We hypothesized that men have a higher mortality than women at any given age but that sex differences will decrease with age as only the healthiest men survive to older ages.
Methods We used population data from the Institut National D'Études Démographiques on cumulative deaths due to COVID-19 from February to June 2020 in 10 European regions: Denmark, Norway, Sweden, The Netherlands, England and Wales, France, Germany, Italy, Spain and Portugal. For each region, we calculated cumulative mortality rates stratified by age and sex and corresponding relative risks for men vs. women.
Results The relative risk of dying from COVID-19 was higher for men than for women in almost all age groups in all regions. The overall relative risk ranged from 1.11 (95% confidence interval, CI 1.01–1.23) in Portugal to 1.54 (95% CI 1.49–1.58) in France. In most regions, sex differences increased until the ages of 60–69 years, but decreased thereafter with the smallest sex difference at age 80+ years.
Conclusion Despite variability in data collection and time coverage among regions, the study showed an overall similar pattern of sex differences in COVID-19 mortality in Europe.

Keywords SARS-CoV-2 · Cumulative mortality rates · Sex difference · Relative risks · European regions

Supplementary Information The online version of this article (https://doi.org/10.1007/s00508-020-01793-9) contains supplementary material, which is available to authorized users.

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Introduction

Despite the fact that women suffer greater morbidity than men, particularly late in life [1], women outlive men in almost all countries of the world [2]. This is the case even under the harshest conditions where mortality is very high, e.g. during severe famines and epidemics [3]. Since December 2019, the emergence of the coronavirus disease 2019 (COVID-19) has been reported in Wuhan, China, with infection outbreaks across China and around the world [4, 5]. Data from early reported cases in China suggested that the mortality rate from COVID-19 is higher for infected men than for infected women [6–8] with fatality rates of 2.8% in men vs. 1.7% in women [8]. A recent study from mainland China found that the case fatality rate (CFR, the risk of dying among persons diagnosed with COVID-19) was lower in female patients (4.0%) than in male patients (7.2%); however, sex differences varied between regions and were age-dependent with significant differences among patients aged 30 years and above [9]. In agreement

with this finding, the Global Health 50/50 research initiative, which presents an overview of sex-disaggregated data from countries worldwide, demonstrated that despite similar numbers of COVID-19 cases in men and women there is an increased CFR in men [10]. A review collecting epidemiological data on confirmed COVID-19 cases in Europe and China until 1 April 2020 found that the male to female COVID-19 CFRs reported from France, Italy, Spain, Germany, Switzerland and China were relatively homogeneous and ranged between 1.7 and 1.8 [11]. In addition, pooled data from Italy, Spain, Germany and Switzerland comprising 227,219 confirmed cases and 14,364 deaths suggested that although the male to female CFR was consistently elevated through all age groups, the sex difference was most pronounced at middle age, particularly at ages 50–59 years [11]. Correspondingly, data on COVID-19 cases and deaths obtained from outbreaks in China, Italy and New York City demonstrated a higher mortality for men than for women at all ages, with the scale of difference between sexes being consistent with that found for more common causes of mortality, such as heart disease [12].

Here we examine the magnitude of sex differences in survival from COVID-19 across age groups and regions in Europe. This will enable us to investigate the consistency of sex differences across regions and thus to map the epidemiology of the disease; however, due to the highly variable rate of COVID-19 by age, also the age-specific mortality from COVID-19 is considered. We hypothesized that men have higher mortality than women at any given age, but that sex differences in mortality from COVID-19 will decrease with age as only the healthiest men survive to older ages [1].

Material and methods

Study population

This study was based on 10 European regions (Denmark, Norway, Sweden, The Netherlands, England and Wales, France, Germany, Italy, Spain and Portugal) that reported daily cumulative deaths due to COVID-19 by sex and age available from the Institut National D'Études Démographiques (INED) website [13]. The data collection methods and the time period covered differed for each region with the earliest date of 14 February 2020 and the latest date of 29 June 2020 (*see* Supplementary Table 1). Sex-specific and age-specific population sizes (numbers) for the 10 European regions can be found in Supplementary Table 2.

Statistical analysis

Sex-specific cumulative mortality rates (CMR) from COVID-19 per 100,000 men and women were calculated for each day for the covered time periods in each region. In addition, CMR and relative risks (RR) with 95% confidence intervals (CI) were calculated in each region in four age groups (<60 years, 60–69 years, 70–79 years and 80+ years) using data from the last day covered by the study. The Wald test was used to investigate differences between the RRs of adjacent age groups.

Results

In all European regions, the CMRs increased with advancing age (Table 1). The highest CMRs were found in England and Wales with 91.0 (95% CI 89.9–92.1) per 100,000 men and 72.4 (95% CI 71.4–73.3) per 100,000 women. High CMRs were also found in two Southern European regions, Italy (66.2, 95% CI 65.3–67.2 per 100,000 men and 45.4, 95% CI 44.7–46.2 per 100,000 women) and Spain (50.3, 95% CI 49.4–51.2 per 100,000 men and 37.2, 95% CI 36.4–38.0 per 100,000 women). The regions with the lowest mortality from COVID-19 were Norway (5.0, 95% CI 4.2–5.9 per 100,000 men and 4.3, 95% CI 3.6–5.2 per 100,000 women), Denmark (11.8, 95% CI 10.6–13.2 per 100,000 men and 8.9, 95% CI 7.9–10.0 per 100,000 women), and Germany (12.1, 95% CI 11.8–12.5 per 100,000 men and 9.5, 95% CI 9.2–9.8 per 100,000 women) (Table 1). The patterns for the CMRs between February and June 2020 revealed an overall similar trend for men and women; however, higher CMRs were found for men than for women, particularly in Western and Southern Europe (Supplementary Fig. 1).

When investigating the RRs for men vs. women, we found higher mortality among men in all age groups except from ages <60 years for Denmark and Norway and ages 80+ years for Norway (Table 1). The overall RRs ranged from 1.11 (95% CI 1.01–1.23) in Portugal to 1.54 (95% CI 1.49, 1.58) in France; however, the overall RR in Norway was non-significant (RR = 1.15, 95% CI 0.89–1.47). In most regions, sex differences increased from ages <60 years to 60–69 years but decreased thereafter (Table 1). Although not all differences in RRs between adjacent age groups were significant, differences in RRs between the oldest age groups were significant in all regions (Table 1). The largest sex differences were found at ages 60–69 years in Norway, England and Wales, Germany and Italy, up to age 69 years in Sweden, up to age 79 years in the Netherlands, France and Portugal, from 60–79 years in Spain and at ages 70–79 years in Denmark. The smallest sex difference was found at ages 80+ years in all regions (Table 1). Supplementary Fig. 2 illustrates the RRs for men vs. women in the four age groups across Europe. We found the largest sex difference in Norway (RR = 4.27, 95% CI 0.92–19.76), Sweden (RR = 3.03, 95% CI 2.17–4.24), and Italy (RR = 2.91, 95% CI 2.59–3.26) for people below age 60 years, in Norway (RR = 5.97, 95% CI 1.76–20.28), Italy (RR = 3.49,

Table 1 Cumulative mortality rates (CMRs) of COVID-19 per 100,000 men and women and relative risks (RRs) for men vs. women with 95% confidence intervals (CIs) over age groups by 10 European regions

	CMR	95% CI	CMR	95% CI	RR	95% CI
Denmark						
Overall	11.84	(10.64–13.18)	8.92	(7.88–10.01)	1.33	(1.13–1.56)
<60 years	0.55	(0.96–0.99)	0.23	(0.08–0.58)	2.33	(0.82–6.61)
60–69 years	11.34	(8.10–1.58)	6.52	(4.19–10.10)	1.74	(1.03–2.95)
70–79 years	45.88	(38.29–54.94)	16.54	(12.36–22.05)	2.77	(1.99–3.86)[a]
80+ years	157.62	(135.28–183.55)	112.92	(97.50–13.07)	1.40	(1.13–1.72)[a]
Norway						
Overall	4.95	(4.17–5.88)	4.32	(3.58–5.21)	1.15	(0.89–1.47)
<60 years	0.43	(0.21–0.84)	0.10	(0.02–0.40)	4.27	(0.92–19.76)
60–69 years	6.17	(3.77–9.96)	1.03	(0.27–3.29)	5.97	(1.76–20.28)
70–79 years	18.04	(12.94–25.03)	8.44	(5.23–13.45)	2.14	(1.23–3.71)[a]
80+ years	76.30	(59.81–97.16)	64.87	(52.53–80.03)	1.18	(0.86–1.61)[a]
Sweden						
Overall	52.27	(50.33–54.29)	46.11	(44.27–48.01)	1.13	(1.07–1.20)
<60 years	3.65	(3.09–4.31)	1.20	(0.87–1.62)	3.03	(2.17–4.24)
60–69 years	40.22	(35.18–45.97)	16.53	(13.40–20.37)	2.43	(1.91–3.10)
70–79 years	142.07	(131.69–153.25)	76.42	(69.11–84.49)	1.86	(1.64–2.10)[a]
80+ years	773.56	(737.25–811.64)	573.95	(548.22–600.86)	1.35	(1.26–1.44)[a]
The Netherlands						
Overall	39.13	(37.83–40.48)	31.59	(30.43–32.80)	1.24	(1.18–1.30)
<60 years	1.98	(1.66–2.36)	0.97	(0.75–1.26)	2.04	(1.50–2.76)
60–69 years	31.98	(28.68–35.66)	15.78	(13.51–18.42)	2.03	(1.68–2.44)
70–79 years	142.95	(134.45–151.95)	74.26	(68.44–80.58)	1.92	(1.74–2.13)
80+ years	601.69	(574.82–629.79)	393.81	(376.57–411.82)	1.53	(1.43–1.62)[a]
England and Wales						
Overall	90.99	(89.90–92.09)	72.36	(71.40–73.32)	1.26	(1.23–1.28)
<60 years	9.00	(8.62–9.40)	5.06	(4.77–5.36)	1.78	(1.66–1.91)
60–69 years	100.84	(97.32–104.48)	50.04	(47.64–52.57)	2.01	(1.90–2.14)[a]
70–79 years	296.63	(289.67–303.75)	156.15	(151.39–161.07)	1.90	(1.82–1.97)[a]
80+ years	1234.8	(1214.91–1254.77)	848.04	(834.55–861.75)	1.46	(1.42–1.48)[a]
France						
Overall	34.81	(34.18–35.46)	22.65	(22.16–23.17)	1.54	(1.49–1.58)
<60 years	3.45	(3.22–3.69)	1.69	(1.54–1.86)	2.04	(1.81–2.29)
60–69 years	42.82	(40.78–44.97)	15.88	(14.71–18.65)	2.70	(2.46–2.95)[a]
70–79 years	114.51	(110.45–118.71)	43.42	(41.14–45.82)	2.64	(2.47–2.81)
80+ years	390.98	(381.06–401.15)	203.60	(19.82–20.91)	1.92	(1.85–1.99)[a]
Germany						
Overall	12.11	(11.77–12.45)	9.50	(9.21–9.80)	1.27	(1.22–1.33)
<60 years	1.01	(0.91–1.14)	0.40	(0.33–0.48)	2.55	(2.06–3.16)
60–69 years	12.63	(11.67–13.67)	4.21	(3.69–4.81)	2.99	(2.57–3.49)[a]
70–79 years	38.79	(36.77–40.92)	15.76	(14.59–17.02)	2.46	(2.42–2.70)[a]
80+ years	131.46	(126.53–136.57)	89.09	(85.94–92.35)	1.48	(1.40–1.55)[a]
Italy						
Overall	66.24	(65.31–67.17)	45.42	(44.68–46.18)	1.46	(1.43–1.49)
<60 years	5.37	(5.06–5.69)	1.85	(1.67–2.04)	2.91	(2.59–3.26)
60–69 years	73.80	(70.99–76.71)	21.12	(19.70–22.64)	3.49	(3.23–3.78)[a]
70–79 years	226.55	(220.96–232.28)	83.51	(80.41–86.73)	2.71	(2.59–2.83)[a]
80+ years	594.16	(582.36–606.20)	373.17	(365.98–380.49)	1.59	(1.55–1.63)[a]
Spain						
Overall	50.27	(49.37–51.20)	37.18	(36.41–37.96)	1.35	(1.32–1.39)
<60 years	3.76	(3.48–4.06)	1.74	(1.55–1.95)	2.17	(1.89–2.48)
60–69 years	50.41	(47.70–53.26)	19.72	(18.11–21.47)	2.56	(2.31–2.83)[a]
70–79 years	187.42	(181.13–193.93)	73.52	(69.95–77.28)	2.55	(2.40–2.70)
80+ years	597.80	(583.26–612.70)	362.22	(353.52–371.13)	1.65	(1.60–1.70)[a]

Table 1 (Continued)

	CMR	95% CI	CMR	95% CI	RR	95% CI
Portugal						
Overall	16.12	(15.02–17.30)	14.49	(13.50–15.55)	1.11	(1.01–1.23)
<60 years	1.30	(9.69–1.75)	0.66	(0.44–0.99)	1.96	(1.21–3.19)
60–69 years	16.29	(13.28–19.94)	6.65	(4.93–8.95)	2.45	(1.72–3.48)
70–79 years	43.76	(37.74–50.72)	21.87	(18.21–26.25)	2.00	(1.59–2.52)
80+ years	192.50	(175.44–211.20)	140.14	(129.22–151.98)	1.37	(1.22–1.55)[a]

[a]Significant differences in relative risks between age groups (the specific age group and the age group above)

95% CI 3.23–3.78) and Germany (RR = 2.99, 95% CI 2.57–3.49) for people aged 60–69 years, in Denmark (RR = 2.77, 95% CI 1.99–3.86), Italy (RR = 2.71, 95% CI 2.59–2.83) and France (RR = 2.64, 95% CI 2.47–2.81) for people aged 70–79 years and in France (RR = 1.92, 95% CI 1.85–1.99), Spain (RR = 1.65, 95% CI 1.60–1.70) and Italy (RR = 1.59, 95% CI 1.55–1.63) for people aged 80+ years (Supplementary Fig. 2 and Table 1). Overall, the largest sex differences in COVID-19 mortality were found in France, Italy and Spain.

Discussion

By using population estimates from the INED website (February to June 2020) on daily cumulative deaths by age and sex due to COVID-19 in 10 European regions, we found that the risk of death increased with age, and that men had higher mortality from COVID-19 than women in almost all age groups across Europe. In most regions, sex differences increased from ages <60 years to 60–69 years but decreased thereafter with the smallest sex difference at ages 80+ years.

Generally, women live longer than men in almost all countries of the world [2]. A recent study investigating the survival in seven populations under extreme conditions from famines, epidemics and slavery found that even when mortality is very high, women survived on average longer than men [3]. Although the biggest contribution to these differentials came from the large mortality differences among infants, the authors found that for all populations, the extreme age, defined as the age to which 5% of the population survived, was higher for women than for men, supporting the hypothesis of an overall ability of females to withstand higher mortality crises better than males [3]. The study supports that the survival advantage of women has fundamental biological underpinnings and also that the female advantage is modulated by a complex interaction of biological, environmental and social factors [3].

The higher mortality from COVID-19 for men than for women was overall similar to that found for other coronaviruses during the last two decades, such as the severe respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV) [14–17]. The reasons for the sex differences in COVID-19 are likely multifactorial and include differences in immune response, biological differences between the sexes as well as differences in underlying comorbidities [18–20]. Although recent evidence suggests that European women overall have slightly more comorbidities than European men [21], men are generally reported to have more life-threatening conditions, such as cardiovascular diseases, whereas women tend to have more non-fatal chronic diseases, such as migraine, musculoskeletal and autoimmune diseases as well as physical limitations [22–25]. Thus, the higher risk of death from COVID-19 among men may to some extent be explained by the relatively higher prevalence of underlying comorbidities such as cardiovascular disease, hypertension, diabetes and chronic lung disease [10, 26, 27]. Nevertheless, sex differences in health depend on the selected health dimension and the age group studied, and not all outcomes show differences between sexes or show very little differences [28, 29]. Moreover, men and women occupy different social roles, which makes valid comparisons in health outcomes difficult. When comparing men and women of similar social and economic situations, differences between sexes are generally reduced [28, 30]. Another possible reason for the sex differences in COVID-19 mortality is differences in lifestyle, such as smoking and alcohol consumption between men and women [31]. A systematic review including evidence from five studies found that smokers were 1.4 times more likely than non-smokers to have severe symptoms of COVID-19 and were around 2.4 times more likely to need mechanical ventilation, to be admitted to an intensive care unit or to die compared with non-smokers [32]. Thus, the higher risk-taking behavior in men than in women, including a higher prevalence of male smokers, may also contribute to sex differences in COVID-19 mortality [31, 33, 34].

Although we demonstrated a higher mortality from COVID-19 for men than for women in almost all age groups, we found, as hypothesized, a reduction in the relative risk of mortality for men at later ages, consistent with findings elsewhere [12]. A narrowing of the sex gap with increasing age may be consistent with a survival effect, which leaves the healthiest men in the sample [1]; however, if estrogen protects women from the most serious complications of COVID-19, women may be most protected before the menopause due to the higher serum estrogen levels [35].

Evidence from studies investigating sex differences in COVID-19 mortality stresses the importance of addressing the impact of sex differences on disease epidemics, outbreaks, and pandemics in public health policies and efforts. All regions should report data separately by sex, and research studies should, whenever possible, analyze the interactions between age and sex in COVID-19 morbidity and mortality [11].

The strength of this study was the ability to analyze sex differences in COVID-19 mortality by age groups in 10 European regions showing an overall similar pattern of sex differences, despite the variability in data collection and time coverage among regions. Not all countries have reported data separately by sex, and this study was limited to the European regions providing sex-disaggregated data. Another limitation was that the frequency, recording and reporting of COVID-19 deaths differ from one region to another, but may also differ within regions. The cause of death can be certified by different biological tests, by clinical diagnosis, and by mentioning the infection on the death certificates [13]. Therefore, a cross-national comparison of results should be done with caution.

By using population data on daily cumulative deaths due to COVID-19 from 10 European regions, we confirmed a consistently higher mortality from COVID-19 among European men than among European women in almost all age groups. In most regions, sex differences increased from ages <60 years to 60–69 years but decreased thereafter, with the smallest sex difference at ages 80+ years in all regions. This study highlights the importance of addressing the impact of sex on mortality from disease epidemics, but studies using individual-level data are needed to confirm an interaction between age and sex in COVID-19 mortality in order to guide clinical care personnel and to address questions of whether men require additional surveillance, prevention, and earlier intervention than women.

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Author Contribution All authors contributed to the study conception and design. Material preparation, data collection and analyses were performed by Martina Otavova. Linda Juel Ahrenfeldt assisted data analyses and drafted all versions of the manuscript. All authors revised the paper critically and approved the final manuscript.

Conflict of interest L.J. Ahrenfeldt, M. Otavova, K. Christensen, and R. Lindahl-Jacobsen declare that they have no competing interests.

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