Sex differences in the case-fatality rates for COVID-19—A comparison of the age-related differences and consistency over seven countries

Manfred S. Green1*, Dorit Nitzan2, Naama Schwartz1, Yaron Niv3, Victoria Peer1

1 School of Public Health, University of Haifa, Haifa, Israel, 2 World Health Organization, European Region, Copenhagen, Denmark, 3 Israel Ministry of Health, Jerusalem, Israel

* manfred.s.green@gmail.com

Abstract

Background
Early in the COVID-19 pandemic, it was noted that males seemed to have higher case-fatality rates than females. We examined the magnitude and consistency of the sex differences in age-specific case-fatality rates (CFRs) in seven countries.

Methods
Data on the cases and deaths from COVID-19, by sex and age group, were extracted from the national official agencies from Denmark, England, Israel, Italy, Spain, Canada and Mexico. Age-specific CFRs were computed for males and females separately. The ratio of the male to female CFRs were computed and meta-analytic methods were used to obtained pooled estimates of the male to female ratio of the CFRs over the seven countries, for all age-groups. Meta-regression and sensitivity analysis were conducted to evaluate the age and country contribution to differences.

Results
The CFRs were consistently higher in males at all ages. The pooled M:F CFR ratios were 1.71, 1.88, 2.11, 2.11, 1.84, 1.78 and 1.49, for ages 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80+ respectively. In meta-regression, age group and country were associated with the heterogeneity in the CFR ratios.

Conclusions
The sex differences in the age-specific CFRs are intriguing. Sex differences in the incidence and mortality have been found in many infectious diseases. For COVID-19, factors such as sex differences in the prevalence of underlying diseases may play a part in the CFR differences. However, the consistently greater case-fatality rates in males at all ages suggests that sex-related factors impact on the natural history of the disease. This could provide
important clues as to the mechanisms underlying the severity of COVID-19 in some patients.

Introduction

Early in the course of the COVID-19 pandemic, it was observed that there were sex differences in the incidence of the disease [1]. However, this observation has been inconsistent and it is possible that some of the differences observed were due to differences in exposure [2, 3]. In some countries, many of the cases were healthcare workers, who may be overrepresented by females [2, 3]. In South Korea, a large outbreak of COVID-19 occurred in a religious group whose members were predominantly young women [4]. While incidence rate is directly related to exposure, the case-fatality proportion, which is the proportion of deaths among the cases during a specified period of time is a measure of the severity of the disease. It is commonly referred to as the case-fatality rate (CFR) [5–7] and has been reported as being higher in males than females [8]. Since the CFR does not contain any measure of the population exposed, it is less likely to be affected by exposure of the cases [9, 10].

Evidence of sex differences in the CFR for COVID-19, could provide clues to the mechanisms of the infection [11]. Sex differences have been documented for a number of infectious diseases. In general, males tend to have higher incidence rates for many infectious diseases, although not in all age groups [12, 13]. Pertussis is a notable exception, where females dominate in the incidence rates in most age groups [14]. Regarding sex differences in mortality, in a nationwide study of infectious diseases mortality rates in the United States in 1980, prior to the HIV/AIDS epidemic, the rates in males were about 50% higher than in females [15]. The leading cause of infectious disease mortality was from respiratory diseases [15]. The exact mechanism of the sex differences in the incidence and mortality from infectious diseases is not well-understood [11]. Elucidation of the sex differences in the COVID-19 CFR could contribute to a better understanding of the pathogenesis of COVID-19. In this paper we used meta-analytic methods to examine the magnitude and consistency of sex differences in the COVID-19 CFRs by age group, in seven countries.

Materials and methods

Source of data and search strategy

This was a comparative study of retrospective national cohorts of COVID-19. We searched the internet and national health ministry sites for data on COVID-19 cases and deaths, disaggregated by age group and sex. Although this was not a classical systematic review, we used the PRISMA 2009 checklist for guidance in searching for complete national databases (Fig 1).

We were able to locate complete data with comparable age intervals from official published reports for seven countries: Canada, Denmark, England, Israel, Italy, Mexico and Spain. The number of deaths in each age group and sex for Denmark, England and Spain were obtained from official source [16]. The number of confirmed cases of COVID-19 by age group and sex were available for Denmark (for February 2020—December 2020) from Statista [17] and from the official institutes of England [18] and Italy [19] for January 2020- February 2021. The number of confirmed cases and deaths on COVID-19 in Spain, between January 2020 and February 2021, were available from Instituto de Salud Carlos III [20]. Data on COVID-19 cases and death by age group and sex were extracted from the official websites of the government of Canada for January 2020- February 2021 [21], and the governments of Italy [19] and Mexico from February 2020 to February 2021 [22]. The data on COVID-19 for Israel from February 2020 to December 2020 were obtained directly from the Ministry of Health.
Ethical considerations and informed consent

National, open access aggregative and anonymous data were used and there was no need for ethics committee approval.

Statistical analyses

The COVID-19 CFRs by sex and age group were defined as the number of deaths divided by the number of reported cases in each respective sub-group. The age groups were divided by intervals: 0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80+. The ratio of the male to female
CFRs (CFRR) was calculated by dividing the CFRs for males by the CFRs for females, by age group and country. We used meta-analytic methodology to evaluate the overall magnitude and consistency of the sex differences in the CFR of COVID-19 by age group, across different countries. The outcome variable was the male to female CFRR. The independent variables were age group and country. The data presented (forest plot) are the CFRRs by age group and country. Heterogeneity was evaluated using Cochran’s Q statistic. Tau² and I² were used to estimate the between-group variance. If the Q test yielded a p < 0.1, and/or I² ≥ 50%, the random effects model [23] was used to estimate pooled CFRRs and 95% confidence intervals (CI). Otherwise the fixed-effects model was used. To evaluate the effect of individual county on the risk of COVID-19, we performed leave-one-out sensitivity analysis and recomputed the pooled CFRRs. WE further explored the associations of the CFRRs with age-group and country using meta-regression analyses. The meta-analytic methods were carried out using STATA software version 12.1 (Stata Corp., College Station, TX).

**Results**

The summary of male and female CFRRs in different countries for each age group is presented in Table 1.

The meta-analysis of the male to female CFR ratios is shown in the forest plot by age group and country in Fig 2. The number of deaths in the age groups 0–9 and 10–19 were less than 10 in all countries except England and Mexico. Therefore, the estimates in those age groups are very unstable and were not included in the meta-analysis.

Results for each age group and country are displayed as a square and a horizontal line, representing the effect estimate together with its confidence interval. The area of the square reflects the weight that the age and country contribute to the overall study. The combined effect estimate (with confidence interval) is represented by a diamond. For all age groups and countries, the CFRs were consistently higher among males compared with females with the CFRRs ranging mostly between 1.5 and 2.5.

The age-related trend in the male to female CFRRs is shown in Fig 3. Generally, the CFRR increases up to age 59, and then declines to the lowest at age 80+.

In age groups 40–60, the male CFRs are more than double those of the females, and over the age of 60, the male CFRs were 49% to 84% higher. We also looked for possible trends in male to female CFRR ratio by comparing the current updated data with that available on average three months ago (data not shown). There were moderate changes with smaller differences in the CFRRs between the age groups. However, there was no evidence of a trend in the CFRRs and the overall findings were similar.

**Sensitivity analysis**

To evaluate the effect of individual countries and years on the pooled CFRRs, we performed leave-one-out sensitivity analysis and recomputed the pooled CFRRs. No significant differences were found after omitting one country at a time (Table 2).

Similar results were obtained after omission of another age group at a time (Table 3). Thus, no single country or age group substantially influenced the pooled CFRRs. This confirms that the results of this study are stable and robust.

In the meta-regression analysis, CFRR was the dependent variable and age group and country were the independent variables. The results revealed that both variables were statistically significant (age group p = 0.002 and country p = 0.025). This indicated that both the countries and the age groups contributed to the variability in the findings. However, as mentioned earlier, the higher CFR’s in males than females were consistently present in all age groups and countries.
Table 1. Cases, deaths, CFRs (%) (by age group and sex) and male to female CFRRs (%).

| Age Group | Countries | Males cases | Males death | Male CFR | Females cases | Females death | Female CFR | Male: Female CFRR |
|-----------|-----------|-------------|-------------|----------|---------------|---------------|-----------|------------------|
| 0–9       | Italy     | 61722       | 4           | 0.01     | 57271         | 6             | 0.01      | 0.62             |
|           | Denmark   | 3637        | N/A         | N/A      | 3399          | N/A           | N/A       | N/A              |
|           | England   | 79886       | 2           | 0.00     | 75681         | 4             | 0.01      | 0.47             |
|           | Israel    | 26690       | 3           | 0.01     | 25221         | 1             | 0.00      |                  |
|           | Spain     | 504         | 1           | 0.20     | 435           | 1             | 0.23      | 0.86             |
|           | Canada    | No data     | No data     | No data  | No data       | No data       | No data   | No data          |
|           | Mexico    | 11228       | 153         | 1.36     | 10039         | 129           | 1.28      | 1.06             |
| 10–19     | Italy     | 123123      | 5           | 0.00     | 113091        | 5             | 0.00      | 0.00             |
|           | Denmark   | 10975       | N/A         | N/A      | 10165         | N/A           | N/A       | N/A              |
|           | England   | 168844      | 15          | 0.01     | 190305        | 10            | 0.01      | 1.69             |
|           | Israel    | 45191       | 0           | 0.00     | 34289         | 2             | 0.01      | 0                |
|           | Spain     | 806         | 3           | 0.37     | 955           | 2             | 0.21      | 1.78             |
|           | Canada    | No data     | No data     | No data  | No data       | No data       | No data   | No data          |
|           | Mexico    | 37819       | 82          | 0.22     | 39642         | 99            | 0.25      | 0.87             |
| 20–29     | Italy     | 163197      | 29          | 0.02     | 161123        | 20            | 0.01      | 1.43             |
|           | Denmark   | 12158       | N/A         | N/A      | 10165         | N/A           | N/A       | N/A              |
|           | England   | 289285      | 88          | 0.03     | 354648        | 56            | 0.02      | 1.93             |
|           | Israel    | 42443       | 4           | 0.01     | 41521         | 4             | 0.01      | 0.98             |
|           | Spain     | 278302      | 59          | 0.02     | 301370        | 46            | 0.02      | 1.39             |
|           | Canada    | 78252       | 19          | 0.02     | 76271         | 14            | 0.02      | 1.32             |
|           | Mexico    | 165910      | 1170        | 0.71     | 178436        | 726           | 0.41      | 1.73             |
| 30–39     | Italy     | 164200      | 109         | 0.07     | 172681        | 69            | 0.04      | 1.66             |
|           | Denmark   | 8287        | 1           | 0.01     | 8508          | 2             | 0.02      | 0.51             |
|           | England   | 282615      | 296         | 0.10     | 334428        | 207           | 0.06      | 1.69             |
|           | Israel    | 29240       | 11          | 0.04     | 29997         | 7             | 0.02      | 1.61             |
|           | Spain     | 196390      | 102         | 0.05     | 229839        | 74            | 0.03      | 1.61             |
|           | Canada    | 64455       | 48          | 0.07     | 66974         | 22            | 0.03      | 2.27             |
|           | Mexico    | 212606      | 4605        | 2.17     | 217113        | 2039          | 0.94      | 2.31             |
| 40–49     | Italy     | 203639      | 531         | 0.26     | 231251        | 230           | 0.1       | 2.62             |
|           | Denmark   | 8750        | N/A         | N/A      | 9765          | N/A           | N/A       | N/A              |
|           | England   | 249577      | 1018        | 0.41     | 294308        | 637           | 0.22      | 1.68             |
|           | Israel    | 25618       | 20          | 0.08     | 28044         | 22            | 0.08      | 1                |
|           | Spain     | 244110      | 420         | 0.17     | 277509        | 219           | 0.08      | 2.18             |
|           | Canada    | 57065       | 101         | 0.18     | 63694         | 61            | 0.10      | 1.85             |
|           | Mexico    | 202369      | 12882       | 6.37     | 206134        | 5826          | 2.83      | 2.25             |
| 50–59     | Italy     | 234433      | 2203        | 0.94     | 250416        | 803           | 0.32      | 2.93             |
|           | Denmark   | 8740        | 18          | 0.21     | 9055          | 11            | 0.12      | 1.7              |
|           | England   | 244738      | 3359        | 1.37     | 282393        | 1927          | 0.68      | 2.01             |
|           | Israel    | 20005       | 93          | 0.46     | 20948         | 44            | 0.21      | 2.21             |
|           | Spain     | 221061      | 1510        | 0.68     | 248460        | 674           | 0.27      | 2.52             |
|           | Canada    | 53968       | 329         | 0.61     | 56998         | 226           | 0.40      | 1.54             |
|           | Mexico    | 169787      | 23525       | 13.86    | 168598        | 12767         | 7.57      | 7.83             |
| 60–69     | Italy     | 161196      | 6490        | 4.03     | 144962        | 2279          | 1.57      | 2.56             |
|           | Denmark   | 4784        | 49          | 1.02     | 4440          | 34            | 0.77      | 1.34             |
|           | England   | 141785      | 7575        | 5.34     | 141420        | 4213          | 2.98      | 1.79             |
|           | Israel    | 14298       | 237         | 1.66     | 13151         | 122           | 0.93      | 1.79             |
|           | Spain     | 152088      | 4234        | 2.78     | 151938        | 1666          | 1.10      | 2.54             |

(Continued)
Discussion

Based on a comparative study of national data from seven countries, we found that the CFRs for COVID-19 were higher in males in all age groups and the sex ratio of the CFRs varied from 1.49 higher in males in the age 80+, to 2.11 in the age 40–49 and 50–59. Although the CFRR's varied between countries, the excess CFR in males in each age group was a consistent finding with comparable magnitude. Our findings provide evidence of a large and consistent excess CFR in males for COVID-19, for all age groups, over seven countries. This study supports and extends the findings in other studies [6, 7, 24].

A major strength of the study is that it is based on data from countries with large populations and large numbers of deaths and cases. Selection bias has been minimized by using national data, which should be representative of each country. The larger number of female cases in many countries may reflect more exposure in the workplace [2–4]. The inclusion of seven countries, from different geographic location allowed us to evaluate the consistency of the findings over different populations. It does not seem likely that excluding countries that have poor diagnostic facilities or reporting has created an important source of selection bias which would influence the male to female CFRR and affect generalizability of the findings [25]. However, we cannot exclude the possibility that there could be different results from low-income countries, where detailed data are difficult to access.

There are several possible sources of bias in the study. Information bias can be present in both the numerator and denominator of the CFRs. If only those with more severe symptoms are tested this will affect the denominator of the CFR and will depend on the testing strategy of each country. For example, if tests are restricted to the more severe cases and if females tend to have a less severe disease, this would selectively underestimate the number in the CFR denominator and inflate the female CFR [26]. In such a case the male excess in CFR would be underestimated. There may be differences in the policy of performing tests and determining cause of

### Table 1. (Continued)

| Age Group | Countries   | Males cases | Males death | Male CFR | Females cases | Females death | Female CFR | Male: Female CFRR |
|-----------|-------------|-------------|-------------|----------|---------------|---------------|------------|------------------|
| Canada    | 36333       | 1006        | 2.77        | 33915    | 604           | 1.78          | 1.55       |                  |
| Mexico    | 110557      | 30011       | 27.15       | 99277    | 18672         | 18.81         | 1.44       |                  |
| 70–79     | 118023      | 15389       | 13.04       | 110632   | 7137          | 6.45          | 2.02       |                  |
| Denmark   | 2797        | 192         | 6.86        | 2723     | 75            | 2.75          | 2.49       |                  |
| Italy     | 100566      | 9368        | 9.32        | 104748   | 4734          | 4.52          | 2.06       |                  |
| England   | 82610       | 16711       | 20.23       | 80328    | 10425         | 12.98         | 1.56       |                  |
| Israel    | 6771        | 474         | 7.00        | 6496     | 228           | 3.51          | 1.99       |                  |
| Spain     | 35191       | 156331      | 28.95       | 170243   | 30286         | 17.79         | 1.63       |                  |
| Mexico    | 60437       | 24188       | 40.02       | 50052    | 15607         | 31.18         | 1.28       |                  |
| 80+       | 94917       | 27478       | 28.95       | 170243   | 30286         | 17.79         | 1.63       |                  |
| Denmark   | 1339        | 281         | 20.99       | 1963     | 298           | 15.18         | 1.38       |                  |
| England   | 80381       | 35191       | 43.78       | 125379   | 36573         | 29.17         | 1.50       |                  |
| Israel    | 2975        | 787         | 26.45       | 4667     | 803           | 17.21         | 1.54       |                  |
| Spain     | 87861       | 20364       | 23.18       | 156331   | 22388         | 14.32         | 1.62       |                  |
| Canada    | 20482       | 6411        | 31.30       | 39381    | 8366          | 21.24         | 1.47       |                  |
| Mexico    | 25855       | 12560       | 48.58       | 22457    | 8533          | 38.00         | 1.28       |                  |

CFR = case-fatality rates, CFRR = male to female CFR ratio
*N/A—The data for Denmark were excluded since there were no deaths recorded
**Detailed disaggregated data for ages 0–9 and 10–19 in Canada were missing

https://doi.org/10.1371/journal.pone.0250523.t001
death. However, it is unlikely differ between males and females. There may be variability in the coding of causes of death, particularly in people over 80 with multiple co-morbidities. This could differ between the sexes due to differences in comorbidities. Deaths may be underestimated because of a lack of testing after death and in some countries and it is possible that some COVID-19 deaths occurring out of hospital may be missed. However, this should not affect the male to female CFRR. The findings are strengthened by data from the Central Bureau of Statistics in Israel, demonstrating that during 2020 there was more excess mortality in men than in women (personal communication—unpublished data). Although data are lacking for the infection fatality rate (IFR), any sex differences in the IFRs should largely be reflected in the male to female CFRR. Finally, there is a lag time in the occurrence of the deaths relative to the number of cases reported, so the actual CFRRs should be based on the cases reported about two weeks earlier. These data are generally not available and we do not believe that they would have any substantial effect on the CFRRs [27].

Fig 2. Forest plot of the ratio of the male to female CFRRs (CFRR) in seven countries for each age group.

https://doi.org/10.1371/journal.pone.0250523.g002
Sex differences in mortality rates from other infectious diseases have been reported. A male excess in the case-fatality rates was observed in patients diagnosed with MERS in South Korea [28]. In China, the CFR for SARS-Cov-1 in 2002–3 was higher in males [29]. In the United States, infectious disease mortality, prior to the HIV/AIDS epidemic, was more than 50% higher in males [15]. Most of the infectious disease mortality was from lower respiratory tract infections. Other infectious diseases for which a male excess in CFRs include HIV/AIDS during the post-treatment era [30], leptospirosis [31], invasive pneumococcal disease [32], and in HIV patients suffering from tuberculosis [33]. In addition, mortality rates from sepsis appear to be lower in females [34] and there appears to be a more efficient immune response to gram-negative bacteria in female mice [35]. On the other hand, for measles there appears to be excess female mortality under the age of 50 [36] and higher case-fatality rates were observed in females in cases of hemorrhagic fever with renal syndrome in China [37].

While this study cannot provide information on the mechanisms in the sex differences observed, it is possible to postulate some explanations. Regarding possible cultural factors, in the countries in this study, there is no evidence that the sex of the patient influenced the

![Fig 3. The pooled male to female CFRR (for seven countries) by age group together with the 95% CI lower and upper limits, derived from the meta-analysis.](https://doi.org/10.1371/journal.pone.0250523.g003)

Sex differences in mortality rates from other infectious diseases have been reported. A male excess in the case-fatality rates was observed in patients diagnosed with MERS in South Korea [28]. In China, the CFR for SARS-Cov-1 in 2002–3 was higher in males [29]. In the United States, infectious disease mortality, prior to the HIV/AIDS epidemic, was more than 50% higher in males [15]. Most of the infectious disease mortality was from lower respiratory tract infections. Other infectious diseases for which a male excess in CFRs include HIV/AIDS during the post-treatment era [30], leptospirosis [31], invasive pneumococcal disease [32], and in HIV patients suffering from tuberculosis [33]. In addition, mortality rates from sepsis appear to be lower in females [34] and there appears to be a more efficient immune response to gram-negative bacteria in female mice [35]. On the other hand, for measles there appears to be excess female mortality under the age of 50 [36] and higher case-fatality rates were observed in females in cases of hemorrhagic fever with renal syndrome in China [37].

While this study cannot provide information on the mechanisms in the sex differences observed, it is possible to postulate some explanations. Regarding possible cultural factors, in the countries in this study, there is no evidence that the sex of the patient influenced the

Table 2. Sensitivity analysis of the pooled CFRRs for each age group, by removing one country at a time.

| Country removed | Age groups | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80+ |
|-----------------|------------|-------|-------|-------|-------|-------|-------|-----|
| Canada          |            | 1.72 (1.57–1.87) | 1.83 (1.47–2.28) | 2.14 (1.88–2.43) | 2.24 (1.87–2.68) | 1.89 (1.47–2.43) | 1.84 (1.47–2.24) | 1.49 (1.38–1.61) |
| Denmark         |            | -     | -     | -     | 2.13 (1.8–2.53) | 1.9 (1.5–2.41) | 1.7 (1.41–2.05) | 1.5 (1.4–1.61) |
| England         |            | 1.69 (1.55–1.85) | 1.94 (1.57–2.41) | 2.19 (1.92–2.5) | 2.12 (1.67–2.69) | 1.83 (1.35–2.49) | 1.83 (1.44–2.32) | 1.49 (1.35–1.63) |
| Israel          |            | 1.71 (1.57–1.86) | 1.89 (1.54–2.32) | 2.17 (1.95–2.42) | 2.1 (1.76–2.51) | 1.84 (1.45–2.35) | 1.75 (1.44–2.11) | 1.48 (1.38–1.59) |
| Italy           |            | 1.72 (1.57–1.87) | 1.92 (1.55–2.39) | 2 (1.75–2.3) | 1.98 (1.74–2.24) | 1.74 (1.41–2.13) | 1.73 (1.45–2.06) | 1.46 (1.36–1.58) |
| Mexico          |            | 1.58 (1.27–1.96) | 1.7 (1.49–1.94) | 2.02 (1.67–2.44) | 2.17 (1.78–2.66) | 1.94 (1.6–2.35) | 1.87 (1.62–2.15) | 1.54 (1.47–1.61) |
| Spain           |            | 1.73 (1.58–1.88) | 1.94 (1.57–2.4) | 2.08 (1.79–2.41) | 2.04 (1.7–2.44) | 1.74 (1.39–2.17) | 1.73 (1.44–2.07) | 1.47 (1.36–1.58) |
| All countries together |     | 1.71 (1.57–1.86) | 1.88 (1.54–2.29) | 2.11 (1.87–2.38) | 2.11 (1.79–2.49) | 1.84 (1.47–2.3) | 1.78 (1.49–2.12) | 1.49 (1.39–1.59) |

CFRR = case-fatality rate ratio
CI = confidence interval

[https://doi.org/10.1371/journal.pone.0250523.t002](https://doi.org/10.1371/journal.pone.0250523.t002)
medical care given for COVID-19. There is evidence from some countries that women are more likely to seek medical care [38]. However, there is no evidence to suggest that in these countries, adult men are more likely than women to delay medical care for acute conditions of comparable severity. Sex differences in exposure due to behavioural factors could play a part in the incidence of the cases. However, since this study focuses on CFRs that should not influence the result. The severity of COVID-19 has been shown to be strongly associated with underlying conditions in the patients [39]. These include hypertension, diabetes, and obesity. However, in a large study in the United Kingdom, males were still at higher risk of death after controlling for co-morbidities [40].

The genetic and hormonal differences between males and females have been suggested as possible explanations for the higher case-fatality in males [6]. The SARS-CoV-2 virus uses the ACE2 receptor to enter the cells. It has been reported that circulating ACE2 levels are increased in male compared with female subjects, in patients with diabetes or cardiovascular diseases, and in prostate epithelial cells [41, 42]. The different hormonal environment could have extended pathophysiological role in SARS-CoV-2 occurrence, with testosterone, causing men to develop more serious complications related to the SARS-CoV-2 infection [43]. In general, for SARS-CoV, it has been reported, that estrogen signaling in females may directly suppress SARS-CoV replication via effects on cellular metabolism [44].

Estradiol promotes innate immune signaling pathways, and enhances production of pro-inflammatory cytokines and chemokines, a phenomenon that may explain the superior immune response to infection in pre-menopausal females [45–47]. In COVID-19 infected women, the production of inflammatory IL-6 (one of the main components of cytokine storm) is lower than in males and is often correlated with a better longevity [48]. Testosterone has the effect of depressing the innate and adaptive immune response [11, 49]. Thus, it is conceivable that sex hormones are implicated in the mechanism of infection by COVID-19.

However, sex hormone involvement in ACE2 regulation is likely to be important under the age of 50, when differences in hormone levels between men and women are large [50–52]. At older ages, after the age of 50–60, hormone differences probably have less significance because of profound changes in the hormonal milieu in both women and men. Although estrogen concentrations in men are about 200 times lower than that of testosterone, over the age of 50, they are higher than the concentrations in postmenopausal women [53]. In this study, the male excess in CFR’s was evident at all ages, but somewhat lower with increasing age. This could be due to a reduced effect of the differences in sex hormones.

### Table 3. Sensitivity analysis of the pooled CFRRs for each country by removing each age group at a time.

| Excluding age group | Canada | Denmark | England | Israel | Italy | Mexico | Spain |
|---------------------|--------|---------|---------|--------|-------|--------|-------|
| 20–29               | 1.49 (1.45–1.52) | -       | 1.73 (1.58–1.88) | 1.69 (1.57–1.81) | 2.2 (1.82–2.67) | 1.68 (1.41–2) | 2.08 (1.72–2.5) |
| 30–39               | 1.49 (1.45–1.52) | -       | 1.74 (1.59–1.9) | 1.68 (1.57–1.81) | 2.21 (1.82–2.77) | 1.6 (1.36–1.89) | 2.05 (1.7–2.48) |
| 40–49               | 1.49 (1.45–1.52) | -       | 1.71 (1.56–1.87) | 1.7 (1.58–1.82) | 2.07 (1.69–2.52) | 1.61 (1.39–1.86) | 1.97 (1.63–2.39) |
| 50–59               | 1.49 (1.45–1.52) | 1.68 (1.1–2.56) | 1.67 (1.55–1.8) | 1.66 (1.55–1.78) | 2.02 (1.68–2.43) | 1.66 (1.4–1.98) | 1.92 (1.59–2.31) |
| 60–69               | 1.48 (1.45–1.52) | 1.8 (1.12–2.9) | 1.72 (1.58–1.87) | 1.67 (1.55–1.8) | 2.08 (1.73–2.49) | 1.73 (1.4–2.14) | 1.92 (1.62–2.27) |
| 70–79               | 1.49 (1.45–1.53) | 1.39 (1.21–1.59) | 1.78 (1.56–2.04) | 1.6 (1.47–1.72) | 2.13 (1.59–2.84) | 1.77 (1.47–2.12) | 1.96 (1.53–2.53) |
| 80+                 | 1.52 (1.45–1.59) | 1.85 (1.18–2.9) | 1.79 (1.61–2) | 1.89 (1.69–2.12) | 2.29 (1.94–2.72) | 1.77 (1.47–2.12) | 2.15 (1.89–2.45) |
| Original country CFRR [95% CI] | 1.49 (1.45–1.52) | 1.68 (1.17–2.42) | 1.73 (1.59–1.89) | 1.68 (1.57–1.8) | 2.14 (1.78–2.58) | 1.69 (1.43–1.98) | 2 (1.68–2.39) |

CFRR = case-fatality rate ratio
CI = confidence interval

https://doi.org/10.1371/journal.pone.0250523.t003
The severity of SARS-CoV-2 appears to depend on the interaction between the virus and the individual’s immune system differentially by sex and age [54]. Genetic factors could play a part through an interaction with sex hormones [55]. The ACE2 and Ang-II receptor type 2 gene are both located on the X-chromosome and this may impact male susceptibility to COVID-19. X-chromosome genes could encourage mosaic advantage in females and sexual dimorphism that might mitigate viral infection and inflammation due to cytokine storms [56]. At older ages, genetic factors could be more dominant. With ageing, sex chromosomes undergo changes that influence their possible contribution to risk for diseases [57].

Conclusions

In conclusion, the remarkably consistent excess COVID-19 CFRs in males in a number of countries and in all age groups, suggests that sex-specific factors influence the severity of COVID-19. The higher CFRs in males in the younger age groups could be related to a hormonal factor. These findings should stimulate research on sex as a biological variable in the pathogenesis of COVID-19.

Acknowledgments

We thank the official institutions of all countries for the providing their national data on COVID-19.

Author Contributions

Conceptualization: Manfred S. Green, Dorit Nitzan, Yaron Niv, Victoria Peer.

Data curation: Manfred S. Green, Yaron Niv, Victoria Peer.

Formal analysis: Manfred S. Green, Naama Schwartz.

Methodology: Manfred S. Green, Dorit Nitzan, Naama Schwartz, Victoria Peer.

Supervision: Manfred S. Green.

Writing – original draft: Manfred S. Green, Dorit Nitzan, Victoria Peer.

Writing – review & editing: Manfred S. Green, Dorit Nitzan, Naama Schwartz, Yaron Niv, Victoria Peer.

References

1. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020 (In press). https://www.jacionline.org/article/S0091-6749(20)30495-4/pdf Accessed on June 17, 2020. https://doi.org/10.1016/j.jaci.2020.04.006 PMID: 32294485

2. Delivered by women, led by men: a gender and equity analysis of the global health and social workforce. 2019. World Health Organization. https://www.who.int/hrh/resources/health-observer24/en/. Accessed on April 25, 2020.

3. Kim R, Nachman S, Fernandes R, Meyers K, Taylor M, LeBlanc D, et al. Comparison of COVID-19 infections among healthcare workers and non-healthcare workers. PLoS One 2020; 15:e0241956. https://doi.org/10.1371/journal.pone.0241956 PMID: 33296367

4. Korean Society of Infectious Diseases; Korean Society of Pediatric Infectious Diseases; Korean Society of Epidemiology; Korean Society for Antimicrobial Therapy; Korean Society for Healthcare-associated Infection Control and Prevention; Korea Centers for Disease Control and Prevention. Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020. J Korean Med Sci 2020; 35:e112. https://doi.org/10.3346/jkms.2020.35.e112 PMID: 32174069

5. A Dictionary of Epidemiology. Edited by Miquel Porta. Oxford University Press. 6th Edition. 2014.
6. Lipsitch M. Estimating case fatality rates of COVID-19. Lancet Infect Dis 2020:S1473-3099(20)30245-0. https://doi.org/10.1016/S1473-3099(20)30245-0.

7. Green MS, Peer V, Schwartz N, Nitzan D. The confounded crude case-fatality rates (CFR) for COVID-19 hide more than they reveal—a comparison of age-specific and age-adjusted CFRs between seven countries. PLoS One 2020 21; 15:e0241031. https://doi.org/10.1371/journal.pone.0241031 PMID: 33085731

8. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020; 11:29. https://doi.org/10.1186/s13293-020-00304-9 PMID: 32450906

9. Ravi S, Kapoor M. COVID-19 trends from Germany show different impacts by gender and age. Brookings Institute. May 1, 2020. https://www.brookings.edu/blog/technologystream/2020/05/01/covid-19-trends-from-germany-show-different-impacts-by-gender-and-age/. Accessed on June 10, 2020.

10. Dudel C, Riffe T, Acosta E, van Raalte A, Strozza C, Myrskylä M. Monitoring trends and differences in COVID-19 case-fatality rates using decomposition methods: Contributions of age structure and age-specific fatality. PLoS One. 2020; 15:e0238904. https://doi.org/10.1371/journal.pone.0238904 PMID: 32913365

11. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016; 16:626–38. https://doi.org/10.1038/nri.2016.90 PMID: 27546235

12. Green MS. The male predominance in the incidence of infectious diseases in children: a postulated explanation for disparities in the literature. Int J Epidemiol. 1992; 21:381–6 https://doi.org/10.1093/ije/21.2.381 PMID: 1428496

13. Guerra-Silveira F, Abad-Franch F, Nishiura H. Sex bias in infectious disease epidemiology: patterns and processes. PLoS One. 2013; 8 e62390. https://doi.org/10.1371/journal.pone.0062390 PMID: 23638062

14. Peer V, Schwartz N, Green MS. A multi-country, multi-year, meta-analytic evaluation of the sex differences in age-specific pertussis incidence rates. PLoS One. 2020; 15:e0231570. https://doi.org/10.1371/journal.pone.0231570 PMID: 32347490

15. El Bcheraoui C, Mokdad AH, Dwyer-Lindgren L, Bertozzi-Villaume A, Stubbs RW, Morozoff C, et al. Trends and patterns of differences in infectious disease mortality among US counties, 1980–2014. JAMA. 2018; 319:1248–60. https://doi.org/10.1001/jama.2018.2089 PMID: 29584843

16. The Demography of COVID-19 Deaths (2020). National Institute for Demographic Studies (INED). https://dc-covid-site.ined.fr/en/data/. Accessed at February 2020.

17. Statista. https://www.statista.com/. Accessed at February 2020.

18. Public Health England. https://coronavirus.data.gov.uk/details/cases. Accessed at February 2020.

19. Istituto Superiore di Sanità. Epidemiology for public health. https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-dashbaord. Accessed at February 2020.

20. Instituto de Salud Carlos III. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx. Accessed at February 2020.

21. The official website of the Government of Canada: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html?topic=tileLink#a2. Accessed at February 2020.

22. Gobierno de México: https://datos.covid-19.conacyt.mx/. Accessed at February 2020.

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177–88. https://doi.org/10.1016/0197-2456(86)90046-2 PMID: 3802833

24. Alkhouli M, Nanjundappa A, Annie F, Bates MC, Bhatt DL. Sex differences in case fatality rate of COVID-19: Insights From a multinational registry. Mayo Clin Proc. 2020; 95:1613–1620. https://doi.org/10.1016/j.mayocp.2020.05.014 PMID: 32753136

25. Phillips P, Ross-Degnan D, Wagner AK. Does access to medicines differ by gender? Evidence from 15 low and middle income countries. Health Policy. 2013; 110:60–6. https://doi.org/10.1016/j.healthpol.2013.01.016 PMID: 23422029

26. Ancocchea I, Izquierdo JL, Soriano JB. Evidence of Gender Differences in the Diagnosis and Management of Coronavirus Disease 2019 Patients: An Analysis of Electronic Health Records Using Natural Language Processing and Machine Learning. J Womens Health (Larchmt). 2020. https://doi.org/10.1089/jwh.2020.8721 PMID: 33416429

27. Gianicolo E, Riccetti N, Blettner M. Epidemiological Measures in the Context of the COVID-19 Pandemic.Karch A. Dtsch Arztebl Int. 2020; 117:336–42. https://doi.org/10.3238/arztebl.2020.0336 PMID: 32527379
28. Kim KH, Tandi TE, Choi JW, Moon JM, Kim MS. Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications. J Hosp Infect. 2017; 95:207–13. https://doi.org/10.1016/j.jhin.2016.10.008 PMID: 2815358

29. Jia N, Feng D, Fang LQ, Richardus JH, Han XN, Cao WC, et al. Case fatality of SARS in mainland China and associated risk factors. Trop Med Int Health. 2009; 14: 21–7. https://doi.org/10.1111/j.1365-3156.2008.02147.x PMID: 19508439

30. Castilho JL, Melekhin VV, Sterling TR. Sex differences in HIV outcomes in the highly active antiretroviral therapy era: a systematic review. AIDS Res Hum Retroviruses. 2014; 30:446–56. https://doi.org/10.1016/j.aid.2013.02.008 PMID: 24401107

31. Jansen A, Stark K, Schneider T, Schöneberg I. Sex differences in clinical leptospirosis in Germany: 1997–2005. Clin Infect Dis. 2007; 44:e69–72. https://doi.org/10.1086/513431 PMID: 17407027

32. Backhaus E, Berg S, Andersson R, Ockborn G, Malmström P, Dahl M, et al. Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors. BMC Infect Dis. 2016; 16:367. https://doi.org/10.1186/s12879-016-1648-2 PMID: 27487784

33. Gupta-Wright A, Fielding K, Wilson D, van Oosterhout JJ, Grint D, Mwandumba HC, et al. Tuberculosis in hospitalised patients with HIV: clinical characteristics, mortality, and implications from the STAMP trial. Clin Infect Dis. 2019;ciiz1133.

34. Kahlke V, Dohm C, Mees T, Broßmann K, Schreiber S, Schroeder J. Early interleukin-10 treatment improves survival and enhances immune function only in males after hemorrhage and subsequent sepsis. Shock. 2002; 18: 24–8. https://doi.org/10.1097/00024382-200207000-00005 PMID: 12095129

35. Zeng Z, Surewaard BGJ, Wong CHY, Guettler C, Burkhard R, et al. Sex-hormone-driven innate immunity improves survival and enhances immune function only in males after hemorrhage and subsequent sepsis. Shock. 2002; 18: 24–8. https://doi.org/10.1097/00024382-200207000-00005 PMID: 12095129

36. Klein SL, Marks MA, Li W, Glass GE, Fang LQ, Ma JO, et al. Sex differences in the incidence and case fatality rates from hemorrhagic fever with renal syndrome in China, 2004–2008. Clin Infect Dis. 2011; 52: 1414–21. https://doi.org/10.1093/cid/cir232 PMID: 21628481

37. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. J Fam Pract. 2000; 49:147–52. PMID: 10718692

38. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020; S0163-4453(20)30234-6.

39. Xie HJ, Zhang GH, Wang RR, Zheng YT. The influence of age and sex on the cell counts of peripheral blood leukocyte subpopulations in Chinese rhesus macaques. Cell Mol Immunol. 2009; 6:433–40. https://doi.org/10.1038/s41590-018-0211-2 PMID: 30250184

40. Salonia A, Corona G, Giwercman A, Maggi M, Minhas S, Nappi RE, et al. SARS-CoV-2, Testosterone and frailty in males (PROTEGGIMI): A multidimensional research project. Andrology 2020.

41. Patel SK, Velkoska E, Burrell LM. Emerging markers in cardiovascular disease: where does angiotensin-converting enzyme 2 fit in? Clin Exp Pharmacol Physiol. 2013; 40:551–9. https://doi.org/10.1111/1440-1681.12069 PMID: 23432153

42. Song H, Seddighzadeh B, Cooperberg MR, Huang FW. Expression of ACE2, the SARS-CoV-2 receptor, and TMPRSS2 in prostate epithelial cells. bioRxiv 2020.04.24.056259

43. Xia HJ, Zhang GH, Wang RR, Zheng YT. The influence of age and sex on the cell counts of peripheral blood leukocyte subpopulations in Chinese rhesus macaques. Cell Mol Immunol. 2009; 6:433–40. https://doi.org/10.1038/cmi.2009.55 PMID: 20003819

44. Bereshchenko O, Bruscoli S, Riccardi C. Glucocorticoids, sex hormones, and immunity. Front Immunol. 2018; 9:1–10. https://doi.org/10.3389/fimmu.2018.00001 PMID: 29403488

45. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical Response to viral infection. J Biol Regul Homeost Agents. 2020; 34. https://doi.org/10.23812/Editorial-Conti-3 PMID: 32253888
49. Liva SM, Voskuhl RR. Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production. J Immunol. 2001; 167:2060–7. https://doi.org/10.4049/jimmunol.167.4.2060 PMID: 11489988

50. Fischer M, Baessler A, Schunkert H. Renin angiotensin system and gender differences in the cardiovascular system Cardiovasc Res. 2002; 53:672–7. https://doi.org/10.1016/s0008-6363(01)00479-5 PMID: 11861038

51. Regitz-Zagrosek V, Oertelt-Prigione S, Seeland U, Hetzer R. Sex and gender differences in myocardial hypertrophy and heart failure. Circ J. 2010; 74:1265–73. https://doi.org/10.1253/circj.cj-10-0196 PMID: 20558892

52. Seeland U, Regitz-Zagrosek V. Sex and gender differences in cardiovascular drug therapy. Handb Exp Pharmacol. 2012; 214:3–22. https://doi.org/10.1007/978-3-642-30726-3_11 PMID: 23027453

53. Vermeulen A, Kaufman JM, Goemaere S, van Pottelberg I. Estradiol in elderly men. Aging Male. 2002; 5:98–102. PMID: 12198740

54. Li X, Geng M, Peng Y, Meng L, Lu S, Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020; 10:102–108. https://doi.org/10.1016/j.jpaha.2020.03.001 PMID: 32282863

55. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genomics 2019; 13:2. https://doi.org/10.1186/s40246-018-0185-z PMID: 30621780

56. Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V. COVID-19 and individual genetic susceptibility/receptivity: Role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 Compared to the single X-Chromosome in Males? Int J Mol Sci. 2020; 21:E3474. https://doi.org/10.3390/ijms21103474 PMID: 32423094

57. Machiela MJ, Zhou W, Karlins E, et al. Female chromosome X mosaicism is age-related and preferentially affects the inactivated X chromosome. Nat Commun. 2016; 7:11843. https://doi.org/10.1038/ncomms11843 PMID: 27291797