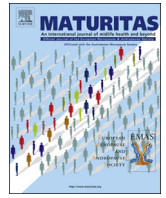




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Coronavirus disease 2019 and gender-related mortality in European countries: A meta-analysis

Faustino R. Pérez-López^{a,*}, Mauricio Tajada^b, Ricardo Savirón-Cornudella^c,
Manuel Sánchez-Prieto^d, Peter Chedraui^{e,f}, Enrique Terán^g

^a Instituto de Investigación Sanitaria de Aragón and University of Zaragoza Faculty of Medicine, Zaragoza, Spain

^b Hospital Universitario Miguel Servet and University of Zaragoza Faculty of Medicine, Zaragoza, Spain

^c Hospital General de Villalba, Collado Villalba, Madrid, Spain

^d Instituto Universitario Dexeus, Barcelona, Spain

^e Instituto de Investigación e Innovación en Salud Integral, Facultad de Ciencias Médicas, Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador

^f Facultad de Ciencias de la Salud, Universidad Católica Nuestra Señora de la Asunción, Asunción, Paraguay

^g Colegio de Ciencias de la Salud, Universidad San Francisco de Quito, Quito, Ecuador

ARTICLE INFO

Keywords:

COVID-19
Coronavirus 2019
Fatalities
Gender
Global health 50/50
Mortality
SARS-CoV-2

ABSTRACT

Objective: To examine mortality rates related to coronavirus disease 2019 (COVID-19) by gender among European countries.

Methods: PubMed, preprint medRxiv and bioRxiv repositories, and Google were searched for the terms COVID-19, mortality rates, gender, and Europe. Only Google provided a website with appropriate information. COVID-19 cases and deaths from European countries were extracted by gender from the Global Health 50/50 repository up to May 23, 2020. Extracted data included country, the total number of COVID-19 cases and the number of related deaths by gender. Random effects models with the inverse variance method were used for meta-analyses. Results are reported as death risk ratios (RRs).

Results: We identified information from 23 European countries that reported separately by gender mortality rates related to COVID-19. The sample comprised 484,919 men and 605,229 women positive for COVID-19. The mortality rate was significantly higher in men than in women (risk ratio = 1.60, 95 % confidence interval [CI] 1.53, 1.68). The trend was similar when countries reporting < 5000, or < 10,000 cases were excluded from the analysis (RR = 1.60, 95 % CI 1.52, 1.69 and RR = 1.68; CI 1.62, 1.76, respectively).

Conclusion: In Europe, the new zoonotic coronavirus causes significantly more deaths in men than in women.

1. Introduction

The novel coronavirus disease 2019 (COVID-19) is generating a large amount of scientific literature and controversies since its detection on December 2019 in Wuhan (China). The infection rapidly spread worldwide, becoming pandemic in a few weeks probably through the large amount of international air travel, many mass public gatherings and the lack of appropriate precautions. There is no doubt that this is one of the greatest and worst pandemics in human history. It should be an alert for the promotion of changes in lifestyles. Information from initial hospitalized patients in China suggested that older age and having comorbidities were associated with more severe disease and mortality. In addition, in men COVID-19 is a more severe disease, with a higher mortality rate than in women [1–3].

Xie et al. [3] reported 168 Chinese patients who died during the

acute phase of the disease. Of these, 126 were men, with a median age of 70 (interquartile range 64–78); 161 (95.8 %) were older than 50 years, and 74.4 % had one or more co-morbidities. Guan et al. [1] also reported data from 1099 laboratory-confirmed COVID-19 patients from 552 hospitals of 30 Chinese provinces through January 2020. A total of 41.9 % were women and those with severe disease were older (by a median of 7 years) than those without severe disease. The presence of any coexisting illness was also more common among those with severe disease as opposed to those with non-severe disease (38.7 % vs. 21.0 %).

A systematic review by Rozenberg et al. [4] suggested a higher mortality risk in men than in women. The authors also reviewed different factors associated with COVID-19-related fatalities. The Zhu et al. [5] meta-analysis summarizes the most relevant aspects of the new disease among Chinese people, and reported that males accounted for

* Corresponding author at: Department of Obstetrics and Gynecology, University of Zaragoza Faculty of Medicine, Zaragoza 50009, Spain.

E-mail address: faustino.perez@unizar.es (F.R. Pérez-López).

53.3 % of all deaths. During the past months, there have been several reports highlighting the fact that mortality is higher in men than in women in England, Wales and Germany [6]. Hence, the objective of the present study was to examine if the mortality risk by gender in Europe is different from or similar to that in China.

2. Method

2.1. Search strategies

A PubMed search strategy was performed using the following terms (COVID-19 OR SARS) AND (Europe) AND (mortality) AND (Gender) that yielded 7 publications. However, there was no information regarding the specific topic in terms of comparing fatalities by gender in different European countries. In addition, the pre-print medRxiv [7] and bioRxiv [8] repository servers of scientific research were searched on May 2, 2020. A search was also performed on Google on May 20, 2020, using the same strategy, rendering a list of 7,020,000 items and sites with relevant information. The first 15 items reported the most consulted information on the matter and were more targeted on the issue of mortality gender differences in patients with COVID-19 [9–23]. This procedure has been previously validated to obtain relevant medical information through Google [24]. The remaining web links, up to the initial 200 top Google references, did not report different specific information regarding COVID-19 mortality by gender in European countries.

2.2. Item selection and data extraction

The only source of information about mortality related to COVID-19 by gender in European countries was the Global Health 50/50 repository [9]. We extracted public information accumulated up to May 23, 2020 from this data repository related to mortality by country and gender. Global Health 50/50 is a nonprofit organization that highlights gender health inequalities and is currently studying along with the Cable News Network [25] the influence of gender on the evolution of COVID-19. For the present analysis we extracted information reported online by country [9] and up to May 23, 2020, from the corresponding national authorities.

2.3. Eligibility criteria and outcomes

Results were eligible if information on mortality and number of cases was separately reported by gender in European countries. Two researchers independently evaluated study eligibility, and discrepancies during the study selection process were discussed and resolved through author consensus.

The primary outcome was mortality due to COVID-19 affecting men and women, separately reported by gender. Other outcomes were not available. Definitions for case inclusion were based on national standards at the time of each country report. Extracted data included country, the total number of COVID-19 cases and the total number of related deaths, both indicators by gender, and as reported by the corresponding national authorities. If some of these variables were not available for extraction, the country was excluded. Meta-analyzed countries are presented in Fig. 1.

2.4. Meta-analysis

Random-effect models with the inverse variance method were used for meta-analyses. Effects were reported as risk ratios (RRs) for cases of mortality by country and gender divided by COVID-19 infected cases by gender with their corresponding 95 % confidence intervals (CIs). A p value of < 0.1 for the χ^2 test was used to define heterogeneity; a τ^2 value of > 1 was defined as the presence of substantial statistical heterogeneity. An I^2 value of 0–30 % was defined as low heterogeneity,

30–65 % moderate heterogeneity, and > 65 % substantial heterogeneity [25]. To explore reasons for heterogeneity we predefined subgroup analyses by excluding countries reporting fewer than 5000 or fewer than 10,000 cases. Publication bias was not assessed since there was one single source of information, although we included more than 10 countries. Statistical analyses were conducted using Review Manager (RevMan 5.3; Cochrane Collaboration, Oxford, UK).

3. Results

Twenty-three countries reported extractable data with the required predefined information, giving a total of 484,919 men and 605,229 women positive for COVID-19. The meta-analysis by gender indicates that men have a significantly higher risk of COVID-19-related death than women (RR = 1.60, 95 % CI 1.53, 1.68; $I^2 = 92$ %; $\tau^2 = 0.01$; $df = 22$, $P < 0.001$) (Fig. 1). The gender mortality trend was similar when countries with fewer than 5000 cases (RR = 1.60, CI 1.52; 1.69, 478,500 women and 597,908 men; $I^2 = 93$ %) or fewer than 10,000 cases were excluded (RR = 1.68; CI 1.62, 1.76; $I^2 = 89$ %; 383,367 women and 495,327 men). Since there is only one source of information, there was a high risk of bias. Sensitivity analyses were performed by omitting each country, one by one, in order to evaluate the stability of the results, and the I^2 was still > 65 %.

4. Discussion

The present analysis of the information from the Global Health 50/50 demonstrates that men are more vulnerable to COVID-19 than women in terms of mortality, and the effect persists even when countries reporting fewer cases are excluded for analysis. Our results suggest that the mortality risk is significantly higher for men than women, and more so than is suggested by results from China [26]. This finding seems to apply regardless of individual baseline health characteristics, and social, economic, and healthcare systems. Indeed, although the studied endpoint was the same (COVID-19 deaths) for all analyzed countries, the sample is heterogeneous in terms of local clinical facilities, political orientations, and structure of healthcare organizations. For instance, some European countries did not recommend confinement measures (e.g. Sweden), while others applied confinement ('lockdown') too late (e.g. Spain) [27].

Although there is no exact information, it seems that the impact of the COVID-19 crisis was focused in some countries, and in general, on the most vulnerable segments of the population: elders, those with comorbid conditions, and those living in residential care for the elderly. Perhaps younger individuals were prioritized for access to the intensive care units. This information is not currently available, and will require appropriate and detailed analysis in order to identify any health disparities, especially in relation to populations who have and have not paid for healthcare cover. Despite all these limitations, our meta-analysis suggests that there are causes inherent to gender that determine a higher mortality rate in males than females.

Differences have been observed among several Asiatic countries in terms of COVID-19 prevalence and related mortality [28]. This situation suggests (i) social and healthcare differences, (ii) heterogeneity of outcomes, including prevalence and mortality, and (iii) other factors related to social organizations and political interventions [28]. In Europe, healthcare policies and social recommendations applied by corresponding national authorities have also been diverse or heterogeneous. In this sense, one can mention the application of confinement measures (e.g. some applied early, while others applied later or too late, or never applied them) [27].

Current research shows that a poor prognosis with COVID-19 is related to factors such as gender (male), age (> 60 years), underlying diseases (hypertension, diabetes, and cardiovascular disease), and secondary acute respiratory distress syndrome (ARDS), among others [4,29]. One narrative review underlined differences related to gender,

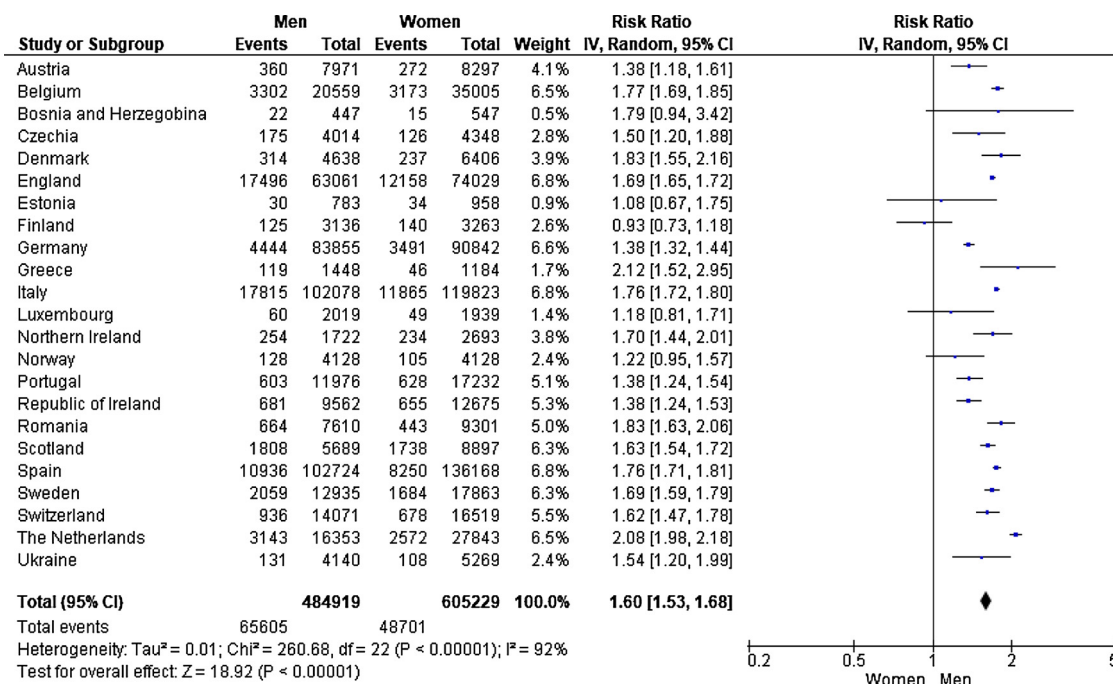


Fig. 1. Risk ratio and 95 % confidence intervals of COVID-19 related deaths reported in 23 European countries: Comparison men versus women.

diagnosis, prognosis and mortality rates among COVID-19 patients [30] but the results were not mathematically analyzed. In this sense, we meta-analyzed and found a significant gender difference in COVID-19 related deaths among Europeans.

4.1. Limitations

There are several limitations related to the available data on mortality associated with the COVID-19 pandemic. At the present time, there is no scientific reports that compare the mortality rate by gender in European countries. Results are reported in a heterogeneous manner in different European countries and the analyzed data from Global Health 50/50 include this limitation. The current total number of COVID-19-related deaths is likely to be higher than the number of confirmed deaths. We suggest different reasons for this: (i) under-recording is most likely a result of limited testing capacity and problems in the attribution of the cause of death; (ii) recorded COVID-19-related in death registries may differ between countries (e.g. some may only count hospital deaths, whilst other have started to include deaths at home or deaths in residential settings for the elderly); (iii) some countries delay reporting COVID-19-related deaths, hence data are not always up to date; and (iv) the available information by gender does not include age, which may be a confounding factor in the current meta-analysis. Despite the aforementioned limitations, to the best of our knowledge, the Global Health 50/50 is the only current source of European information reporting by gender.

4.2. Strength

Despite the mentioned limitations, our analysis has strengths. Indeed, it was based on a potential COVID-19-related outcome that requires reporting (death in relation to the number of cases stratified by gender in European countries that supposedly have the obligation to report health outcomes to supranational organisations).

The current analysis allows the conclusion to be drawn that men living in Europe have a significantly higher risk of COVID-19-related death. However, more detailed information is urgently needed to examine the factors involved in COVID-19 mortality, including age, basal health status, co-morbidity, and lifestyle. In this sense, unfortunately

the European Centre for Disease Prevention and Control [31], which is the agency in charge of information at supranational level, does not report the aforementioned COVID-19-related information. There is an urgent need for this situation to be improved.

In conclusion, during the last months, the mortality rate related to the COVID-19 pandemic was significantly higher in European males than in European females, but the causes or mechanisms and circumstances of this difference were not identifiable with the available evidence. Supranational health authorities should design appropriate strategies to overcome the lack of accurate information.

Contributors

Faustino R. Pérez-López conceived, designed, supervised, and drafted the article, extracted data from the Global Health 50/50 Repository and calculated outcomes of interest.

Mauricio Tajada contributed to the searches on PubMed, Google, and Preprint Repositories.

Ricardo Saviórn-Cornudella contributed to the searches on PubMed, Google, and Preprint Repositories.

Manuel Sánchez-Prieto contributed to the searches on PubMed, Google, and Preprint Repositories.

Peter Chedraui extracted data from the Global Health 50/50 Repository and calculated outcomes of interest.

Enrique Terán extracted data from the Global Health 50/50 Repository and calculated outcomes of interest.

All authors contributed to interpreting the results and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This research was partially supported by the Sistema de Investigación y Desarrollo and the Vice-Rectorado de Investigación & Postgrado of the Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador, through grant No. SIU-318-853-2014 (The Omega

II, Women's Health Project 2014) provided to Peter Chedraui.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

References

- [1] W.J. Guan, Z.Y. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, *N. Engl. J. Med.* (2020), <https://doi.org/10.1056/NEJMoa2002032>.
- [2] J.M. Jin, P. Bai, W. He, et al., Gender differences in patients with COVID-19: focus on severity and mortality, *Front. Public Health* 8 (2020) 152, <https://doi.org/10.3389/fpubh.2020.00152>.
- [3] J. Xie, Z. Tong, X. Guan, B. Du, H. Qiu, Clinical characteristics of patients who died of coronavirus disease 2019 in China, *JAMA Netw. Open* 3 (2020) e205619.
- [4] S. Rozenberg, J. Vandromme, C. Martin. Are we equal in adversity? Does Covid-19 affect women and men differently? *Maturitas*, in press. doi: 10.1016/j.maturitas.2020.05.009.
- [5] J. Zhu, Z. Zhong, P. Ji, et al., Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis, *Fam. Med. Community Health* 8 (2) (2020) e000406, <https://doi.org/10.1136/fmch-2020-000406>.
- [6] R.V. Reeves, T. Ford, COVID-19 Much More Fatal for Men, Especially Taking Age Into Account, *Brookings*, 2020, https://www.brookings.edu/blog/up-front/2020/05/15/covid-19-much-more-fatal-for-men-especially-taking-age-into-account/?utm_campaign=Brookings%20Brief&utm_source=hs_email&utm_medium=email&utm_content=88024035.
- [7] MedRxiv. The preprint server for health sciences. <https://www.medrxiv.org/> (Visited 20 May 2020).
- [8] BioRxiv. The preprint server for biology. <https://www.biorxiv.org/> (Visited 21 May 2020).
- [9] Global Health 50/50. Sex, gender and COVID-19: overview and resources. Tracking differences in COVID-19 illness and death among women and men. <https://globalhealth5050.org/covid19/>.
- [10] A. Palloni, S. Walter. COVID-19: How can we explain differences in mortality? <https://population-europe.eu/policy-insights/covid-19-how-can-we-explain-differences-mortality>.
- [11] Population Europe. Demography and COVID-19. population-europe.eu/news/demography-coronavirus.
- [12] Statista Number of coronavirus (COVID-19 deaths in Germany in 2020, by gender and age. [Statista.com/statistics/1105512/coronavirus-covid-19-deaths-by-gender-germany](https://www.statista.com/statistics/1105512/coronavirus-covid-19-deaths-by-gender-germany).
- [13] A. Di Stadio, G. Ricci, A. Greco, M. de Vicentiis, M. Ralli, Mortality rate and gender differences in COVID-19 patients dying in Italy: a comparison with other countries, *Eur. Rev. Med. Pharmacol. Sci.* 24 (8) (2020) 4066–4067, https://doi.org/10.26355/eurrev_202004_20980 published.
- [14] Ravi S., Kapoor M. Covid-19 trends from Germany show different impacts by gender and age. *Brookings*. <https://www.brookings.edu/blog/techtank/2020/05/01/covid-19-trends-from-germany-show-different-impacts-by-gender-and-age/>.
- [15] Gendered impact of the COVID-19 pandemic. https://en.wikipedia.org/wiki/Gendered_impact_of_the_COVID-19_pandemic.
- [16] J. Aron, J. Muelbauer. Measuring excess mortality: England is the European outlier in the Covid-19 pandemic. <https://voxeu.org/article/excess-mortality-england-european-outlier-covid-19-pandemic>.
- [17] J. Felix-Cardoso, H. Vasconcelos, P. Rodrigues, R. Cruz Correia. Excess mortality during COVID-19 in five European countries and a critique of mortality analysis data. <https://www.medrxiv.org/content/10.1101/2020.04.28.20083147v1>.
- [18] Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update. <https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-coronavirus-disease-2019-eighth-update-8-april-2020.pdf>.
- [19] Euronews. Coronavirus: COVID-19 death rates higher in men doing low-skilled professions, says ONS. <https://www.euronews.com/2020/05/11/coronavirus-covid-19-death-rates-higher-in-men-doing-low-skilled-professions-says-ons>.
- [20] France 24. Coronavirus: Why do more men die of Covid-19 than women? <https://www.france24.com/en/20200331-coronavirus-why-do-more-men-die-of-covid-19-than-women>.
- [21] World Health Organization. Beyond the mortality advantage. Investigating women's health in Europe. <http://www.euro.who.int/en/health-topics/health-determinants/gender/publications/2015/beyond-the-mortality-advantage.-investigating-womens-health-in-europe>.
- [22] Why COVID-19 Is Hitting Men Harder Than Women – Healthline <https://www.healthline.com/health-news/men-more-susceptible-to-serious-covid-19-illnesses>.
- [23] BBC. Why is COVID-19 is different for men and women. <https://www.bbc.com/future/article/20200409-why-covid-19-is-different-for-men-and-women>.
- [24] F.R. Pérez-López, G.R. Pérez Roncero, Assessing the content and quality of information on the treatment of postmenopausal osteoporosis on the World Wide Web, *Gynecol. Endocrinol.* 22 (12) (2006) 669–675, <https://doi.org/10.1080/09513590601012603>.
- [25] K. Polglase, G. Mezzofiore, M. Foster CNN. Here's why the coronavirus may be killing more men than women. The US should take note. <https://edition.cnn.com/2020/03/24/health/coronavirus-gender-mortality-intl/index.html>.
- [26] J. Zhu, Z. Zhong, P. Ji, et al., Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis, *Fam. Med. Community Health* 8 (2) (2020) e000406, <https://doi.org/10.1136/fmch-2020-000406>.
- [27] F.R. Pérez-López, R. Savirón-Cornudella, P. Chedraui, A.R. Genazzani, Severe acute respiratory syndrome coronavirus 19 and human pregnancy, *Gynecol. Endocrinol.* 36 (4) (2020) 277–278, <https://doi.org/10.1080/09513590.2020.1747426>.
- [28] C.C. Lai, C.Y. Wang, C.Y. Wang, S.C. Hsueh, W.C. Ko, P.R. Hsueh, Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status, *Int. J. Antimicrob. Agents* 55 (4) (2020) 105946, <https://doi.org/10.1016/j.ijantimicag.2020.105946>.
- [29] H. Cheng, Y. Wang, G.Q. Wang, Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19, *J. Med. Virol.* (March 27) (2020), <https://doi.org/10.1002/jmv.25785>.
- [30] I. Ambrosino, E. Barbagelata, E. Ortona, et al., Gender differences in patients with COVID-19: a narrative review, *Monaldi Arch. Chest Dis.* 90 (2) (2020), <https://doi.org/10.4081/monaldi.2020.1389> doi:10.4081/monaldi.2020.1389.
- [31] European Centre for Disease Prevention and Control. ecdc.europa.eu/en.