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Research article

Time-related changes in sex distribution of COVID-19 incidence proportion in Italy

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ABSTRACT

Background: Variable sex-disaggregated data on Coronavirus disease 2019 (COVID-19) incidence proportion (IP) have been reported in different datasets and studies. Factors explaining the inconsistent distribution of COVID-19 among sexes are still unclear.

Objectives: This study aimed to analyse time-related variation of sex-disaggregated COVID-19 IP in Italy since March 9th to May 11th 2020, and to test its association with the frequency of swab testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Study design: Sex-disaggregated data on COVID-19 cases were collected from Italian publicly accessible databases along with undisaggregated data on the number of reverse transcriptase–polymerase chain reaction (RT-PCR) SARS-CoV-2 tests. Crude and adjusted associations between the frequency of RT-PCR SARS-CoV-2 testing and male-to-female (M/F) ratio of COVID-19 IP were performed.

Results: COVID-19 IP increased progressively in both sexes. Sex prevalence of COVID-19 IP reversed over time, with the M/F ratio of COVID-19 IP having passed from 1,73 to 0,91. The mean number of daily swabs for RT-PCR SARS-CoV-2 test increased progressively until reaching a plateau in the last three weeks of the study period. The M/F ratio of COVID-19 IP inversely correlated with the number of daily swabs for RT-PCR SARS-CoV-2 test ($r = -0,87$, $p < 0.001$), even after adjusting for the median age of COVID-19 cases ($\beta = -0,66$, $p < 0,001$).

Conclusions: Time-related changes of sex distribution of COVID-19 IP in Italy are strongly influenced by the number of swabs testing for SARS-CoV-2. Whether gender-related disparities in the access to the diagnosis of COVID-19 may explain such a result need to be explored.

1. Introduction

Despite large efforts having been made to understand Coronavirus Disease 2019 (COVID-19) pathophysiology and epidemiology worldwide [1, 2, 3, 4, 5, 6, 7, 8], sex-related differences in COVID-19 outbreak remain unclear based on data available so far. Early reports from different countries, including Italy, have shown significantly higher COVID-19 incidence proportions (IP) in males as compared to females [1, 2, 3, 4]. This has led to hypothesize a different biologically-determined susceptibility to COVID-19 between sexes. However, in other studies COVID-19 cases have been reported to be either more frequent among females than males or even equally distributed between sexes [5, 6]. Thus, whether gender, that is the cluster of socially defined characteristics of sex, may be a significant driver of COVID-19 risk needs to be elucidated. This study aimed to: 1) analyse time-related changes of COVID-19 IP in females and males in Italy since March 9th up to May 11th 2020; 2) investigate whether the temporal trend of sex distribution of COVID-19 IP was associated with concomitant variations in the number of swabs performed daily to diagnose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The median age of COVID-19 cases, which is a strong determinant of the susceptibility to develop and die from COVID-19 [9], has been included as a confounder of the association between sex distribution of COVID-19 IP and the frequency of swab testing.

2. Methods

Sex-disaggregated data on total COVID-19 cases and deaths as well as undisaggregated data on the median age of COVID-19 cases and the frequency of daily swabs for reverse transcriptase–polymerase chain reaction (RT-PCR) SARS-CoV-2 tests were collected from publicly accessible infographics and bulletins (available at http://www.protezionecivi

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le.gov.it and http://www.epicentro.iss.it, respectively). Sex-disaggregated demographic characteristics of Italian population at January 1st 2019 were collected from the Italian National Statistical Institute (ISTAT) database (available at https://www.istat.it). COVID-19 IPs in females and males were calculated as the ratios between COVID-19 total cases (since March 9th up to May 11th 2020) and population size *per* 100.000 persons. Logarithmic (LG)-transformed values of skewed variables were used. Bivariate correlations were performed to assess the relationship between the male-to-female (M/F) ratio of COVID-19 IP and either the median age of COVID-19 cases or the number of daily swabs for RT-PCR SARS-CoV-2 tests. Multivariable regression analysis was performed to test whether the M/F ratio of COVID-19 IP was independently predicted by the number of daily swabs for RT-PCR SARS-CoV-2 tests after correcting for the median age of COVID-19 cases.

3. Results

Since March 9th 2020 up to May 11th 2020 COVID-19 IP increased progressively in both sexes (Figure 1). Concomitantly, sex distribution of COVID-19 IP reversed, with the M/F ratio of COVID-19 IP having passed from 1,73 to 0,91 (Figure 2). In addition, the median age of COVID-19 cases decreased from 65 to 62 years. Over the observed nine consecutive weeks, the mean of daily swabs for RT-PCR SARS-CoV-2 tests increased progressively until reaching a plateau in the last three weeks (Figure 3). A crude positive association was observed between the LG-M/F ratio of COVID-19 IP and the LG-median age of COVID-19 cases ($r = 0,74$, $p < 0,001$). In addition, a crude inverse correlation emerged between the LG-M/F ratio of COVID-19 IP and the number of daily swabs for RT-PCR SARS-CoV-2 tests ($r = -0,87$, $p < 0.001$) (Figure 4). Both the LG-median age of COVID-19 cases and the number of daily swabs for RT-PCR SARS-CoV-2 tests were independent predictors of the LG-M/F ratio of COVID-19 IP ($\beta = 0,26$, $p = 0,018$ and $\beta = -0,66$, $p < 0,001$, respectively) in the multivariable regression analysis.

4. Discussion

We observed that COVID-19 IP increased progressively in both sexes since March 9th to May 11th 2020. However, sex distribution of COVID-19 IP changed over time, with COVID-19 IP having been lower in females than males in the initial phases and having become higher in females than males by the end of the observed period. Accordingly, the M/F ratio of COVID-19 IP decreased progressively, becoming and remaining less than 1 from the second half of April 2020 onwards. The observed temporal changes in the sex prevalence of COVID-19 IP suggest that some gender-related factors may have influenced either the estimation of COVID-19 cases or the susceptibility to develope SARS-CoV-2 infection in males and females over time. In this regard, some speculative hypotheses may be suggested.

First, gender inequalities in the access to health care facilities for RT-PCR SARS-CoV-2 tests might explain the higher COVID-19 IP in males as compared to females at the beginning of the observed period. Indeed, the Italian SARS-CoV-2 testing policy, at least in the initial phases of COVID-19 epidemic, have prioritized the access of symptomatic subjects to diagnostic tests for COVID-19, thereby limiting the possible identification of COVID-19 asymptomatic cases [3, 10]. Therefore, it is likely that males, which have been reported to be at higher risk of developing symptoms and severe clinical manifestations of COVID-19 [11], may have had a higher access to COVID-19 diagnostic tests at the beginning of the observed period as compared to females. Conversely, the progressive temporal increase of COVID-19 IP in females might mirror the fact that women are more likely to become symptomatic and therefore access diagnostic tests later as the disease progresses [11]. Also, it might be related to the expansion of testing policies to asymptomatic cases over time. These speculations are in line with the observed inverse association between the M/F ratio of COVID-19 IP and the number of swabs performed daily for RT-PCR SARS-CoV-2 tests. The availability of sex-disaggregated data on RT-PCR SARS-CoV-2 tests would be crucial to further support this hypothesis. Noteworthy, female and male population sizes and proportions remained almost unchanged over the short observed period (10930 and 17018 COVID-19-related deaths were recorded up to May 7th 2020, which represents the 0.04% 0.06% of estimated female and male population sizes at the beginning of the Italian COVID-19 outbreak, respectively). This makes unlikely the hypothesis that variations occurring in the sample populations may have contributed to determine the observed temporal trend in sex distribution of COVID-19 IP over the same period.

Second, it should be considered that the application of social containment measures were definitively established in Italy on March 21st with the shutting down of all non-necessary businesses and occupations; these measures might have contributed to generate gender-

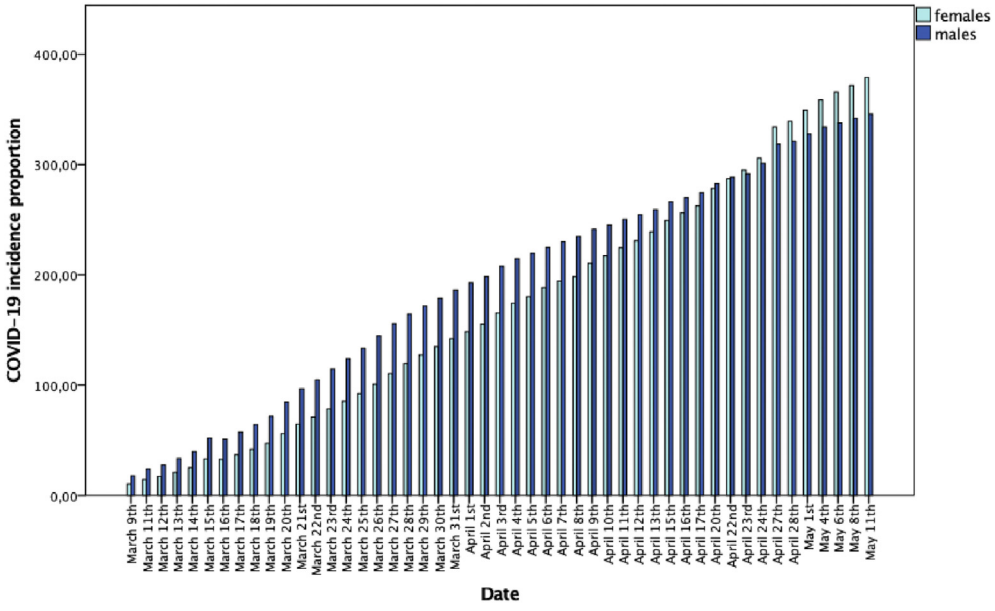

Figure 1. Temporal trend of COVID-19 incidence proportion in females and males.

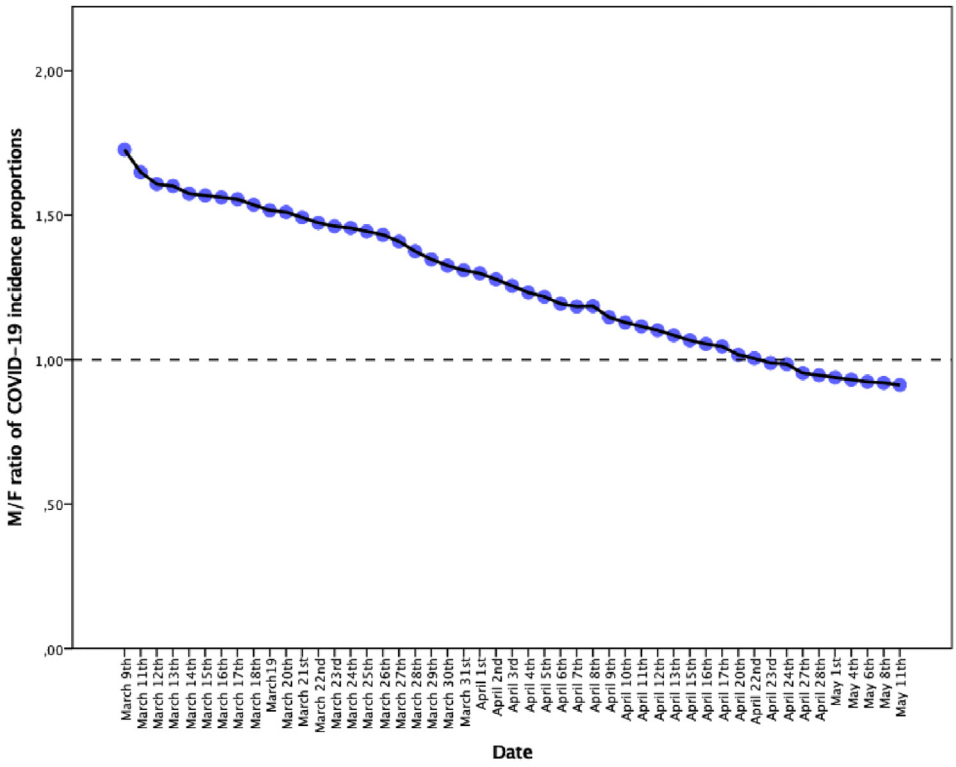

Figure 2. Temporal trend of M/F ratio of COVID-19 incidence proportions.

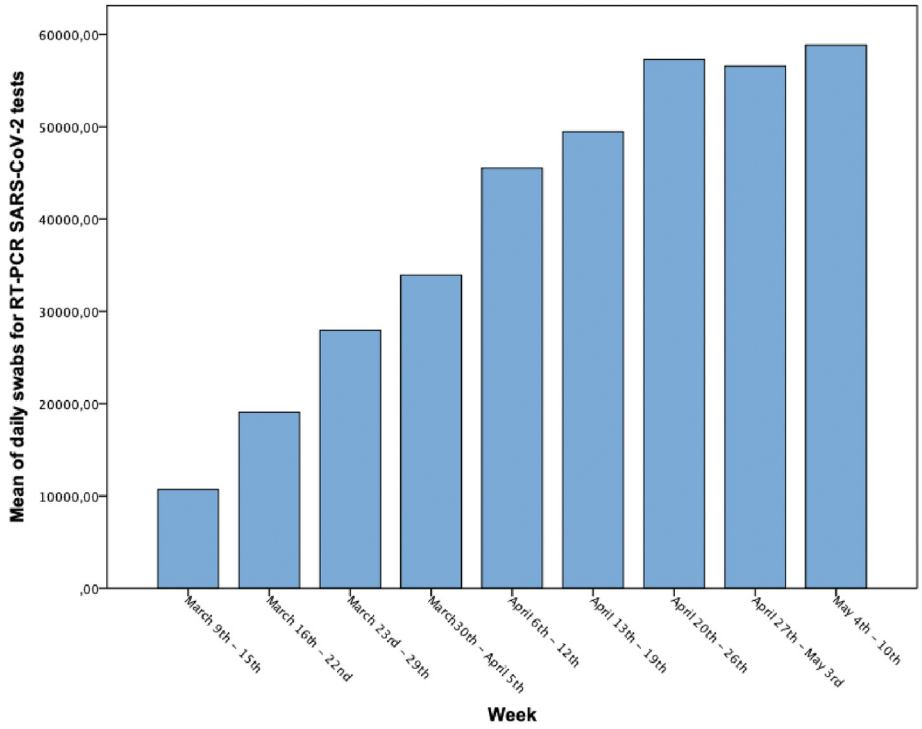

Figure 3. Mean of daily swabs for RT-PCR SARS-CoV-2 tests performed in nine consecutive weeks.

related disparities in the distribution of COVID-19 cases over time. Supporting this hypothesis, in Italian social fabric females more often have primary roles as caregivers within families and front-line interactions with communities for essential demands [11, 12, 13]. These social commitments may have exposed females to a higher risk of contagion in the lockdown period as compared to males. In addition, females are more represented than males in an occupation sector that was not subjected to lockdown during the Italian COVID-19 epidemic, which is the healthcare system [12, 13, 14].

Further to the aforementioned social dynamics, additional factors may contribute to explain the temporal trend of COVID-19 IP in females and males. Thus, for instance, a different biological-determined

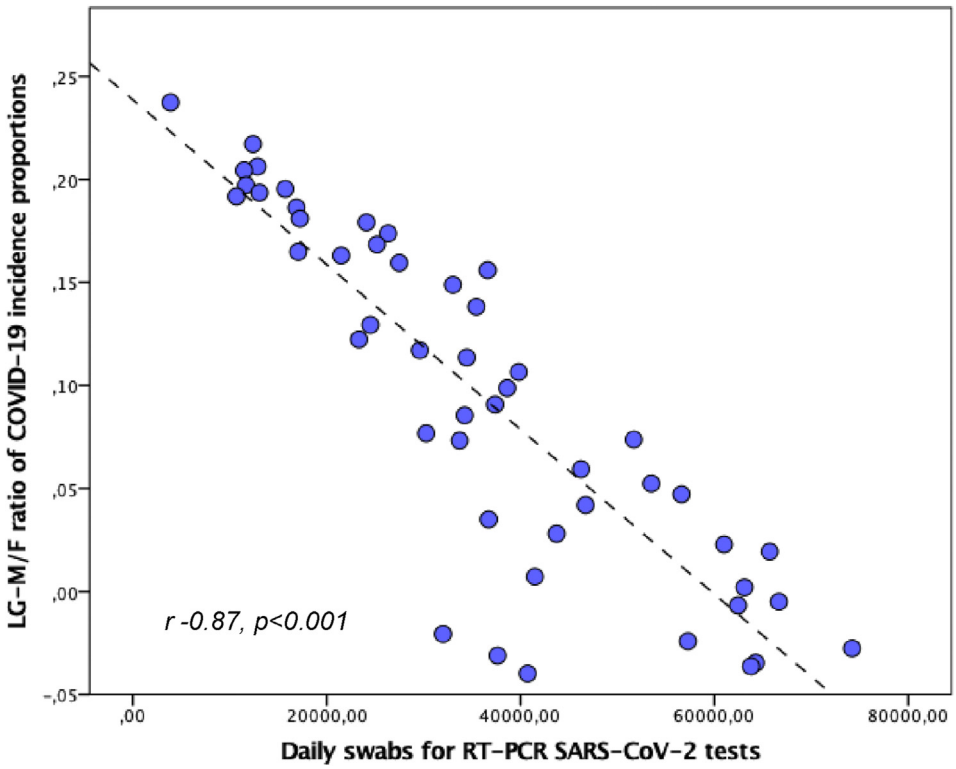

Figure 4. Correlation between daily swabs for RT-PCR SARS-CoV-2 tests and LG-M/F ratio of COVID-19 incidence proportions.

susceptibility between the sexes to develope COVID-19, due to a complex interplay between genetic and hormonal features, may contribute to explain at least in part the decreasing trend of the M/F ratio of COVID-19 IP over time. Although the more unfavourable prognosis of COVID-19 in men than in women might support at least in part a different sex-based susceptibility to SARS-CoV-2 infection and its complications, exposure studies in both sexes will allow more precise conclusions to be reached.

In the present study a positive association emerged between the median age of COVID-19 cases and the M/F ratio of COVID-19 IP over the observed period, suggesting that COVID-19 may have affected younger age groups in females as compared to males. Since asymptomatic COVID-19 cases have been reported to be more likely females and younger [9], a favourable interaction between younger age and female gender may have protected younger women from being affected from more severe and symptomatic forms of COVID-19 at least in the early phase of the epidemic; this may have prevented younger women to be tested for SARS-CoV-2 infection. However, with the massive spread of the epidemic, protection from symptomatic COVID-19 may have been lost progressively in younger women, thus imposing RT-PCR SARS-CoV-2 testing and retarding the peak of COVID-19 IP in this population category.

In conclusion, epidemiological data on Italian COVID-19 outbreak show time-related changes in sex distribution of COVID-19 IP, suggesting that possible gender inequalities may have influenced either the estimation of COVID-19 cases or the susceptibility to COVID-19 over time. Therefore, the implementation of social policies aimed at respecting and promoting gender equity should be considered in order to improve the control of COVID-19 pandemic.

Declarations

Author contribution statement

V. Bianconi and M. Pirro: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

M. Mannarino, P. Bronzo and E. Marini: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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References

[1] Q. Li, X. Guan, P. Wu, et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. 382 (13) (2020) 1199–1207.
[2] P.K. Bhatraju, B.J. Ghassemieh, M. Nichols, et al., Covid-19 in critically ill patients in the seattle region - case series, N. Engl. J. Med. 382 (21) (2020) 2012–2022.
[3] G. Onder, G. Rezza, S. Brusaferro, Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy, J. Am. Med. Assoc. 323 (18) (2020) 1775–1776 [published online, March 23, 2020].
[4] E. Livingston, K. Bucher, Coronavirus disease 2019 (COVID-19) in Italy, J. Am. Med. Assoc. 323 (14) (2020) 1335.
[5] 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.
[6] R. Serge, J. Vandromme, M. Charlotte, Are we equal in adversity? Does Covid-19 affect women and men differently? Maturitas 138 (2020) 62–68 [published online, May 15, 2020].
[7] V. Bianconi, P. Bronzo, M. Banach, A. Sahebkar, M.R. Mannarino, M. Pirro, Particulate matter pollution and COVID-19 outbreak: results from Italian regions

and provinces, Arch. Med. Sci. 16 (5) (2020) 985–992 [published online, May 12, 2020].
[8] Ž. Reiner, M. Hatamipour, M. Banach, et al., Statins and the COVID-19 main protease: in silico evidence on direct interaction, Arch. Med. Sci. 16 (3) (2020) 490–496.
[9] R. Yang, X. Gui, Y. Xiong, Comparison of clinical characteristics of patients with asymptomatic vs symptomatic coronavirus disease 2019 in Wuhan, China, JAMA Netw. Open 3 (5) (2020), e2010182.
[10] C. Indolfi, C. Spaccarotella, The outbreak of COVID-19 in Italy, fighting the pandemic. JACC: case reports, J. Am. Coll. Cardiol. Case Rep. 2 (9) (2020) [published online, April 29, 2020].
[11] A. Mantovani, A. Dalbeni, G. Beatrice, Coronavirus disease 2019 (COVID-19): we don't leave women alone, Int. J. Publ. Health 65 (3) (2020 Apr) 235–236.
[12] C. Wenham, J. Smith, R. Morgan, Gender and COVID-19 Working Group. COVID-19: the gendered impacts of the outbreak, Lancet 395 (10227) (2020) 846–848.
[13] T. Barbieri, G. Basso, S. Scicchitano, Italian workers at risk during the Covid-19 epidemic, SSRN Electron. J. (2020) [published online, April 10, 2020].
[14] G. Bertocchi, COVID-19 susceptibility, women, and work. https://voxeu.org/article/covid-19-susceptibility-women-and-work. (Accessed 1 June 2020).