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## Gender and age effects on the rates of infection and deaths in individuals with confirmed SARS-COV-2 infection in six European countries.

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<b>Manuscript Region of Origin:</b>	ITALY
<b>Abstract:</b>	<p>Background.</p> <p>Identifying whether the COVID-19 outbreak differentially affects males and females is an important step to understand direct and indirect effects of this health emergency. The aim of this study was to describe the effect of sex on the crude cumulative rate of confirmed SARS-COV-2 infections and deaths for different age categories in six European countries.</p> <p>Methods.</p> <p>The most recent available numbers of confirmed cases of SARS-COV-2 infected individuals and deaths, stratified by age and sex were retrieved from the government sources of Italy, Spain, Germany, Switzerland, Belgium, and Norway. Information about the age-sex structure of the resident population of each country on January 1 of 2020 were extracted from the respective National Institutes of Statistics.</p> <p>Findings.</p> <p>The male-to-female ratio of the crude cumulative incidence of cases showed a clear age-dependent pattern in all countries analyzed. We documented a greater rate of confirmed SARS-COV-2 infection among females compared to males between the age of 10 and 50 years. Data from all six countries showed in all age groups from age 20 years and above a higher preliminary fatality rate among males compared to females.</p> <p>Interpretation.</p> <p>The finding of an increased SARS-COV-2infection rate among females during childbearing age, and the higher risk of death among males in all age groups claim a possible role of sex- or gender-related factors in the complex pathogenesis of the COVID-19 pandemic</p> <p>Funding: none.</p>

Gender and age effects on the rates of infection and deaths in individuals with confirmed SARS-COV-2 infection in six European countries.

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## **Abstract**

### **Background.**

Identifying whether the COVID-19 outbreak differentially affects males and females is an important step to understand direct and indirect effects of this health emergency. The aim of this study was to describe the effect of sex on the crude cumulative rate of confirmed SARS-COV-2 infections and deaths for different age categories in six European countries.

### **Methods.**

The most recent available numbers of confirmed cases of SARS-COV-2 infected individuals and deaths, stratified by age and sex were retrieved from the government sources of Italy, Spain, Germany, Switzerland, Belgium, and Norway. Information about the age-sex structure of the resident population of each country on January 1 of 2020 were extracted from the respective National Institutes of Statistics.

### **Findings.**

The male-to-female ratio of the crude cumulative incidence of cases showed a clear age-dependent pattern in all countries analyzed. We documented a greater rate of confirmed SARS-COV-2 infection among females compared to males between the age of 10 and 50 years. Data from all six countries showed in all age groups from age 20 years and above a higher preliminary fatality rate among males compared to females.

### **Interpretation.**

The finding of an increased SARS-COV-2infection rate among females during childbearing age, and the higher risk of death among males in all age groups claim a possible role of sex- or gender-related factors in the complex pathogenesis of the COVID-19 pandemic

**Funding:** none.

## **Research in context**

### Evidence before this study

Six weeks after the first case of COVID-19 was recorded in Europe, we are unable to answer the question whether sex and age combined influence the risk of symptomatic infection by SARS-COV-2 and the outcomes of confirmed cases of COVID-19

### Added value of this study

By using publicly available data from six European countries, we documented a greater susceptibility to SARS-COV-2 infection among females compared to males between 10 and 50 years of age and a decreased risk of death after COVID-19 diagnosis among females compared to males in all age groups.

### Implications of all the available evidence

Identifying whether the COVID-19 outbreak differentially affects male and female is an important step to understand direct and indirect effects of this health emergency, to design policies and interventions for safely reopening activities after the lockdown implemented in almost all European countries to limit the spreading of the virus and to generate hypothesis on the pathogenesis and treatment of this disease.

## **Background**

Epidemiological information on SARS-COV-2 infection are currently reported and updated by almost all countries involved in the pandemic. Unfortunately, official government sources, media, and also medical journals are mainly reporting the number of confirmed cases, case mortality or crude death rates, without stratification by age and sex categories, and without considering the specific population structure.<sup>1</sup> As a result, six weeks after the first case of COVID-19 was recorded in Europe, we are unable to answer the question whether sex and age combined influence the risk of infection by SARS-COV-2 and the outcomes of confirmed cases of COVID-19. Identifying whether the COVID-19 outbreak differentially affects males and females is an important step to understand direct and indirect effects of this worldwide health emergency, to generate hypothesis on the pathogenesis and treatment of this disease and to design policies and interventions for safely reopening activities after the lockdown implemented, to different extent and with different timing, in almost all European countries to limit the spreading of the virus.<sup>2, 3</sup> Global Health 50/50 in collaboration with CNN is currently collecting the number of cases and deaths reported for males and females across the countries with the highest burden of COVID-19.<sup>4</sup> Among the 39 official government sources queried, 14 (36%) report sex-disaggregated cases and deaths, 13 (33%) sex-disaggregated cases, and 12 (31%) sex-aggregated data. For countries with publicly available data, females represents between 43% (Iran, 17<sup>th</sup> March 2020) to 60% (South Korea, 3<sup>rd</sup> April 2020) of confirmed cases, without a clear pattern for a differential likelihood for males and females of being diagnosed with COVID-19.<sup>4</sup> On the other hand, comparing the crude death rates between males and females (estimated as the proportion of deaths among confirmed cases) we observe that in every country males are more likely than females to die from COVID-19 [median male-to-female ratio 1.7; minimum 1.09 (Iran, 17<sup>th</sup> March 2020), maximum 2.39 (Republic of Ireland, 2<sup>nd</sup> April 2020)].<sup>4</sup> To generate more accurate estimates that will allow comparisons across countries, these rates should be expressed as the number of confirmed cases or deaths in the population, using the population size as the denominator. Furthermore, since the number of COVID-19 confirmed cases or deaths varies considerably by age, we also need to stratify these rates by age categories. The aim of this study was to describe the effect of sex on the crude cumulative rate of symptomatic infection by SARS-COV-2 and deaths for different age categories in six European countries with official government sources making available sex- and age-disaggregated data.

## **Methods**

The most recently available numbers of confirmed cases of SARS-COV-2 infected individuals and deaths, stratified by age and sex were retrieved from the following government sources of six

European countries: Istituto Superiore di Sanità (Italy), Ministerio De Sanida, Centro de Coordinación de Alertas y Emergencias Sanitarias (Spain), Robert Koch Institut (Germany), Ufficio Federale della Sanità Pubblica UFSP (Switzerland), Belgian Institute for Health (Belgium) and Norwegian Institute of Public Health (Norway).<sup>5-10</sup> For each of those countries we then obtained the number of residents as of January 1, 2020, stratified for age and sex, from the National Institute of Statistics of Italy, Spain, Germany, Switzerland Belgium, and Norway.<sup>11-16</sup> Total confirmed cases and deaths by country are reported in Table 1. Crude cumulative incidence rates were calculated as the number of confirmed cases or death per 1,000,000 individuals for each age category. Crude preliminary case fatality rate was calculated as the number of reported deaths per reported cases in each age category. Male-to-female ratio was calculated for both cumulative incidence rates and preliminary fatality rates in each age category. We acknowledge that the definition of cases and deaths varies by country, making comparisons between countries challenging. Accordingly, data are presented separately for each of the six European countries considered. The study is exempt from ethics approval since data, documents or records used are all publicly available.

## Results

In all six European countries included in this study, the crude cumulative infection rate of confirmed cases increased with age, although with a different slope (Figure 1): steeper in Italy, Spain and Belgium, much less steep in Norway and Germany, intermediate in Switzerland, explaining, at least in part, the marked differences between countries in the crude preliminary fatality rates. The male-to-female ratio of the crude cumulative infection rate of cases showed a clear age-dependent pattern (Figure 2, panel A and B). Between the age of 10 and 50 years, there were more confirmed cases among females than males [median of the excess cases among females 29.5% (minimum 4.9%; maximum 75%)], while before the age of 10 and after that of 50 years there were more confirmed cases among males than females [median of the excess cases among males 13% (minimum -15%; maximum 37%) and 29 % (minimum 22%; maximum 67%), before the age of 10 years and after the age of 50 years, respectively]. Both crude cumulative infection rates and crude preliminary fatality rates increased with age in all countries, with the highest rates among individuals over the age of 70 years. Data from all six countries showed, in all age groups from age 20 years and above, a higher preliminary fatality rate among males compared to females. The sex-gap in the crude preliminary fatality rate becomes less pronounced with age, with an overall median male-to-female ratio of 3.1:1 (minimum 1.3:1; maximum 3.8:1) up to the age of 60 years and 2.2:1 (minimum 1.7:1; maximum 2.6:1) after the age of 60 years. The effect of sex and age on the crude cumulative infection rates and

crude preliminary fatality rates did not substantially change when we analyzed different time windows of the COVID-19 outbreak, at least in Italy (Figure 2C).

## **Discussion**

Robust sex specific risk estimates for confirmed infection and preliminary case fatality for COVID-19 are still lacking, with available data likely biased by incomplete outcome data and differences in testing policies within and between countries. By using publicly available data from six European countries, we documented a greater susceptibility to SARS-COV-2 infection among females compared to males between the age of 10 to 50 years and a decreased risk of death following COVID-19 diagnosis among females compared to males in all age groups. One possible explanation of the observed effect on mortality after infection with SARS-COV-2 is that co-morbidities, such as hypertension, cardiovascular disease, some chronic lung diseases, rates of tobacco smoking and alcohol abuse are more common among males than females.<sup>17</sup> Preliminary reports on individuals with severe COVID-19 disease have documented the associations between these comorbidities and the risk of death.<sup>18-20</sup> On the other hand, the finding of increased COVID-19 infection among females during childbearing age, and the higher risk of death among males in all age groups, even more evident in the youngest age groups, suggest a potential role for sex hormones, i.e., sex steroids, in the infection with SARS-COV-2 and in the pathogenesis of COVID-19.<sup>21</sup> To further support this hypothesis, there is also evidence that even younger age groups, i.e., well prior to puberty, male children were more likely to be infected than female children, an evidence in agreement with a previous report from a the Wuhan Children's Hospital.<sup>22</sup> A possible alternative explanation for the observed higher rates of infection among females may be the differential exposure during young adulthood and adult life, i.e., females working in jobs that facilitate contacts with both asymptomatic or symptomatic cases, i.e., nurses, physicians in either hospital or general practice, teachers, employees dealing with the public, etc... On the same issue, after retirement males are more likely to spend time in public places (bar, club, gym, etc...) than females.<sup>23</sup> We do acknowledge that our approach to estimate the effects of age and sex is fairly simplistic. More solid estimates of these effects will be provided when higher quality cohort-based analyses will become available. However, in the meantime, we were able to show a relevant effect of sex on the rates confirmed infection and preliminary fatality of COVID-19, supporting the need to investigate in this direction to better understand this new disease which is dramatically changing our world.

## **Acknowledgments**

We dedicate this work to all health professionals in the world who lost their lives caring for COVID-19 patients.



## Figure legends

**Figure 1. Crude cumulative incidence, death and crude preliminary case fatality rate by sex and age.** Data from six European countries are reported (see Table 1 for outbreak data in each country at the time of the analysis). NA: not available.

**Figure 2. Male-to-female ratios.** *Panel A.* Male-to-female ratio for crude cumulative incidence, crude cumulative deaths and crude preliminary case fatality rate for sex and groups were calculated for six European countries. Only ratios with at least 10 events for males and females were reported. Circles instead of lines represent data from countries where the available age category was not by decade. Specifically, for Germany in crude cumulative incidence panel the age intervals were 0-4, 5-14, 15-34, 35-59, 60-79, >80 years; in the crude cumulative death and crude preliminary fatality rate the age intervals were 35-59, 60-79, >80 years, as no deaths were reported in the younger age groups. For Belgium in the crude cumulative death panel the age intervals were 45-64, 65-74, 75-84, >85 years, as no >10 deaths were reported in the younger age groups. *Panel B:* Male-to-female ratio for crude cumulative incidence in children below 18 years of age in Italy on April 02, 2020. *Panel C:* Male-to-female ratio for crude cumulative incidence and crude preliminary fatality rate in Italy at different time windows of the COVID-19 outbreak. For all panels the male-to-female ratio was expressed as natural log. Values higher than one means that the number of cases or deaths is higher among males, values lower than one means the number of cases or deaths value is higher among females. M: male; F: female.

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**Table 1. Confirmed Cases and Deaths by Country**

	First confirmed case reported to WHO Europe	Date of the report used in the analyses (Days from first reported case)	Total confirmed cases (Crude cumulative incidence per 100,000 residents)	Total deaths (Crude cumulative incidence per 100,000 residents)	Crude case fatality rate (Deaths/all confirmed cases)	Total tested for SARS-COV-2 (Crude cumulative incidence per 100,000 residents)
Italy	01/02/2020	02/04/2020 (61)	132547 (219.6)	16523 (27.4)	12.5%	721732 (1195.7)
Spain	02/02/2020	06/04/2020 (64)	135176 (287.0)	13193 (28)	9.8%	355000 (753.7)
Germany	29/01/2020	05/04/2020 (67)	91714 (110.3)	1342 (1.6)	1.5%	918460 (1104.6)
Switzerland	26/02/2020	06/04/2020 (40)	21652 (252.2)	584 (6.8)	2.7%	162500 (1893.0)
Norway	26/02/2020	05/04/2020 (38)	5640 (105.1)	58 (1.1)	1.0%	108709 (2025.3)
Belgium	05/02/2020	05/04/2020 (60)	19691 (172.3)	1447 (12.7)	7.5%	75724 (662.7)

Male

Female

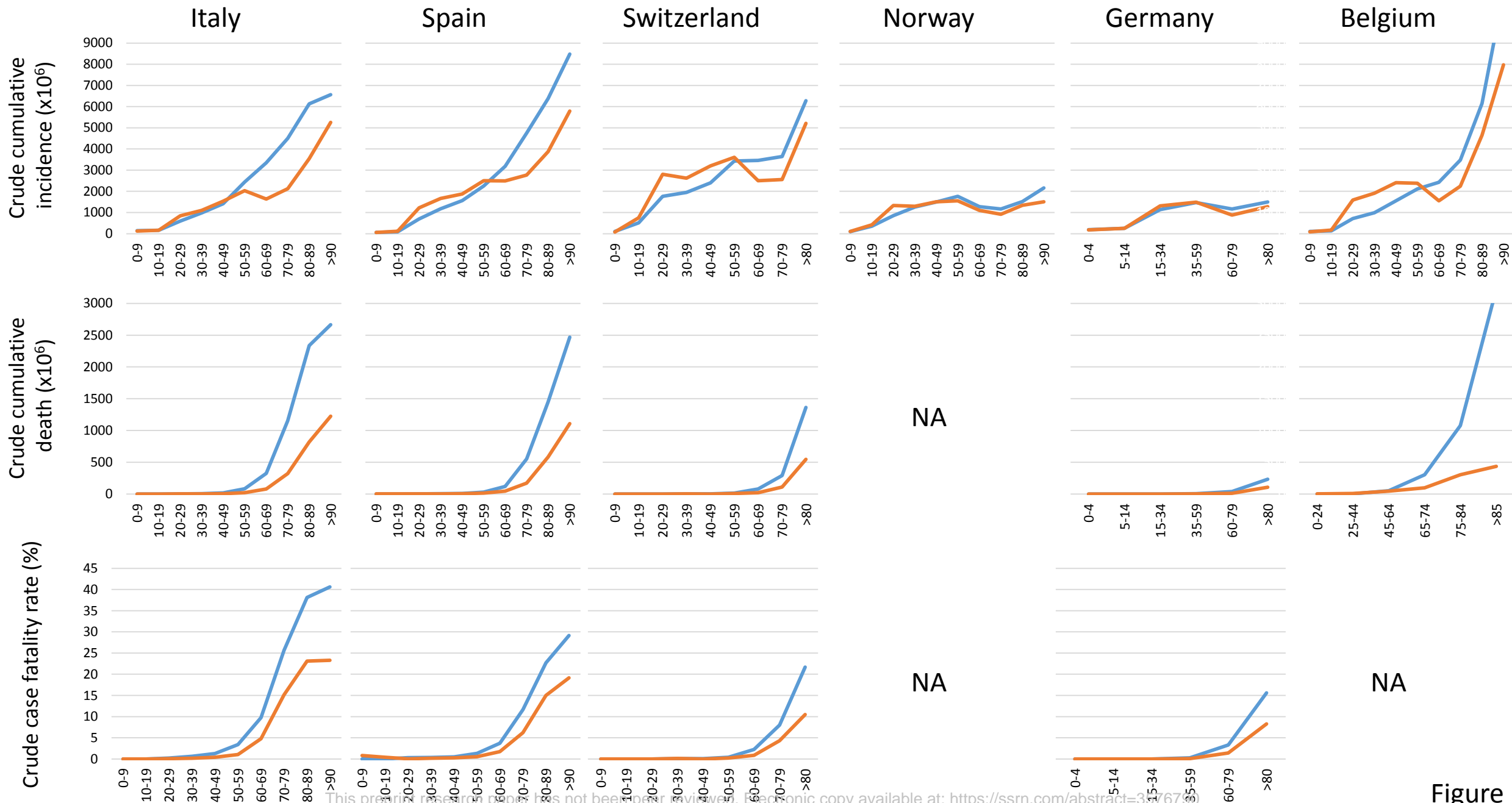
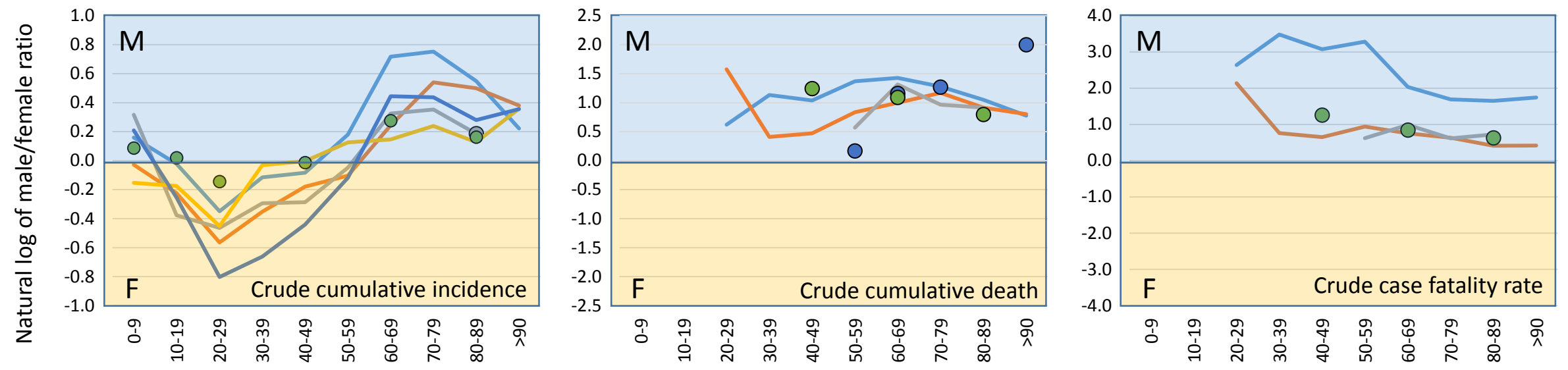
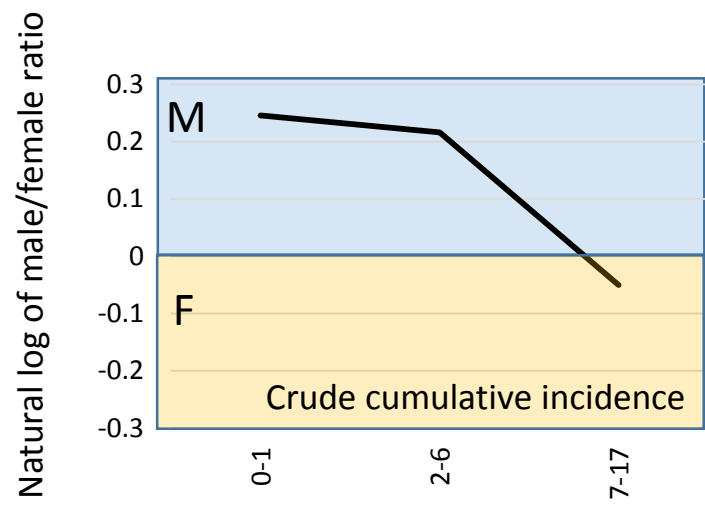
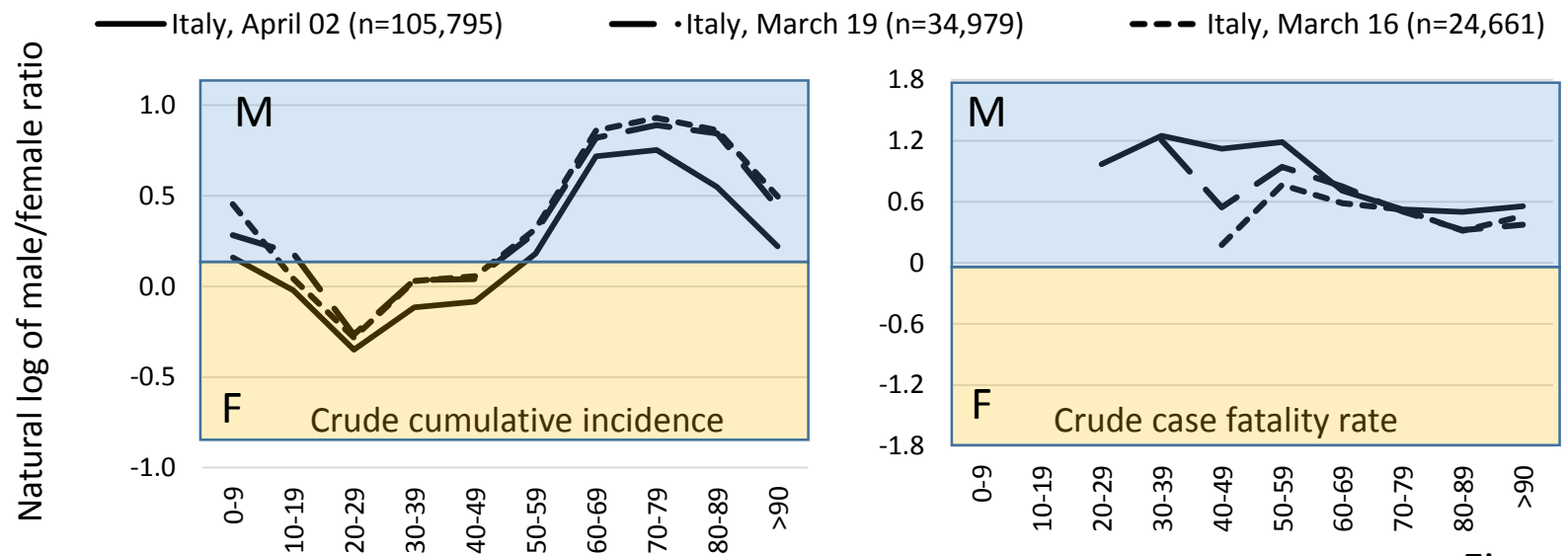


Figure 1

**A**

Italy Spain Norway Switzerland Belgium Germany

**B****C**



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