

Gender and age factors affecting the mortality during the COVID-19 epidemic in Italy

Effetti del genere e dell'età sugli eccessi di mortalità durante l'epidemia di COVID-19 in Italia

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ABSTRACT

BACKGROUND: the COVID-19 epidemic severely affected Italy among European countries causing a considerable number of deaths across the country, especially in Northern Italy, leading also to serious problems to the Italian healthcare system, in particular the overcrowding of Intensive Care Units (ICU). In literature, the debate on the overall mortality during the COVID-19 epidemic, directly and indirectly, associated with the disease, is still open.

OBJECTIVES: to describe the time trend of the mortality in Italy during the COVID-19 pandemic accounting for age, gender, and geographical areas.

DESIGN: analysis of mortality trend, by region, age, and gender
SETTING AND PARTICIPANTS: the Italian mortality data, released by the Italian National Institute of Statistics (Istat), have been considered for the analyses. The data refer to the first four months of 2015-2019 and 2020, involving 7,270 municipalities, corresponding to 93% of the Italian population.

MAIN OUTCOME MEASURES: the mortality rates in the first four months of 2015-2019 and 2020, age-adjusted, have been calculated together with the percent variation. The data were analysed by gender, age class (<65; ≥65 years), Region, and geographical areas (Northern versus Central-Southern Italy). The overall daily mortality series have been represented as rates over 100,000 resident population.

RESULTS: in addition to the geographical location, the age component was a major determinant of the mortality pattern. The greater increase in the overall mortality was evidenced among elderly subjects in the Northern Italian Regions most affected by the epidemic. In these areas, also gender component played an important role in determining the mortality excess: higher mortality rates in the first four months of 2020 are observed for males in comparison to female populations.

CONCLUSIONS: this research reveals that the population components are an important issue in determining the COVID-19 mortality excess. For this reason, it is of primary importance to monitor mortality (overall and by COVID-19) by age and gender and to consider these components and the related factors (comorbidity, exposures affecting the lung) in the public prevention policies towards the protection of the most fragile population groups.

Keywords: COVID-19, mortality, age, gender

RIASSUNTO

INTRODUZIONE: l'epidemia di COVID-19 ha colpito duramente l'Italia tra i Paesi europei causando un numero considerevole di decessi in tutto il Paese, soprattutto nel Nord Italia, e

WHAT IS ALREADY KNOWN

■ The COVID-19 epidemic is severely affecting Italy among European countries causing a considerable number of deaths across the country, especially in Northern Italy.

■ Despite this certain figure, the debate overall mortality during the COVID-19 epidemic is directly and indirectly associated with the disease is still open.

WHAT THIS STUDY ADDS

■ The study analyses the role of the population components (proportion of over-65 and under-65 and gender) contributing to the risk of mortality during the COVID-19.

■ The mortality excess during the COVID-19 epidemic was mainly determined by the aging component, as well as by the geographical location. This evidence is now provided by observation including over 93% of the Italian population.

■ It is of primary importance to consider the sociodemographic components of the population to properly tailor the public prevention policies towards the protection of the most fragile population groups and to investigate on the preventable determinants (comorbidities and exposures).

gravi problemi al sistema sanitario italiano, in particolare il sovraccollamento delle Unità di terapia intensiva (ICU). In letteratura è ancora aperto il dibattito sulla mortalità complessiva direttamente e indirettamente associata alla malattia, durante l'epidemia di COVID-19.

OBIETTIVI: descrivere l'andamento temporale della mortalità in Italia durante la pandemia di COVID-19 per età, genere e aree geografiche.

DISEGNO: analisi dell'andamento temporale della mortalità, per regione, età e genere

SETTING E PARTECIPANTI: per le analisi sono stati presi in considerazione i dati sulla mortalità italiana rilasciati dall'Istat. I dati si riferiscono ai primi quattro mesi del 2015-2019 e al 2020, coinvolgendo 7.270 comuni, pari al 93% della popolazione italiana.

PRINCIPALI MISURE DI OUTCOME: i tassi di mortalità nei primi quattro mesi del 2015-2019 e del 2020, corretti in base all'età, sono stati calcolati insieme alla variazione percentuale. I dati sono stati analizzati per genere, classe di età (<65 anni; ≥65 anni), regione e aree geografiche (Nord rispetto al Centro-Sud Italia). Le serie complessive di mortalità giornaliere sono state rappresentate come tassi per 100.000 abitanti.

RISULTATI: oltre alla posizione geografica, la componente dell'età è stata una delle principali determinanti del modello di mortalità. Il maggiore aumento della mortalità complessiva si è messo in evidenza tra i soggetti anziani nelle regioni del Nord Italia più colpite dall'epidemia. In queste aree, anche la componente di genere ha giocato un ruolo importante nel

determinare l'eccesso di mortalità: nei primi quattro mesi del 2020 si osservano tassi di mortalità più elevati per i maschi rispetto alle popolazioni femminili.

CONCLUSIONI: questa ricerca rivela che la struttura della popolazione è un fattore importante nel determinare l'eccesso di mortalità di COVID-19. Per questa ragione, è fondamentale il

monitoraggio della mortalità (complessiva e per COVID-19) per età e genere con i relativi fattori di rischio (comorbidità, esposizioni polmonari), allo scopo di orientare le politiche pubbliche verso la protezione dei gruppi di popolazione più fragili.

Parole chiave: COVID-19, mortalità, età, genere

INTRODUCTION

Among European countries, Italy, the UK, and Spain were the countries initially more severely affected by the first wave of the COVID-19 epidemic and related mortality. The first cases not directly related to China appeared in Italy on 20 February in the province of Lodi (Lombardy region).^{1,2} Since that date, the virus has spread rapidly, especially in Northern Italy, first in Lombardy, Veneto, and Emilia-Romagna and then in Piedmont, causing serious problems to the health system, in particular, due to overcrowding of Intensive Care Units (ICU).³

On 27 June 27, a total of 239,410 cases (median age 61 years) had been diagnosed with a real-time reverse transcriptase PCR (RRT-PCR) testing procedure together with a cumulative number of 33,680 deaths (14%).⁴ Sixty-nine percent of cases were reported among subjects older than 50 years.⁴

The COVID-19 pandemic in Italy reached a peak of 6,557 new cases on the 21 March; the epidemic growth then declined until 175 new cases on 27 June.⁴ A similar pattern, lagged forward of 10 days, was observed for deaths.^{5,6}

In Italy, the policies to contain the epidemic came into practice in the first ten days of March. On 9 March, an urgent Decree-Law to contain the contagion on the entire national territory was implemented, creating a single Italian Protection Zone. The containment measures were based on the social distancing, closure of workshops, shops and schools, and a travel ban.⁷ Containment policies were progressively removed from 4 May.⁸

The COVID-19 epidemic in Italy had a considerable impact on the healthcare management system, especially in Lombardy and generally in Northern Italy; although in some Regions such as Veneto, containment policies have been able to contain the ICU overload.^{9,10}

The COVID-19 pandemic has certainly caused a considerable number of fatalities across the country, especially in Northern Italy, but despite this certain figure, the debate on the mortality during the COVID-19 epidemic directly and indirectly associated with the COVID-19 disease is still open.⁵

Some authors, using the Surveillance System of Daily Mortality (SiSMG) including 19 medium and large cities, showed an increase in overall mortality since the first decade of March 2020 in the municipalities of Northern Italy, compared to a stable situation in the other Regions.¹¹ Nevertheless, the study design involved only a limited number of municipalities and was not tailored to

generalize the results at the national and regional levels.⁵ The excess of COVID-19 related mortality might arise, in the disease infected population, but also not infected population. An indirect part of the mortality excess may be related to modified access to the healthcare services or the socioeconomic effects of the pandemic.¹² An indirect component of the COVID-19 mortality burden may also be related to the undetected COVID-19 cases.⁵ The number of undiagnosed infections is controversial in the literature. Some studies suggested a considerable number of undetected cases among elderly subjects reporting a higher COVID-19 fatality rate.¹³

The mortality excess may be estimated and monitored by comparing the observed number of deaths during the COVID-19 epidemic with the baseline risk of mortality (before the COVID-19 outbreak) in the population.^{11,14} This strategy was adopted by the authors of this paper in previous research, based on a more limited database, that identified an excess of the mortality rate during the COVID-19 epidemic in Italy.⁵

At the time of the preparation of the present study, the most recent report released by the Italian National Institute of Statistics (Istat), in collaboration with the Italian National Health Institute (ISS), involving 7,357 Italian municipalities, concluded that the March-April 2020 COVID-19 excess of mortality has concluded in May, as result of the implemented containment policies.¹⁵

Despite all the research conducted to quantify the overall mortality during the COVID-19 epidemic in Italy, few efforts have been performed to stratify the COVID-19 mortality according to the gender and macro age categories. Gibertoni and colleagues¹⁶ described mortality in some Northern Italy Regions (Lombardy, Veneto, and Emilia-Romagna) for the period from 1 January to 31 March 2020, observing that COVID-19 mortality was higher in males in comparison to females also for subjects less than 75 years.

Evaluating the total mortality during the COVID-19 epidemic, considering gender, age, and related comorbidities may be useful for monitoring purposes leading to tailor the research and the public health efforts,¹⁷ in particular in the event of recurrent epidemics in the future.

The present study aims at describing the time trend of mortality during the first wave of the COVID-19 epidemic in Italy stratifying the population by gender, age classes, and broad geographical areas by considering the January-April 2020 mortality data released by Istat.¹⁸

MATERIALS AND METHODS

Daily mortality figures by the municipality, age, and gender in the first four months of 2015-2019 (pre-COVID-19 period, used as reference) and 2020, were downloaded by the Istat public repository including mortality data for 7,270 municipalities (92% of the Italian municipalities and 93.5% of the Italian resident population).¹⁸ The Istat technical report declared that the selected municipalities are not a random sample, the study sample is composed of the cities agreeing to the project of early release of mortality data, with no further selections.¹⁸

The resident population figures have been retrieved from the demo-Istat repository. The last available data were referred to as the first of January 2019.¹⁹

COVID-19 deaths were provided by the Italian Civil Protection Department,²⁰ as elaborated by the Padua University data warehouse.⁶ These data were made available only as daily mortality figures by Region, without age or gender stratification. In Italy, a COVID-19 death is defined only by considering the positivity to the RRT-PCR testing procedure without taking into account other pre-existing comorbidities.²¹ These data were used to describe in the analyses the daily mortality attributed to COVID-19.

In the analyses, age classes were categorized as 0-64 and 65+, based on evidence on COVID-19 lethality by age⁴ and previous analyses by the authors of this paper.⁵ Regions were classified using 'a priori' grouping,^{11,19} comparing Northern Italy Regions (Piemonte, Valle D'Aosta, Lombardia, Trentino-Alto Adige, Veneto, Friuli Venezia Giulia, Liguria, and Emilia-Romagna) with the rest of Italy. Further analyses by Region were also conducted and are available on request.

The daily crude mortality rates have been analysed overall and by gender, region, and age categories (0-64 and 65+). The daily mortality figures were obtained by summing up the corresponding number of deaths in the 7,270 municipalities, for Italy, and each Region. Crude daily mortality rates have been calculated over the resident population, using respectively the 2017 (mid-year) population for the 2015-2019 period and the 2019 population for 2020. The 95% percent confidence intervals (95%CI) of daily mortality rates were computed using a Poisson approximation.²² The curves have been smoothed using a five-day moving average procedure.

Mortality indicators have been computed stratified by Region and gender. In particular, the mortality rate per 100,000 inhabitants (age-standardised using the direct procedure to the population in January 2019) for 2015-2019 and 2020 and the percent variation of 2020 mortality rate over 2015-2019 were included. The mortality rates were projected to the total population of each Region¹⁹ and the absolute difference in the estimated number of deaths between 2020 and 2015-2019 was computed. Mortality Rate Ratio (RR, the ratio between directly standardized rates) and mortality differences (absolute

and percent) were also computed to compare the variation between 2020 and 2015-2019 or the figures for different subgroups. Mortality indicators are presented in the tables, focused on the 2 months from 1 March to 30 April each year.

RESULTS

Figure 1 presents the moving average (5-days) of daily mortality rates (per 100,000 inhabitants) in 2020 and in the baseline period (2015-2019), for the total population (panel A) and stratified by gender (panels B for males, and C for females). The green line in panel A presents the sum of COVID-19 daily mortality series and of the 2015-2019 mortality for the overall population, as an estimation of the contribution of COVID-19 to the total mortality burden; the data which the authors were given access to were not separated by age or gender and therefore the presentation of COVID-19 mortality is limited. The 2020 mortality rates remained lower than 2015-2019 until the last days of February 2020. Subsequently, the 2020 daily mortality rates increased rapidly, showed a peak in the last week of March, and declined since then. At the end of April, rates were again close to 2015-2019 reference values. The increase of 2020 daily mortality rates over the 2015-2019 expected rates were much greater than the increase from the COVID-19 mortality rates (figure 1, panel A). Within that growth pattern, it should be noted that mortality rates for males are higher and presented a few days anticipation in comparison to females (figure 1, panels B and C).

The period from 1 March to 30 April showed the largest occurrence of COVID-19 diagnoses and deaths. Table 1 presents for the period 1 March to 30 April the number of deaths in 2020, the age-standardised rates in 2020 and 2015-2019, the percent variation between 2015-2019 and 2020, and the number of deaths in excess in 2020, estimated for the total areas (Italy or Regions) based on the municipalities included in the dataset. Results are stratified by gender and Region. Overall, Italian data showed increased rates in 2020 for both genders. In men, the increase in 2020 was 39.8% and in women 32.2%, corresponding to 21,740.8 excess deaths for men and 19,129.7 for women. The pattern of increased mortality is common to the regions in Northern Italy, as well as Marche and, at a lower extent Tuscany in Centre Italy. As regards Southern Italy, a limited increase was observed only in Abruzzo and Puglia. No large differences were observed in the gender RR (male versus female) (Supplementary materials, table S1).

The 2020 daily mortality rates in the Northern Regions (see figure S1, panel A, on-line Supplementary materials) evidenced the same growth shape already observed, with the highest mortality rates for males (figure S1, Panel B) in comparison to females (figure S1, Panel C). In the Southern Regions (figure S2), the mortality rates in 2020

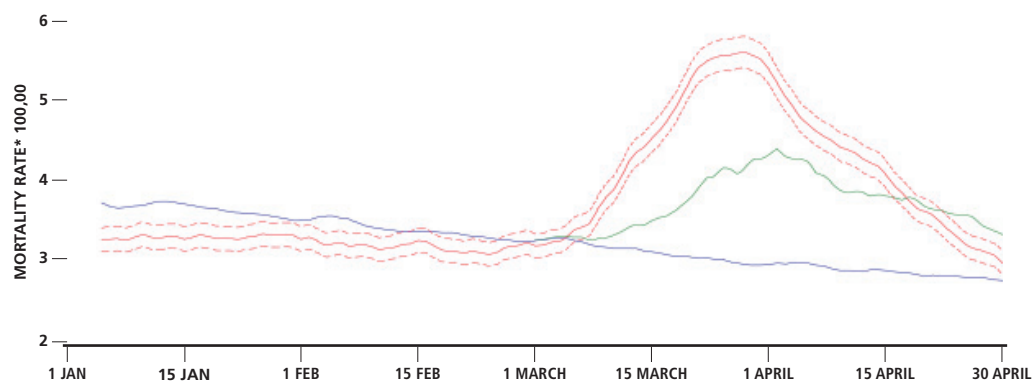
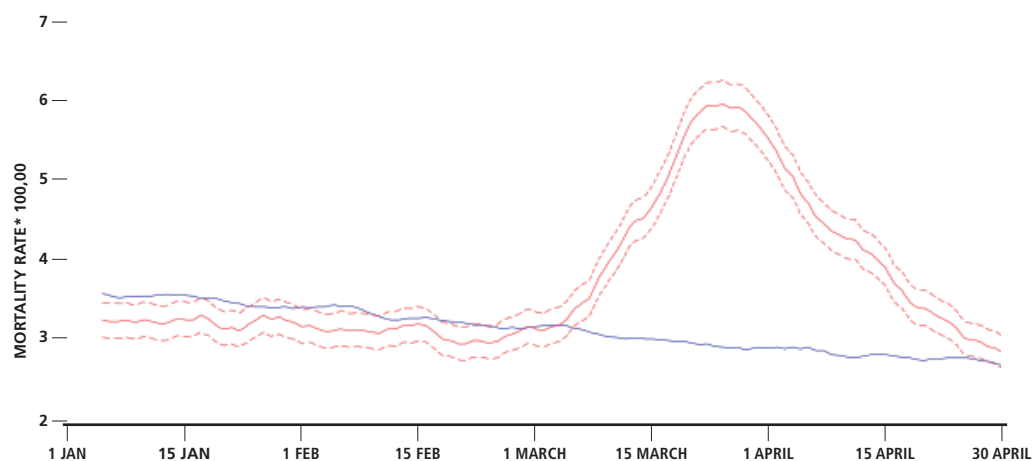
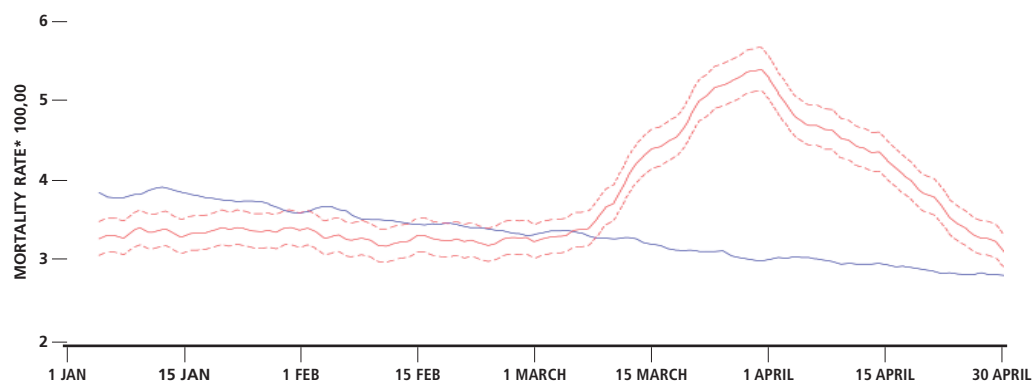
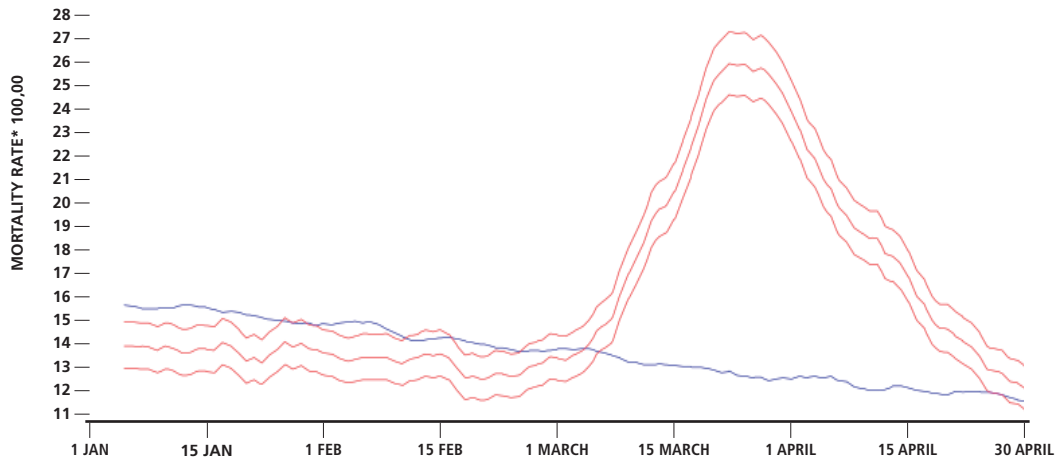
PANEL A DAILY ALL-CAUSE MORTALITY TOTAL POPULATION**PANEL B DAILY ALL-CAUSE MORTALITY MALE****PANEL C DAILY ALL-CAUSE MORTALITY FEMALE**

Figure 1. Daily mortality rates (5-days moving average) in 2020 (red lines: mean and 95%CI) and 2015-2019 periods (blue line): (A) total population, (B) males, (C) female. Limited to the total population COVID-19 mortality rates added to the 2015-2019 rates (green line) are presented.

Figura 1. Tassi di mortalità giornaliera (5-days moving average) nei periodi 2020 (linee rosse: medie e IC95%) e 2015-2019 (linea blu): (A) popolazione totale, (B) maschi, (C) femmine. Tassi di mortalità per COVID-19 limitati alla popolazione totale aggiunti alla mortalità del periodo 2015-2019 (linea verde).

PANEL A OVER 65 DAILY ALL-CAUSE MORTALITY MALE



PANEL B OVER 65 DAILY ALL-CAUSE MORTALITY FEMALE

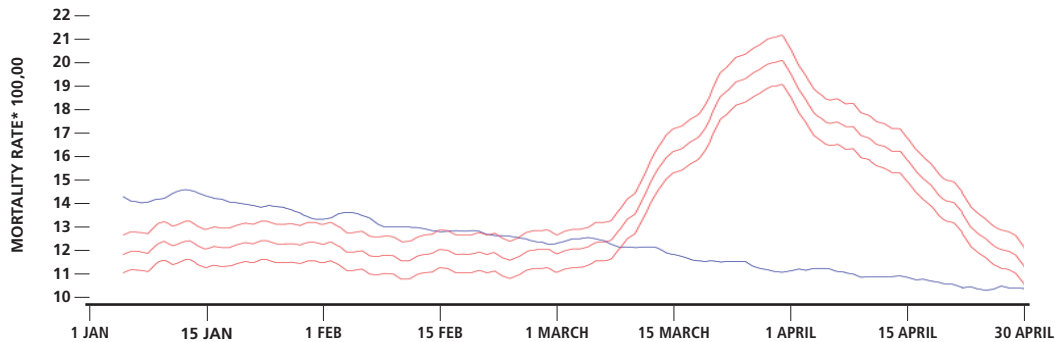


Figure 2. Daily mortality rates (5-days moving average) in the population aged ≥ 65 in 2020 (red lines: mean and 95%CI) and the average of 2015–2019 periods (blue line), by gender.

Figura 2. Tassi di mortalità giornaliera (5-days moving average) nella popolazione ≥ 65 nel 2020 (linee rosse: media e IC95%) e media del 2015-2019 (linea blu), per genere.

are instead similar to the baseline time (2015-2019) for both men and women and the increase observed in the total mortality is close to the COVID-19 additional mortality curve (figure S2, panel A).

Figure 2 presents the daily mortality rates in ≥ 65 populations. Daily mortality rates are higher in men (highest rate 26 per 100,000 inhabitants) (figure 2, panel A) than in women (highest rate 20 per 100,000) (figure 2, panel B), given the same growing shape in both genders. Corresponding figures for the population aged < 65 years are presented in supplementary materials, figure S3. The increase in mortality in this age class could be observed in men only.

Table 2 presents mortality analyses by gender in the subjects aged 65 and older. The increase in mortality in Italy was 43.1% in men and 34.0% in women, corresponding to an estimated number of 21,381.3 excess deaths in men and 19,156.1 in women in the two months of March and April. The percent variation and its pattern by Region were similar to the observation for the overall population

shown in table 1, not surprising, given the large proportion of COVID-19 mortality in this age class. The pattern of differences in 2020 rates by gender was not uniform, however, it is noted that Lombardy, Emilia-Romagna, and Marche showed the largest percent difference in 2020 rates for men and women. Similar conclusions are reached by observing the results expressed in terms of RR (Supplementary materials, table S2).

Data on mortality in the subjects aged less than 65 is presented in the supplementary tables S3 and S4. The increase in mortality in 2020 was more evident in men, which showed a 15.7% increase in mortality rates, corresponding to an estimation of 1,186.8 deaths in excess. The excess was observed in a few Regions only, in particular Lombardy (89%) and other regions of Northern Italy. In women, only Lombardy, Trentino Alto Adige and, at a lower level Emilia-Romagna, showed an increase in mortality. Similar results were provided in the analysis of the RR (Supplementary materials, table S4). However, in all the Regions, the RR (males vs females) was greater than 1.5.

REGION	MALE					FEMALE				
	OBSERVED DEATHS IN 2020 STUDY PERIOD	MORTALITY RATE 2020	MORTALITY RATE 2015-2019	PERCENT VARIATION OF MORTALITY RATE	ESTIMATED DIFFERENCE IN DEATHS IN TOTAL POPULATION	OBSERVED DEATHS IN 2020 STUDY PERIOD	MORTALITY RATE 2020	MORTALITY RATE 2015-2019	PERCENT VARIATION OF MORTALITY RATE	ESTIMATED DIFFERENCE IN DEATHS IN TOTAL POPULATION
Italy	71,546	260.1	186.1	39.8%	21,740.8	73,770	253.6	191.8	32.2%	19,129.7
Piedmont	6,371	315.4	209.2	50.8%	2,247.1	6,691	312.8	215.8	45.0%	2,174.5
Valle d'Aosta	181	320.8	203.8	57.4%	71.9	204	342.7	212.0	61.6%	83.9
Lombardy	20,730	427.1	169.0	152.7%	12,709.2	20,353	401.6	181.2	121.7%	11,322.8
Trentino-Alto Adige	1,206	245.3	159.6	53.8%	453.2	1,391	273.7	163.6	67.3%	598.7
Veneto	4,692	213.7	174.9	22.1%	929.5	5,095	221.6	185.5	19.4%	903.3
Friuli Venezia Giulia	1,272	230.9	207.6	11.2%	137.7	1,457	249.6	222.7	12.1%	167.5
Liguria	2,655	368.1	236.7	55.6%	975.2	3,000	381.23	254.1	50.0%	1,028.5
Emilia-Romagna	6,670	318.7	190.2	67.6%	2,786.8	6,726	303.6	206.5	47.0%	2,224.1
Tuscany	4,060	234.8	203.9	15.2%	556.1	4,257	229.6	211.8	8.4%	341.8
Umbria	824	202.9	212.9	-4.7%	-42.6	951	217.6	212.4	2.5%	23.8
Marche	2,005	291.8	198.6	47.0%	690.9	1,937	266.8	209.0	27.6%	453.0
Lazio	4,078	158.5	175.2	-9.5%	-474.4	4,339	156.1	177.3	-12.0%	-643.9
Abruzzo	1,293	218.6	206.0	6.1%	80.4	1,379	222.1	200.1	11.0%	148.0
Molise	248	209.2	231.7	-9.7%	-33.9	281	231.3	229.7	0.7%	2.5
Campania	4,360	167.9	170.6	-1.6%	-76.7	4,232	155.0	170.3	-9.0%	-455.8
Puglia	3,490	190.4	179.7	5.9%	208.4	3,594	185.4	175.1	5.9%	213.7
Basilicata	445	190.3	206.9	-8.0%	-45.9	492	204.2	207.9	-1.8%	-10.4
Calabria	1,677	190.2	190.7	-0.3%	-5.2	1,701	185.5	190.4	-2.6%	-48.4
Sicily	3,900	184.1	196.3	-6.2%	-296.7	4,198	187.4	196.6	-4.7%	-236.3
Sardinia	1,389	192.1	191.2	0.5%	7.0	1,492	198.5	184.3	7.7%	118.8

Table 1 Number of deaths, mortality rate (age-standardized over the 2019 population) per 100,000 inhabitants in the periods 01.03-30.04.2020 and 2015-2019, percent variation of mortality rate and estimated difference in the total number deaths in the total population comparing 2020 with the expected from 2015-2019.

Tabella 1. Numero di morti, tasso di mortalità (standardizzata per l'età sulla popolazione del 2019) per 100.000 abitanti nei periodi 01.03-30.04.2020 e 2015-2019, variazione percentuale del tasso di mortalità e differenza stimata del numero totale di morti nella popolazione totale, confrontando il 2020 con la attesa nel periodo 2015-2019.

REGION	MALE					FEMALE					M TO F DIFFERENCES IN 2020 MORTALITY RATES
	OBSERVED DEATHS IN 2020 STUDY PERIOD	STANDARDIZED MORTALITY RATE 2020	STANDARDIZED MORTALITY RATE 2015-2019	PERCENT VARIATION OF MORTALITY RATE	ESTIMATED DIFFERENCE IN DEATHS IN TOTAL POPULATION	OBSERVED DEATHS IN 2020 STUDY PERIOD	STANDARDIZED MORTALITY RATE 2020	STANDARDIZED MORTALITY RATE 2015-2019	PERCENT VARIATION OF MORTALITY RATE	ESTIMATED DIFFERENCE IN DEATHS IN TOTAL POPULATION	
Italy	66,513	905.6	633.0	43.1%	21,381.3	70,972	772.1	576.3	34.0%	19,156.1	17.3%
Piedmont	5,995	1,006.8	651.4	54.6%	2,215.8	6,496	875.0	593.6	47.4%	2,188.5	15.1%
Valle d'Aosta	173	1,093.7	671.4	62.9%	72.7	198	1,018.7	622.2	63.7%	83.1	7.4%
Lombardy	19,507	1,549.5	592.9	161.4%	1,2218.2	19,770	1,244.0	549.0	126.6%	11,192.9	24.6%
Trentino-Alto Adige	1,131	936.0	587.4	59.4%	452.5	1,336	906.1	536.5	68.9%	583.2	3.3%
Veneto	4,362	742.8	594.9	24.9%	948.5	4,907	674.3	558.0	20.9%	922.5	10.2%
Friuli Venezia Giulia	1,194	732.4	641.9	14.1%	158.4	1,416	681.5	599.5	13.7%	182.3	7.5%
Liguria	2,523	1,094.2	684.9	59.9%	970.7	2,926	971.0	635.8	52.7%	1,038.3	12.7%
Emilia-Romagna	6,261	1,084.4	634.7	70.9%	2,690.0	6,512	896.1	601.8	48.9%	2,211.1	21.0%
Tuscany	3,802	754.4	648.5	16.3%	555.8	4,083	640.7	591.8	8.3%	324.4	17.7%
Umbria	760	633.3	668.5	-5.3%	-44.1	912	607.0	592.1	2.5%	23.4	4.3%
Marche	1,888	957.0	636.8	50.3%	681.1	1,861	758.0	594.7	27.5%	433.1	26.3%
Lazio	3,723	567.3	617.1	-8.1%	-360.5	4,106	486.1	550.4	-11.7%	-593.1	16.7%
Abruzzo	1,187	714.7	670.2	6.6%	80.0	1,324	651.1	583.1	11.7%	149.5	9.8%
Molise	229	671.7	741.7	-9.4%	-30.3	272	655.2	643.9	1.8%	6.0	2.5%
Campania	3,827	643.5	650.6	-1.1%	-46.0	3,944	537.0	587.9	-8.7%	-406.8	19.8%
Puglia	3,176	660.4	621.9	6.2%	198.1	3,404	574.8	542.9	5.9%	201.7	14.9%
Basilicata	410	639.1	682.9	-6.4%	-33.2	477	616.5	615.6	0.1%	0.8	3.7%
Calabria	1,529	659.9	655.3	0.7%	11.5	1,625	591.8	597.4	-1.0%	-16.8	11.5%
Sicily	3,582	667.5	700.3	-4.7%	-202.2	3,982	597.8	624.3	-4.2%	-202.2	11.7%
Sardinia	1,254	609.9	599.5	1.7%	23.8	1,421	567.2	521.1	8.9%	128.2	7.5%

Table 2 Population ≥65 years old: number of deaths, age-standardized mortality rate per 100,000 inhabitants in the periods 01.03-30.04.2020 and 2015-2019, percent variation of mortality rate and estimated difference in the total number deaths comparing 2020 with the expected from 2015-2019, percent difference for male vs female 2020 death rates.

Tabella 2. Popolazione ≥65 anni: numero delle morti, tasso di mortalità ogni 100.000 abitanti standardizzato per età nei periodi 01.03-30.04.2020 e 2015-2019, variazione percentuale del tasso di mortalità e differenza stimata nel numero totale di morti confrontando il 2020 con le attese nel periodo 2015-2019, Differenza percentuale nei tassi di mortalità per maschi vs femmine nel 2020.

Figure S4 in supplementary materials presents daily mortality rates by age (<65; ≥65) and area (North; Centre-South Regions). In the area most affected by COVID-19 epidemic, the mortality peak in March and April was observed in both age classes, albeit with very different mortality rates. In Central-Southern Regions instead, the increase was more limited and observed only in the population ≥65 years old.

Separate analyses by region, not presented in detail but available on request, showed evidence of a peak in daily mortality in Northern Italy Regions and, also, in Tuscany and Marche regions.

DISCUSSION

This research article confirms a large excess in total mortality during the COVID-19 epidemic in Italy, estimated in 40,870 deaths in excess in March-April 2020 and largely exceeding the mortality attributed to the infection (27,967 deaths on 30 April 2020).^{6,20} It highlights the role of age and gender components on the total mortality excess. The excess in total mortality was greater in the regions more affected by the epidemic and in subjects aged ≥65. Men also showed higher rates and anticipation in the epidemic curve compared to women. These findings are consistent with the SiSMG study quantifying the COVID-19 excess of mortality in a subgroup of 19 cities, representative of the Italian Regions.¹¹

The contribution of COVID-19 was estimated adding the mortality rates attributed to the infection to the 2015-2019 mortality rates (figure 1), as if all COVID-19 deaths were added to the burden of deaths in the population, with no consideration of the possible anticipation of the death of people already in terminal stages. The 'anticipation' effect is suggested by the observation of the curves in the last days of observation when total mortality was returned to the 2015-2019 values, but the curve of COVID-19 mortality still showed an excess of deaths. The contribution of COVID-19 as a component cause of death and not as an independent cause could not be assessed with data shown here, however, the focus of this study is on total mortality, and its main results are not affected by such a limitation.

The geographical location showed to be the major determinant of the COVID-19 excess mortality in Italy. Consistently with the literature, the greatest increase in mortality is evident in the Northern Regions most affected by the epidemic,¹¹ but also by the consequent disruption of the normal activity of the health service.²³ The findings identified a mortality increase (over the previous 5 years) in Lombardy of 161.4% for males and 126.6% for females aged 65 and over. In Piedmont, the corresponding mortality increase was 54.6% and 47.4%, respectively, and in Emilia-Romagna it was 67.6% and 47.0%, respectively.

The grouping of Regions in the two categories (North vs Centre-South) was based on 'a priori' criteria and corre-

sponds to other studies on COVID-19 related mortality,^{11,19} making a comparison between the studies possible. However, it may introduce a dilution in the observed effects as two Regions in Central Italy (Marche and to a lesser extent Tuscany) were seriously affected by the epidemic and presented a mortality peak.

As shown in the analyses presented in this study and corresponding to what is widely reported in the literature, COVID-19 disease is most harmful to male aged people²¹ and Italy has one of the oldest populations in the world. In Italy, the elderly component of the population is well integrated into social and family networks.²⁴ This phenomenon has also facilitated the circulation of the virus in the most fragile segments of the Italian population during the period of the epidemic spread.²⁵ A component of the mortality during the COVID-19 epidemic may be also related to the unidentified COVID-19 cases, since the use of diagnostic tests has been limited in the first period of the epidemic.⁵ Some studies suggest a considerable number of undetected cases among elderly subjects, reporting the higher COVID-19 fatality rate.¹³ For example, in Italy, since the outbreak emerged in the Northern Region of Lombardy, the nursing homes reported a steep increase in fatalities, although many patients died without being tested and COVID-19 was not diagnosed.²⁵ Elderly subjects show a higher prevalence of comorbidities that caused higher fatality rates in COVID-19 patients, including hypertension, type 2 diabetes, heart, and vascular diseases, cancer, chronic kidney disease, and COPD.²¹

The effect of the NHS disruption has not been measured yet, but the relation of mortality with the number of ICU admissions²³ and the observed increase of out-of-hospital cardiac arrests in Lombardy²⁶ strongly indicates its relevance. Data presented here show an excess of total mortality even in subjects aged <65 in the Northern Regions, but not having the COVID-19 mortality data by age it was not possible to separate its direct contribution.

Concerning the gender effect on the mortality during the COVID-19 epidemic especially in the Northern Regions and among elderly subjects, the gender component also played a role in determining the mortality excess in the first four months of 2020. In the literature, it is widely assessed that gender is one of the COVID-19 mortality risk factors; a literature review showed a COVID-19 mortality rate significantly higher in men than in women (RR=1.60, 96%CI 1.53-1.68) among the European countries.²⁷ The results of these study underscore that the gender component plays a role in affecting the risk of mortality during the COVID-19 epidemic in combination with the age and the geographical location. Possible causes include both the higher prevalence of comorbidities in men but also the higher prevalence of smokers and subjects exposed to occupational exposures affecting the lung.

The demographic composition is an indicator to be considered for the prevention of the COVID-19 mortality excess.

Some studies evidenced that, when compared to younger countries, the vulnerability to COVID-19 mortality is shown to be higher in several industrialized countries of East Asia and Europe showing a relationship between the demographic vulnerability to COVID-19 mortality and the current COVID-19 death rates.²⁸ Consistently with the literature, this study suggests that the COVID-19 disease mortality during the COVID-19 epidemic should be quantified considering the demographic population composition of the COVID-19 exposed population. The impact of the epidemic in terms of mortality could be different depending on the demographic composition. An important presence of a vulnerable component of elderly male subjects accomplished with uncontrolled exposure to the virus circulation could have large effects on the mortality burden compared to a younger population. This raises a warning to be considered for plans in the event of secondary waves of the pandemic. Further studies should be conducted with a finer aggregation of data to take into account also socioeconomic variables. For this reason, it is relevant to continue monitoring the impact of mortality during the COVID-19 epidemic, tak-

ing into account the demographic composition of the exposed population, not only for research and monitoring reasons, but also to tailor the public prevention policies towards the protection of the most fragile population groups.

CONCLUSIONS

The population composition plays an important role in contributing to the risk of mortality during the COVID-19 epidemic. For these reasons, it is of primary importance to monitor mortality (overall and by COVID-19) by age and gender and to consider the sociodemographic population components to properly tailor the public prevention policies towards the protection of the most fragile population groups.

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