



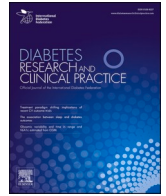
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Diabetes as a cause of death across different COVID-19 epidemic waves

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ABSTRACT

Aims: The aim of this study is to assess the role of diabetes as a cause of death through different epidemic waves of COVID-19.

Methods: The annual percentage change in age-standardized rates (APC) was estimated for diabetes as the underlying (UCOD) and as multiple causes of death (MCOD) in 2008–2019. Diabetes-related deaths in 2020 were compared to the 2018–2019 average. SARIMA models were applied to monthly excess in mortality considering seasonality and long-term trends.

Results: 2018–2019-Age-standardized mortality rates decreased, especially among females (MCOD: APC -2.49 , 95%CI $-3.01/-1.97\%$). In 2020, deaths increased by 19% (95%CI 13–25%) for UCOD, and by 27% (95%CI 24–30%) for MCOD. Diabetes and COVID-19 accounted for 74% of such excess. During the first epidemic wave, the increase in observed rates vs predicted by the model was larger in males (March +39%, April +46%) than in females (+30% and +32%). In the second wave, a huge excess of similar magnitude was observed in the two sexes; rates in December exceeded those predicted by more than 100%.

Conclusions: The COVID-19 pandemic abruptly interrupted a long-term declining trend in mortality associated to diabetes. MCOD analyses are warranted to fully estimate the impact of epidemic waves on diabetes-related mortality.

1. Introduction

During the COVID-19 pandemic an increase in mortality from diabetes has been reported in the US and in a number of European countries. In March–April 2020 in Italy diabetes mortality showed a large excess; an increase, although more limited, was observed also in Spain and England [1]. It must be remarked that in England most of excess deaths due to diabetes/cardiovascular diseases occurred during the first half of the first wave of the pandemic (April to mid-May), with a second, smaller increase from mid-July to August [2]. In Norway, the most striking finding of mortality analyses was the large and significant growth in deaths from diabetes [3]. Mortality from non-COVID-19 causes, including heart disease, Alzheimer disease, and diabetes was reported to rise in the US during the pandemic period [4], with excess deaths observed among all racial/ethnic groups, although being higher among Black, Asian/Native, and Latino populations [5].

Underreporting of COVID-19 can partly explain the mortality increase for diabetes and other chronic diseases; older individuals with

cardiovascular comorbidities and diabetes mellitus were particularly vulnerable to COVID-19 [6]. However, the excess mortality could also be related to the indirect effects of the pandemic: some patients inappropriately avoided contact or experienced difficulties in accessing healthcare professionals, which may have contributed to poor glucose control or inadequate clinical management of the complications of the disease.

The increase in diabetes mortality during the pandemic represents a consistent finding based on a standardized source of data: due to international harmonization, cause of death data are less affected by the differences that can occur between the national SARS-CoV-2 epidemic surveillance systems [1]. However, the above mortality data are limited to the underlying cause of death (UCOD), defined as the disease or injury which initiated the train of morbid events leading directly to death [4]. In the presence of elderly populations with multiple comorbid conditions, there may be no simple etiologic chain leading to the identification of a single underlying cause; instead, death often results from complex interaction among multiple factors. Within this context, the

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analysis of all conditions mentioned in death certificates, the so-called multiple causes of death (MCOd) approach, allows to better estimate the burden of mortality associated to chronic conditions. This holds true especially for diseases often reported in death certificates but more rarely selected as the UCOD: in analyses from Northern Italy, diabetes was mentioned in 12.3% but selected as the UCOD only in 2.9% of overall deaths [7]. Analyses of MCOd for diabetes are more robust to changes in certification practices between countries [8] and over time [9]. Therefore, MCOd analyses are warranted to validate findings based on the UCOD, and to investigate the interplay of COVID-19 and diabetes as causes of death.

To this purpose, we analyzed mortality records for the period 2008–2020 in the Veneto Region (Northeastern Italy, 4.9 million population). Diabetes mortality was demonstrated to decline in Veneto through 2008–2017, especially in the female gender and in deaths associated to cardiovascular events [10]. Aims of the study are: to confirm the impact of the pandemic on diabetes mortality with more complete estimates based on MCOd, and within the frame of the pre-existing long-term declining trend; to assess the impact of different COVID-19 epidemic waves on diabetes mortality, also compared with the excess mortality usually observed in winter months during the flu epidemics.

2. Subjects materials and methods

In Veneto, all conditions reported in death certificates, both in Part I (causal chain of events leading directly to death) and Part II (other significant conditions contributing to death), are coded according to the International Classification of Diseases, 10th Edition (ICD-10). In standard mortality statistics, a single UCOD is identified from all diseases reported in the certificate based on rules set by the World Health Organization [4]. Usually, the UCOD corresponds to the underlying cause chosen by the physician who fills in the certificate, but in some cases another disease reported in Part I or (more rarely) Part II, or a derived condition, is selected. To standardize the UCOD assignment, the Automated Classification of Medical Entities (ACME) software has been applied until 2017 [11], and the IRIS software, already adopted in most European countries, from 2018 onwards [12].

All deaths of residents in Veneto aged ≥ 40 years with any mention of diabetes (ICD-10 codes E10-E14) were retrieved from January 1, 2008, to December 31, 2020. Truncated age-standardized rates (direct standardization, 2013 European standard), and proportional mortality (share out of all deaths) were computed for diabetes as the UCOD and as any mention in death certificates (MCOd). To confirm long-term trends preceding the pandemic, the annual percentage change in age-standardized rates (APC) with 95% confidence intervals (CI) was estimated for the period 2008–2019 from linear regression models, separately for males and females, with the logarithm of age-standardized rates weighted by the inverse of their variance as the dependent variable, and the corresponding year as the independent variable.

The impact of the pandemic on diabetes mortality was assessed by two approaches. In a first descriptive analysis, the monthly number of diabetes-related deaths (based both on the UCOD and on MCOd) observed in 2020 was compared with the corresponding monthly average of the previous two years, when the IRIS software was already adopted for UCOD selection. The ratio of observed vs. expected (2018–2019 average) deaths was computed with 95% CI based on the Poisson distribution. Among deaths with mention of diabetes, those associated to COVID-19 were identified by ICD-10 codes U07.1, U07.2. To obtain a more accurate estimate of the excess mortality during the pandemic, a time-series approach was also adopted. Monthly age-standardized mortality rates based on MCOd were plotted from January 2008 to December 2020 to identify peaks in diabetes-related mortality. Thereafter, Seasonal Autoregressive Integrated Moving Average models (SARIMA) taking into account the components of the time series (seasonality and trend) were applied to 2008–2019 data to

forecast monthly age-standardized diabetes-related mortality rates in 2020, for males and females respectively. The best fitting SARIMA models were selected based on the lowest corrected Akaike Information Criteria value. The excess mortality was estimated as the percentage change between observed rates and those expected from the model. Statistical analyses were performed using STATA 15 and R language (version 4.1.3).

3. Results

During the whole study period (2008–2020), diabetes was reported in 74,796 death certificates of residents aged ≥ 40 yrs, and was selected as the UCOD in 17,845. Diabetes as the UCOD accounted for 2.9% of all deaths; such proportion increased to 12.3% for any mention of the diseases. In MCOd analyses, through 2008–2019 proportional mortality was rather stable in males, whereas declined in females (from 13.1% to 10.8%); in 2020 the share of all deaths associated to diabetes increased in both genders, being 14.1% in males and 11.8% in females.

Age-standardized mortality rates decreased through 2018–2019; such decline was steeper among females in analyses based both on the UCOD (APC -1.12% , CI $-1.73/-0.50\%$ in males and -2.73 , CI $-3.65/-1.80\%$ in females), and on MCOd (APC -1.43 , CI $-1.76/-1.11$ in males and -2.49 , CI $-3.01/-1.97\%$ in females). By contrast, an increase in mortality rates could be observed for the year 2020, more evident for MCOd among males (Fig. 1).

When the monthly number of deaths registered in 2020 was compared with the corresponding 2018–2019 average, two distinct peaks could be observed especially from MCOd, corresponding to the two COVID-19 epidemic waves involving Italy in March-May and in October-December 2020 (Fig. 2). According to the UCOD, deaths due to diabetes in 2020 increased by 19% (CI 13–25%), whereas from MCOd overall diabetes-related deaths increased by 27% (CI 24–30%). This latter figure was mainly accounted by the March-May (+33%, CI 27–39%) and October-December (+69%, CI 62–75%) epidemic waves. The overall increase observed for MCOd in 2020 corresponds to 1,543 excess diabetes-related deaths; in most of these deaths ($n = 1,140$, 74%), COVID-19 was reported in the death certificate together with diabetes. It is worth of notice that such proportion was limited to 65% in the first epidemic wave and increased to 80% during the second wave.

Fig. 3 shows monthly diabetes-related mortality rates. A clear seasonal pattern can be observed, with higher mortality registered in winter months. Peaks in diabetes-related mortality were registered for both sexes in January 2009, January-February 2012, January 2015, and January 2017, corresponding to excess overall mortality already reported in association with cold spells or high flu activity (13). In 2020, the first COVID-19 epidemic wave in March-April resulted in a peak in diabetes-related mortality of similar magnitude to that usually observed earlier (January-February) during flu epidemics. By contrast, the October-December wave produced an unprecedented increase in diabetes-related mortality.

The time-series analysis accounted both for the long-term declining trend in diabetes-related mortality and for its seasonality. SARIMA (0,0,0)(0,1,2)₁₂ with drift and SARIMA (0,0,0)(2,1,0)₁₂ with drift models were selected for males and females, respectively, as those minimizing the value of the corrected Akaike Information Criteria. During the first epidemic wave the increase in observed rates with respect to those predicted by the model was larger in males (+39% in March and +46% in April) than in females (+30% and +32%). In the second wave, a huge excess of similar magnitude was observed in the two sexes, with rates in December exceeding those predicted by more than 100% (Table 1).

4. Discussion

The COVID-19 pandemic interrupted a long-term declining trend in diabetes-related mortality in Northern Italy. The growth in mortality

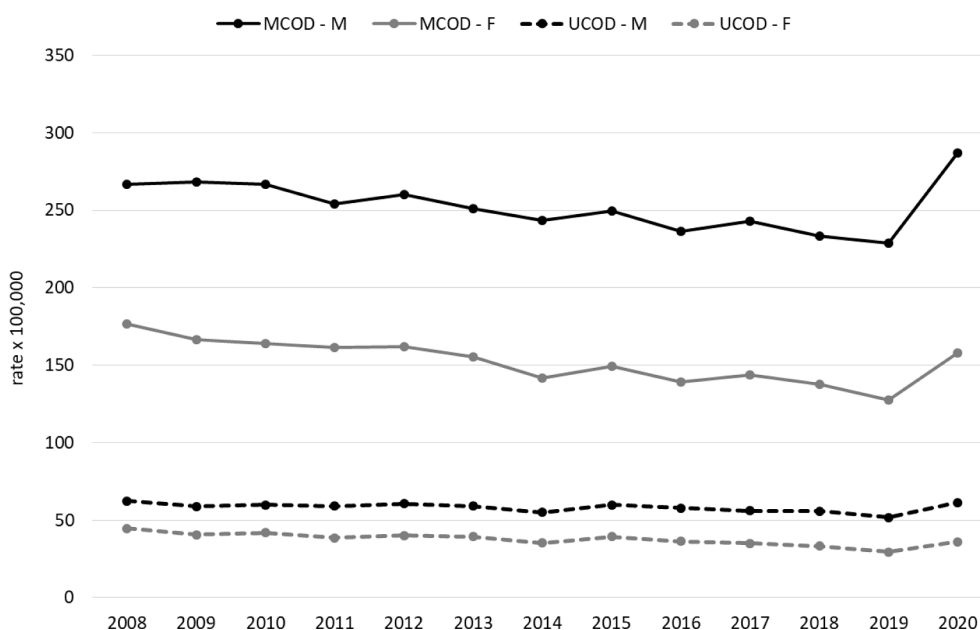


Fig. 1. Age-standardized mortality rates (European standard population 2013) for diabetes as the underlying cause of death (UCOD) and as multiple causes of death (MCOD), by gender and year. Veneto Region, Italy, 2008–2020.

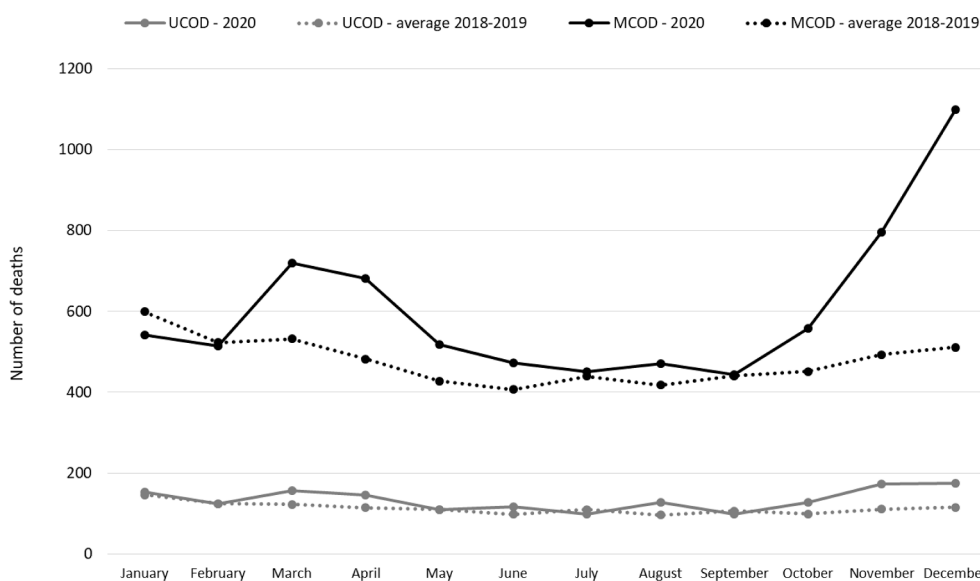


Fig. 2. Observed number of diabetes-related deaths by month in 2020 plotted against the average observed in 2018–2019, based on the underlying cause of death (UCOD) and on multiple causes of death (MCOD). Veneto Region, Italy.

usually observed with flu epidemics in January-February was not registered in 2020. By contrary, diabetes-related mortality peaked in March-April when the Veneto region was hit by the first COVID-19 epidemic wave; such excess mortality was larger in the male gender. During the second epidemic wave in late 2020, when mortality from all causes reached the highest peak in the region [6], unprecedented high levels of diabetes-related mortality were observed in both genders.

In the Veneto region, the first lockdown imposed just after the first few cases of COVID-19 were detected, along with other public health measures, was very efficient in reducing the diffusion of the virus, thus containing the impact of the first wave [13,14]. On the contrary, the second and larger wave might have been propelled by the summer-autumn period, when free movements and contacts among people may have contributed to a larger and uncontrolled diffusion of the virus. An additional factor was the appearance of new variants of the virus [15]. A

recent study on COVID-19 variants reported the phylogenetic tree based on subsampling of globally circulating sequences, showing that nearly all variants of concern (Alpha, Beta, Gamma and Delta) emerged independently beginning in late 2020. In particular, the Alpha and Delta variants were each associated with increased transmissibility and greater disease severity because of immune evasion and potentially because of higher virus levels [15]. As a consequence, in Veneto the peak in diabetes-related mortality during the first COVID-19 wave reached a magnitude similar to that observed during seasonal flu. By contrary, the second wave was associated with highest mortality, confirming that with respect to seasonal flu, COVID-19 has a higher potential for respiratory pathogenicity, leading to more respiratory complications and to increased mortality [16].

The main strength of the study is the adoption of the MCOD approach to fully assess diabetes-related mortality. In fact, analyses limited to the

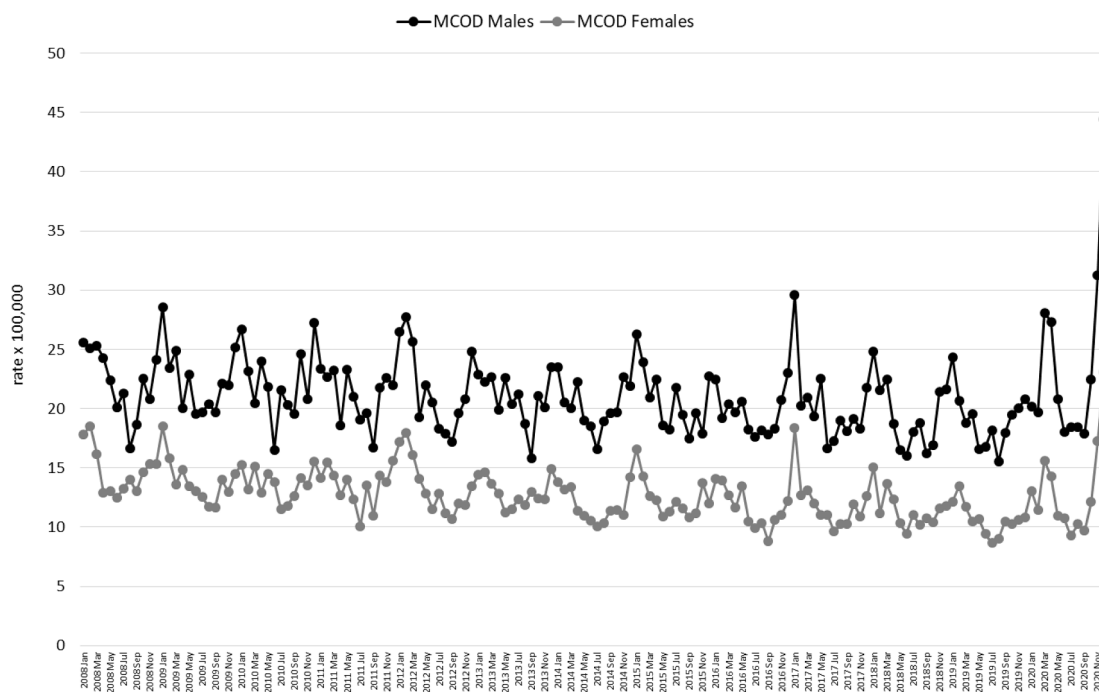


Fig. 3. Age-standardized monthly mortality rates (European standard population 2013) for deaths with any mention of diabetes (MCOD), by gender. Veneto Region, Italy, 2008.

Table 1

Age-standardized monthly mortality rate associated to diabetes (European standard population 2013) observed in 2020 and percentage change ($\Delta\%$) with respect to rates predicted based on the 2008–2019 time series, by gender. Veneto region, Italy.

Month	Males		Females	
	Rate \times 100,000	Δ %	Rate \times 100,000	Δ %
January	20.2	-14.8	13.1	-12.8
February	19.7	-3.7	11.5	-4.8
March	28.1	38.5	15.6	29.9
April	27.3	46.3	14.3	31.6
May	20.8	10.0	11.0	8.3
June	18.1	9.1	10.7	12.6
July	18.4	7.2	9.3	5.4
August	18.5	7.9	10.3	12.6
September	17.9	12.2	9.7	-0.3
October	22.5	24.2	12.1	16.1
November	31.3	67.0	17.3	69.5
December	44.4	108.6	23.1	106.2

UCOD may significantly undercount deaths attributable to diabetes [17], and this limit has been amplified by the pandemic. Based on the UCOD, diabetes-related deaths in 2020 increased by 19% with respect to the 2018–2019 average (when the same software was adopted for mortality coding); excess deaths were as high as 27% in MCOD analyses. Such discrepancy is attributable to competing causes of death (mainly, deaths attributed to COVID-19 in subjects affected by diabetes). Furthermore, the analysis of all conditions reported in death certificates helps to disentangle the direct and indirect effects of the pandemic on diabetes-related mortality. In fact, subjects with diabetes have been demonstrated to be at increased risk of SARS-CoV-2 infection, admission to hospital, intensive care unit, and mortality from COVID-19 during the first epidemic wave in Italy [18]. As regards indirect effects, a growth in mortality might be explained by patients experiencing barriers in the access to healthcare during lockdown periods, or inappropriately avoiding care due to fear of the contagion. These latter mechanisms might have led to increased mortality from diabetes in Australia in 2020 in spite of containment of SARS-CoV-2 infection and reduced mortality

from all causes [19]. In MCOD analyses, 1,140 death certificates reported both COVID-19 and diabetes as causes of death; this figure corresponds to 74% of estimated excess diabetes-related deaths during 2020. A portion of the remaining excess mortality can be explained by undiagnosed infection, especially in the first phase of the pandemic, due to limited testing resource: the proportion of excess mortality attributable to COVID-19 increased from 65% in the first to 80% in the second largest epidemic wave.

5. Conclusions

In conclusion, the present study shows a large impact of the pandemic on diabetes-related mortality in the Veneto region, especially during the second wave in late 2020. Analyses on all conditions reported in death certificates are warranted to fully assess the role of diabetes as a cause of death in the next pandemic and post-pandemic years.

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CRediT authorship contribution statement

Ugo Fedeli: Conceptualization, Formal analysis. Veronica Casotto: Formal analysis. Elena Schievano: Formal analysis. Enzo Bonora: Validation. Giacomo Zoppini: Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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