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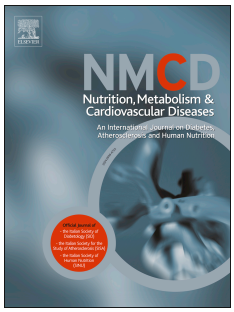

Excess diabetes-related deaths: the role of comorbidities through different phases of the COVID-19 pandemic

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PII: S0939-4753(23)00227-2

DOI: https://doi.org/10.1016/j.numecd.2023.05.028

Reference: NUMECD 3332

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 23 December 2022

Revised Date: 28 April 2023

Accepted Date: 26 May 2023

Please cite this article as: Fedeli U, Amidei CB, Casotto V, Schievano E, Zoppini G, Excess diabetes-related deaths: the role of comorbidities through different phases of the COVID-19 pandemic, *Nutrition, Metabolism and Cardiovascular Diseases*, https://doi.org/10.1016/j.numecd.2023.05.028.

Excess diabetes-related deaths: the role of comorbidities through different phases of the COVID-19 pandemic

Short title: COVID-19, diabetes and comorbidities

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Key words: Diabetes, trend, COVID-19, comorbidities, mortality

Word counts: abstract 196, text 2316, 1 table, 4 figures and 22 references

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Abstract

Background and Aims, Diabetes confers an excess risk of death to COVID-19 patients. Causes of death are now available for different phases of the pandemic, encompassing different viral variants and COVID-19 vaccination. The aims of the present study were to update multiple causes of death (MCOD) data on diabetes-related mortality during the pandemic and to estimate the impact of common diabetic comorbidities on excess mortality.

Methods and Results, Diabetes-related deaths in 2020-2021 were compared with the 2018-2019 average; furthermore, age-standardized rates observed during the pandemic were compared with expected figures obtained from the 2008-2019 time series through Generalized Estimating Equation (GEE) models. Changes in diabetes mortality associated with specific comorbidities were also computed. Excess diabetes-related mortality was +26% in 2020 and +18% in 2021, after the initiation of the vaccination campaign. The presence of diabetes and hypertensive diseases was associated with the highest mortality increase especially in subjects aged 40-79 years, +41% in 2020 and +30% in 2021.

Conclusion, The increase in diabetes-related deaths exceeded that observed for all-cause mortality and the risk was higher when diabetes was associated with hypertensive diseases. Notably, the excess mortality decreased in 2021, after the implementation of vaccination against COVID-19.

Introduction

An increase in mortality from diabetes has been reported since the early phase of the COVID-19 pandemic [1,2] and observed worldwide, even in countries only marginally hit by the pandemic in 2020 such as Australia [3]. However, most studies investigated only the underlying cause of death (UCOD), the single condition selected according to international coding rules from all those reported in each death certificate [4]. Especially during the pandemic, with COVID-19 acting as a strong competing cause for the UCOD, analyses extended to all conditions mentioned in death certificates (multiple causes of death, MCOD) are warranted to fully assess the burden of mortality related to diabetes. MCOD analyses carried out in the US [5], in Italy [6], and in Spain [7] demonstrated an excess in diabetes-related deaths larger than estimates relying only on the UCOD; such increase far surpassed that observed for all-cause mortality. The emergence of COVID-19 as a leading UCOD may substantially alter proportional mortality from other causes, further reinforcing the importance of the recourse to the MCOD approach during the pandemic [8].

Causes of death data are now available spanning subsequent phases of the pandemic, characterized by the surge of different viral variants and the increasing COVID-19 vaccination coverage. Notably, in the US, the excess in diabetes-related mortality estimated by means of the MCOD methodology remained above 30% across the whole pandemic period, substantially unchanged in 2021 with respect to 2020 [5]. Data from large cohort studies have suggested that comorbidities among diabetic patients as well as complicated diabetes significantly increase the mortality risk from COVID-19 [9]. However, similar analyses based on causes of death data are lacking. The present study updates MCOD data in the Veneto region (northeastern Italy) [6], with the aim to examine the role of COVID-19 and common comorbidities in excess diabetes-related mortality thorough multiple epidemic waves in 2020 and 2021.

Methods

Study setting

The Veneto region (about 4.9 million inhabitants) was among the first and hardest hit areas in Europe in the early phase of the pandemic [10]. Subsequent epidemic waves were registered in the region: the first in March-April 2020, the second in October 2020-January 2021 (alpha variant), the third in March-April 2021 (prevalently alpha and gamma variants), and the fourth in December 2021 (initially delta and then progressively omicron). The

national vaccination campaign against COVID-19 in Italy began in the late December 2020 among healthcare workers, nursing home residents and personnel, and was subsequently extended to all people aged 80 years or more. In March-April 2021, vaccination was extended to frail subjects, irrespective of age, including those with type 1 diabetes or with complicated type 2 diabetes o with type 2 diabetes in polypharmacotherapy [11]. Thereafter, the vaccination campaign was progressively extended to younger age groups regardless of comorbidities.

Analysis of diabetes-related mortality

In the mortality register of the Veneto region, all deaths of any resident of the region are recorded. All conditions reported on death certificates are coded according to the International Classification of Diseases, 10th Revision (ICD-10). To standardize UCOD identification, the Automated Classification of Medical Entities (ACME) software was applied to regional records until 2017 and the IRIS software from 2018 onward [6]. All deaths from January 1, 2008, to December 31, 2021 with any mention of diabetes (ICD-10 codes E10-E14) either in Part I of the death certificate (chain of events leading directly to death), or in Part II (other significant diseases, conditions, or injuries that contributed to death) were retrieved (MCOD approach).

A first descriptive analysis compared the monthly number of diabetes-related deaths in 2020-2021 with the average registered in the corresponding months in 2018-2019; the ratio of observed vs. expected (2018-2019 average) deaths was computed with 95% CI based on the Poisson distribution. The proportional mortality (share of diabetes-related deaths out of all deaths) was also calculated. Among deaths with diabetes, those associated to COVID-19 were identified by ICD-10 codes U07.1, U07.2.

In each year from 2008 to 2021, out of all death certificates with mention of diabetes, the proportion reporting the following conditions was assessed: ischemic heart disease (ICD-10 I20-I25), cerebrovascular diseases (I60-I69), hypertensive diseases (I10-I13), atrial fibrillation (I48), neoplasms (C00-D48), dementia/Alzheimer's disease (F01-F03,G30), chronic obstructive pulmonary disease (COPD) (J40-J44,J47). As above, deaths related to specific comorbidity patterns (e.g., mention of both diabetes and ischemic heart disease) in 2020 and in 2021 were compared with the average registered in 2018-2019.

Lastly, to measure excess mortality taking into account both long-term time trends and seasonality, similarly to previous studies [12], mortality figures expected during the pandemic were estimated by generalized estimating equation (GEE) models applied to

monthly diabetes-related mortality rates registered from 2008 to 2019. Age-standardized rates (2013 European Standard Population) restricted to the population aged ≥40 years were modelled assuming a Gamma distribution with a log-link function. A first-order autoregressive structure was adopted to take into account the different pattern of correlation among monthly rates within each year and assuming independence of the years. In order to model both seasonality and the long-term declining trend in diabetes-related mortality, dummy variables for each month and a linear trend across months of the study period were included as predictors. Observed age-standardized mortality rates were plotted against expected rates with 95% confidence intervals. The same approach was applied separately for subjects aged 40-79 and ≥80 years with/without mention of hypertensive diseases. All analyses were carried out using Stata version 16.

Results

Diabetes was mentioned in 13,992 death certificates in 2020-2021, but was selected as the UCOD only in 3,171 (23%). Peaks in deaths with any mention of diabetes were observed in each of the four COVID-19 epidemic waves hitting Italy in 2020-2021 (Figure 1). The peaks corresponded to a rise also in proportional mortality, confirming that the increase in diabetes-related mortality surpassed that observed for all-cause mortality. Overall, deaths with mention of diabetes represented 12.7% of all deaths in 2020-2021, compared to 11.8% in 2018-2019. The proportional mortality peaked at 14.5% in December 2020, when the largest increase of both all-cause and diabetes-related mortality was observed in the region.

Compared to numbers registered in 2018-2019, a +27% excess (CI 24-30%) in diabetes-related deaths was estimated in 2020 (corresponding to 1,543 more deaths than expected); the excess was less marked in 2021 and corresponded to +17% (CI 15-20%) (995 deaths). The corresponding increase in all-cause mortality was +17% (CI 16-18%) in 2020 and +9% (CI 8-10%) in 2021. Except for the beginning of the first epidemic wave and the last wave in late 2021, deaths reporting both diabetes and COVID-19 accounted for most of the excess: 74% in 2020 and 86% in 2021 (Figure 2). Overall, in the two pandemic years, deaths with COVID selected as the UCOD or anyway mentioned in the certificate represented 67% and 79% of excess diabetes deaths, respectively.

Table 1 shows the prevalence of the main comorbidities among diabetic patients both in the pre-pandemic period and in pandemic years. Through 2008-2019, diabetes-related

deaths with mention of ischemic heart diseases, cerebrovascular diseases, and COPD declined; the proportion of diabetic decedents with hypertensive diseases and neoplasms remained stable; deaths reporting also atrial fibrillation and dementia increased. During the pandemic, diabetes associated with specific comorbidities increased more than overall diabetes-related deaths: diabetes and COPD in 2020 (+30%); diabetes and atrial fibrillation in 2021 (+24%); diabetes and hypertensive diseases both in 2020 and 2021 (+39% and +25%, respectively).

Increases in diabetes related-mortality estimated by time-series analyses based on GEE models were similar to figures derived from death counts: +26% in 2020 and +18% in 2021 (Figure 3). During the pandemic's second year, excess mortality decreased more among subjects aged ≥80 years (+25% in 2020, +16% in 2021) than in those aged 40-79 years (+26% in 2020, +20% in 2021, data not shown). Figure 4 shows age-stratified monthly excess mortality for diabetes with and without mention of hypertensive diseases, the most commonly reported comorbidity before the pandemic and that with the most pronounced increase in 2020-2021 among diabetes-related deaths. The largest excess was observed for deaths with mention of both diabetes and hypertensive diseases in the 40-79 age class: +41% in 2020, +30% in 2021. In the first epidemic wave, a peak was observed especially for deaths reporting the association of diabetes and hypertensive diseases, in both age classes. In the second wave, mortality peaked in all groups of age and comorbidities. In the third wave, excess deaths were mostly recorded in diabetic subjects younger than 80 years with hypertensive diseases. The impact of the fourth wave in late 2021 needs to be confirmed by 2022 mortality data.

Discussion

This study, carried-out in northeastern Italy, partly confirms findings from US 2020-2021 mortality records [5]: MCOD data should be analyzed to obtain a comprehensive estimate of the excess in diabetes-related mortality during the pandemic; such excess is larger than that observed from all-cause mortality, and is mostly explained by deaths associated to COVID-19. However, in the US, excess mortality remained very high through the whole period, +33% in 2020 and +35% in 2021, without the reduction in 2021 found in the present study. Notably, the increase in mortality rates among younger age classes was more pronounced in 2021, paralleling the shift of COVID-19 deaths toward younger ages already reported in the overall US population [13]. In the Veneto region, an excess in

diabetes-related mortality could still be observed in the second year of the pandemic, but smaller than in 2020. The analysis of comorbidities and age at death provided further insights into risk factors associated to mortality, and into the role of vaccination in reducing excess diabetes-related deaths.

Subjects with diabetes were demonstrated to be at increased risk of infection, severe disease, and mortality from COVID-19 already in the first epidemic wave in Italy [14]. Among hospitalized COVID-19 patients, a synergistic role of diabetes and hypertension in increasing the mortality risk has been extensively reported [15]. In the US, among decedents from COVID-19, diabetes was the second most prevalent cardiovascular risk factor/disease mentioned in death certificates after hypertensive diseases [16]. In Veneto, hypertensive diseases represented the most commonly reported comorbidity among diabetes-related deaths already in the pre-pandemic period. During the pandemic, hypertensive diseases were associated to a further excess in diabetes-related deaths, supporting a joint effect in increasing the mortality risk. However, such risk declined during epidemic waves hitting the region in 2021. A positive impact of the vaccination campaign is suggested by the mortality pattern registered during the third epidemic wave (spring 2021): a sharp peak in deaths related to diabetes and hypertensive diseases could still be observed among subjects aged <80 years, but not among those aged 80 years or more. This latter group was among the first to be involved by the early stages of the national vaccination campaign.

The large increase in diabetes-related mortality observed worldwide has suggested a relevant role could have been played by indirect effects of the pandemic: people with diabetes might have hesitated to access hospital services due to concerns about transmission of COVID-19; furthermore, restrictions in outpatient care and reduced social support might have contributed to a suboptimal management of the disease [17]. In Mexico, a 41% increase in mortality from diabetes as the UCOD registered in 2020 compared to 2017-2019 was mainly attributed to difficulties in providing adequate healthcare support for people with diabetes during the pandemic [18]. However, it is difficult to disentangle the indirect impact of the pandemic from the effect of under-diagnosis of COVID-19. In Veneto, at the beginning of the first epidemic wave, with an overwhelmed healthcare system and limited diagnostic capabilities, deaths with mention of COVID-19 only partly accounted for excess diabetes-related mortality, but their share progressively increased through the pandemic.

The study has limits associated with underreporting of diabetes in death certificates, a problem already observed in Italy as well as other countries [19,20]. We do not have data to assess if such underreporting changed during the pandemic, either increasing due the huge workload for physicians further reducing time devoted to the completion of death certificates, or declining due to awareness of diabetes, obesity and hypertension as major risk factors for severe COVID-19 [5]. Furthermore, the disease was mostly reported as unspecified diabetes, hindering the possibility to provide reliable estimates separately for type 1 and type 2 diabetes. In descriptive analyses based on death counts, only the 2018-2019 period was taken as a reference for excess mortality estimates; however, results were confirmed by time series analyses spanning over a longer period and accounting for trend and seasonality.

MCOD data represents a major study strength; such approach is warranted because in Italy diabetes is often mentioned only in part II of the death certificate, and not selected as the UCOD [19]. In fact, differences across countries in mortality rates from diabetes as the UCOD can be partially explained by diverging certification practices, with diabetes mostly cited in part I in some countries and in part II in others [21]. Therefore, especially during the pandemic, with COVID-19 acting as a strong competing cause for selection as the UCOD, excess diabetes mortality should be investigated based on MCOD. The adopted approach allows for a straightforward comparison with estimates obtained in the US [5]. Furthermore, by means of the MCOD methodology, changes in comorbidity patterns in the pre-pandemic period as well as in pandemic years could be assessed. Comorbidities included in the present report represented the most common chronic diseases registered among decedents in the Veneto region; the mortality pattern observed in 2020 for the most common circulatory diseases was reported in a previous study [22]. Lastly, the study spanned over the whole 2020-2021 period, including different pandemic waves and phases of the national vaccination program.

In conclusion, in northeastern Italy the increase in diabetes-related deaths exceeded that observed for all-cause mortality in 2020-2021, being associated to specific comorbidity patterns, especially diabetes and hypertensive diseases. However, such excess was reduced by the progressive implementation of the national vaccination campaign against COVID-19.

Contributors

UF, GZ conceived the study and the analyses plan. CBA, ES and VC reviewed the analyses plan. UF and VC searched the data and made statistical analyses. GZ, UF,and CBA drafted the manuscript. All authors contributed to interpretation of data and revision of the manuscript. All authors approved the final version of the manuscript.

Declaration of interest

None of the authors have any interest to disclose pertaining to this study.

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Table 1. Number of death certificates with mention of diabetes per year (2008-2021), with the percentage of those mentioning the most common comorbidities*, along with the percent variation during pandemic years with respect to the 2018-2019 average (Veneto region, Italy).

	Diabetes No.	IHD %	Cerebro %	Hyp %	AF %	Tum %	Dem %	COPD %
2008	5465	36.8	22.4	34.1	12.3	25.2	10.2	9.9
2009	5390	36.0	22.1	35.4	13.2	26.3	10.5	10.3
2010	5424	33.1	23.2	34.6	13.6	26.2	11.0	10.0
2011	5492	34.0	20.3	33.6	11.9	27.5	10.3	8.9
2012	5756	32.7	18.2	34.4	13.4	25.5	11.2	9.4
2013	5678	31.3	19.3	34.2	13.0	25.5	10.3	9.1
2014	5508	32.4	17.9	33.3	12.9	26.8	10.5	9.3
2015	5865	30.3	17.7	34.8	14.4	24.6	11.3	9.1
2016	5638	29.6	17.2	33.4	15.9	24.6	12.4	8.1
2017	5921	29.4	16.4	32.7	15.6	25.1	12.4	9.1
2018	5793	28.9	17.1	33.1	16.6	25.8	13.3	7.9
2019	5661	26.9	15.4	32.6	16.7	25.4	13.0	8.0
2020	7270	25.1	15.4	35.9	16.0	22.2	12.8	8.2
2021	6722	25.5	14.4	34.9	17.6	23.2	11.5	7.7
Δ 20 vs 18-19	*+27%*	*+14%*	*+20%*	*+39%*	*+22%*	*+10%*	*+24%*	*+30%*
Δ 21 vs 18-19	*+17%*	*+7%*	*+4%*	*+25%*	*+24%*	*+6%*	*+2%*	*+13%*

*Ischemic heart diseases (IHD), cerebrovascular diseases (Cerebro), hypertensive diseases (Hyp), atrial fibrillation (AF), neoplasms (Tum), dementia/Alzheimer's disease (Dem); chronic obstructive pulmonary disease (COPD)

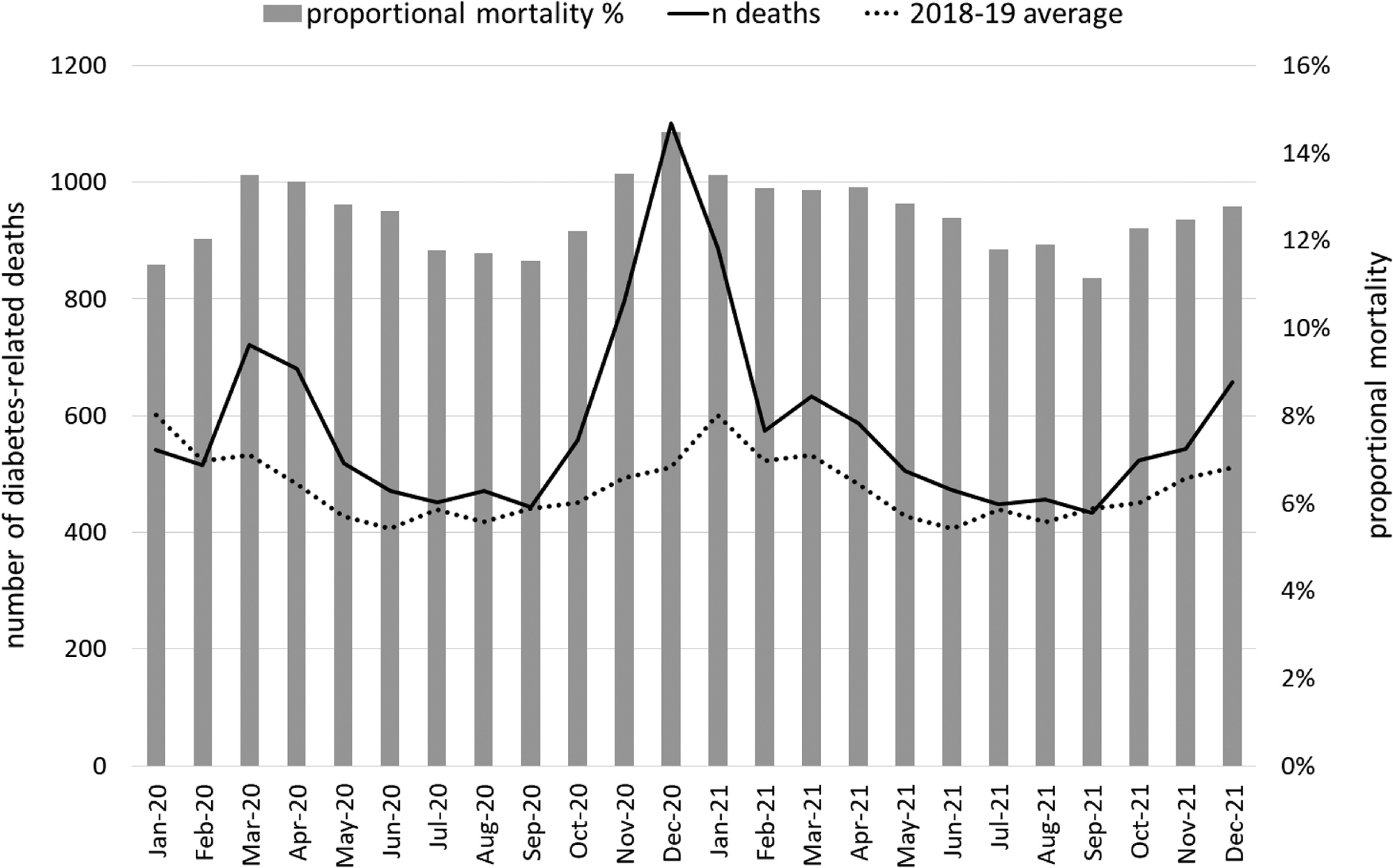
Legends to figures

Figure 1. Monthly number of diabetes-related deaths registered in the Veneto region (Italy) in 2020-2021 compared to the 2018-2019 average, and monthly proportional mortality (share of all deaths).

Figure 2. Monthly variation of diabetes-related deaths and number of death certificates with mention of both diabetes and COVID-19 in the Veneto region, Italy (2020-2021).

Figure 3. Monthly age-standardized diabetes-related mortality rates observed in 2020 and 2021 compared with expected figures (with 95% Confidence Intervals) obtained through a GEE model applied to the 2008-2019 time series; Veneto region (Italy).

Figure 4. Excess diabetes-related mortality by mention of hypertensive diseases (Hyp) and age group in the Veneto region (Italy): percentage variation of monthly age-standardized rates registered in 2020-2021 compared with expected figures based on GEE models.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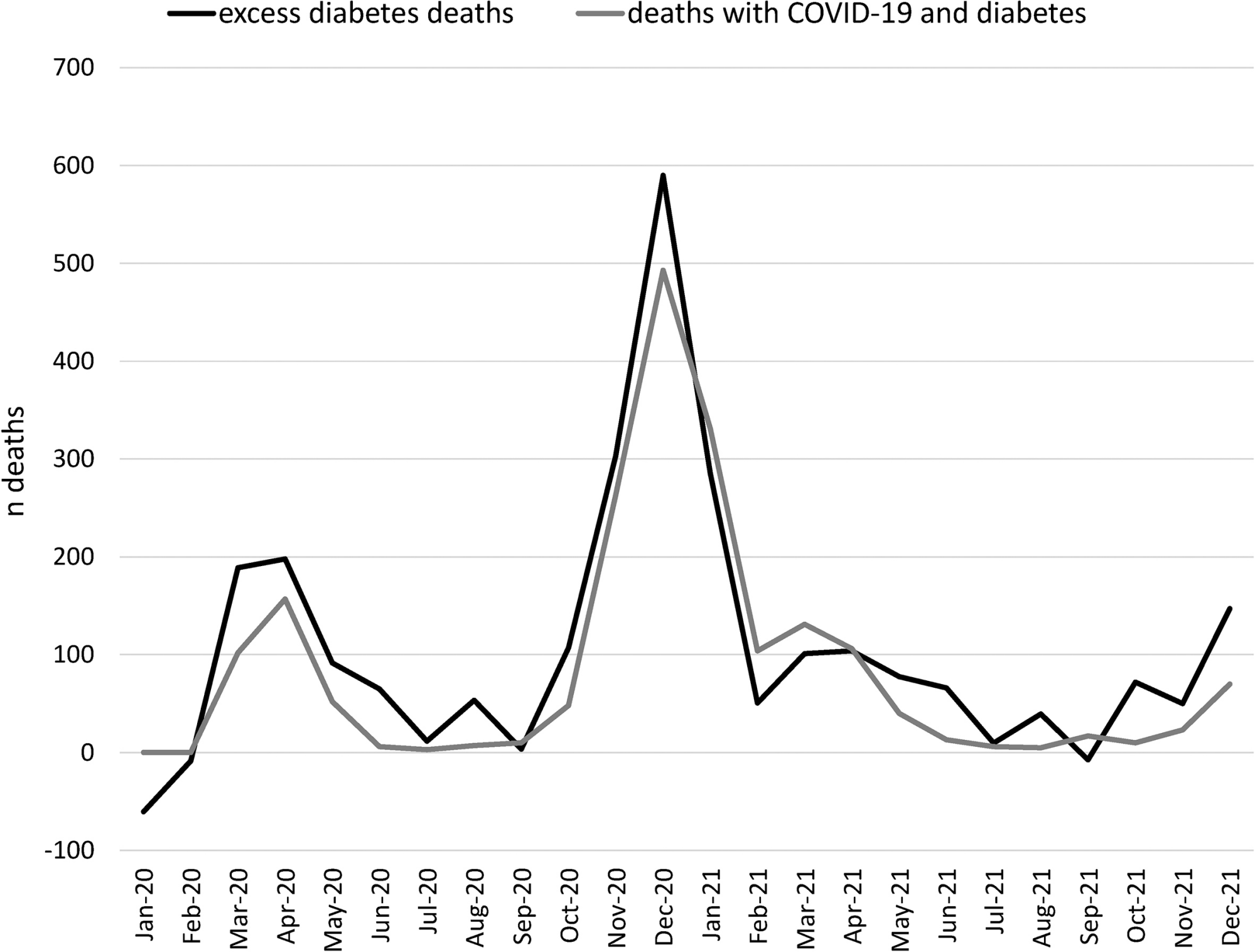
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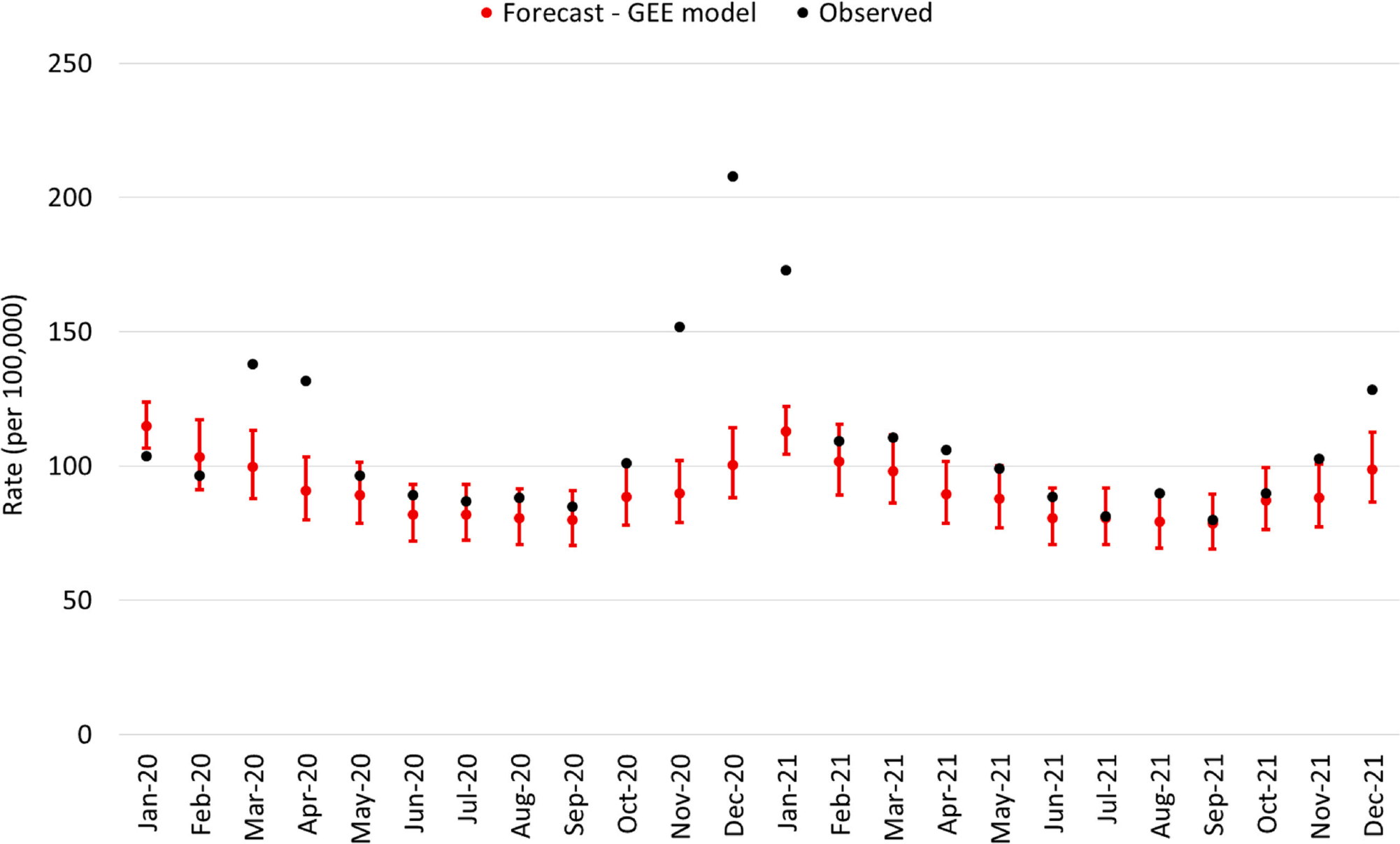
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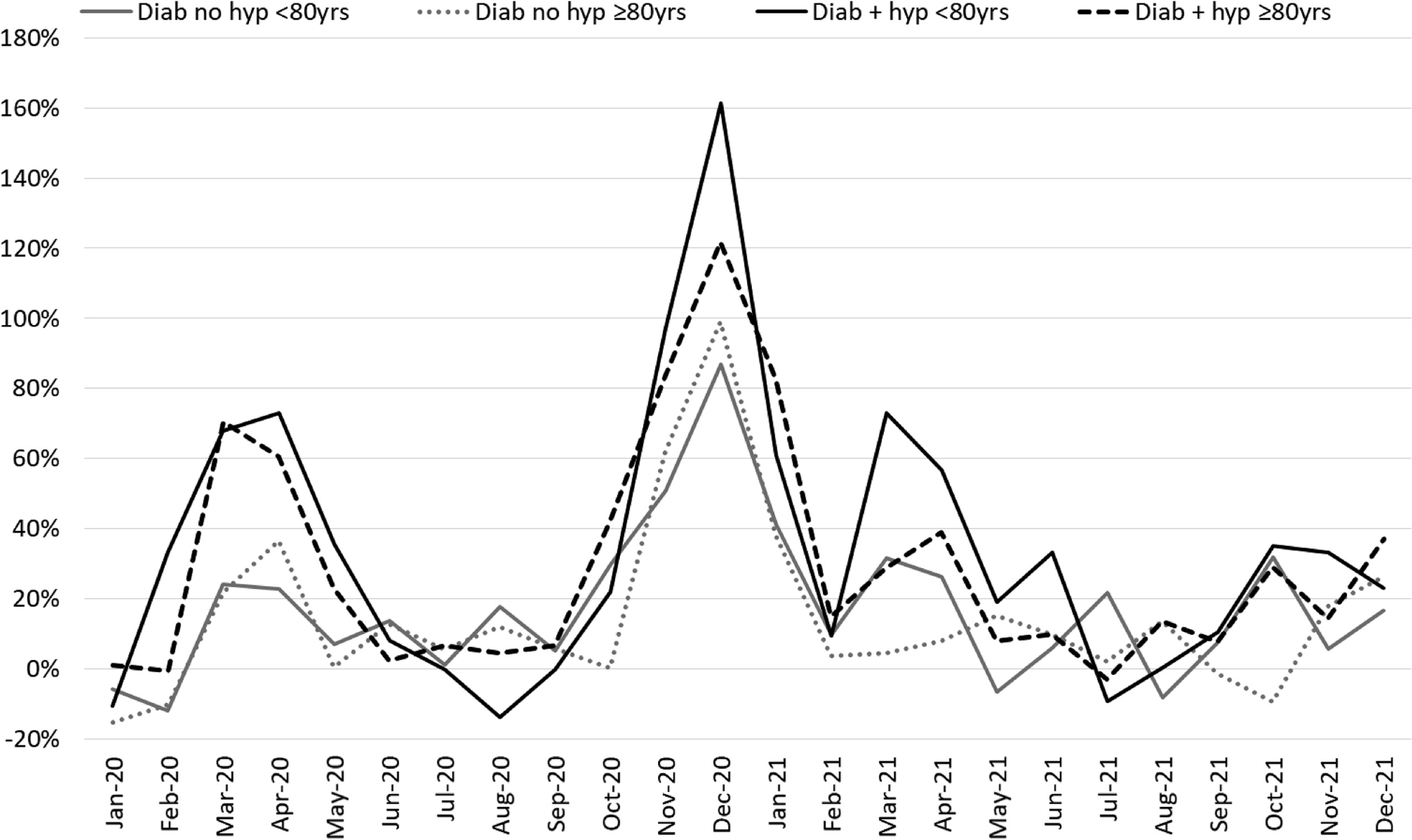
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Dec-21

HIGHLIGHTS

- Diabetes-related mortality was strongly increased during the COVID-19 pandemic.
- Further excess mortality was observed for diabetes plus hypertensive diseases.
- Vaccination campaign was followed by a reduction of excess diabetes-related deaths.