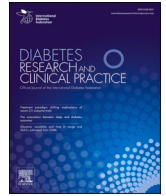




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# Effect of diabetes on short-term mortality and incidence of first hospitalizations for cardiovascular events after recovery from SARS-CoV-2 infection

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## ABSTRACT

**Aim:** To evaluate the impact of diabetes and COVID-19 on all-cause-mortality and first hospitalizations for cardiovascular events (CVE): myocardial infarction or stroke, within six months after being tested positive and having recovered from SARS-CoV-2 infection.

**Methods:** Resident population in Tuscany, Italy of age 45–94 yr without prior hospitalization for CVE, tested positive for SARS-CoV-2 by March 1st, 2020 and afterwards recovering from COVID-19 was compared with age, gender and diabetes matched controls without infection, for incidence rate ratio (IRR) of all-cause-deaths or first CVE at six months follow up.

**Results:** 46,152 subjects of whom 4,597 with diabetes, tested positive and recovered from SARS-CoV-2 were compared with 1:1 age, gender and diabetes matched controls without infection. COVID-19 was associated with higher all-cause-mortality: IRR:1.92(95 %CI:1.63–2.25) while diabetes with increased risk of first CVE hospitalizations: IRR:2.24(2.18–4.25). Co-presence of COVID-19 and diabetes didn't add any additional excess risk. Being women and statins' use significantly reduced death risk.

**Conclusions:** After recovery from COVID-19, independently of diabetes, all-cause-mortality risk at six months was twofold increased, while risk of first CVE hospitalization remained unmodified. Diabetes, independently of prior COVID-19, resulted in higher six-months risk of first CVE not of death. Female gender and statins' use reduced both excess risks.

## 1. Introduction

Coronavirus 19 disease 2019 (COVID-19), associated with SARS-CoV-2 virus pandemic, leads to a significant increase in the risk of death, mainly affecting elderly people with chronic diseases including diabetes [1–5]. Moreover, COVID-19 shares with diabetes an increased risk of thrombotic or thromboembolic events leading to acute cardiovascular events [6–10]. In addition, mortality linked to diabetes or to incident myocardial infarctions are significantly augmented during COVID-19 acute manifestations [11,12]. Scarce data, however, exist about the mutual role of diabetes and of COVID-19 on the risk of mortality as well as of the risk of first-ever cardiovascular events in people tested positive for SARS-CoV-2 infection after its recovery. Aims of this study were, therefore, to evaluate the impact of diabetes and of COVID-19 on the risk of death as well as of first hospitalizations for cardiovascular events (CVE) within six months from a positive nasopharyngeal

swab in people who had afterwards recovered from SARS-CoV-2 infection. Finally, to better elucidate the possible independent effect of diabetes on the risk of death or of hospitalization for CVE we additionally compared the incidence rates of death and of first CVE hospitalizations in people with diabetes during COVID-19 epidemic with those retrospectively observed from a similarly matched cohort with diabetes in pre-COVID-19 year (2019) and followed up for a same time period.

## 2. Material and Methods

### 2.1. Population under study

The population under study included all residents in Tuscany, Italy of age 45–94 years who resulted as being affected with SARS-CoV-2 by March 1st, 2020 as identified by a positive nasopharyngeal swab and who afterwards recovered, querying the regional database including all

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SARS-CoV-2 swabs (COVID+; n = 46,152). Only people who didn't have any prior hospitalization for CVE (stroke, myocardial infarction or heart failure) as to March 1st, 2020 were selected. The regional database including all nasopharyngeal SARS-CoV-2 swabs was continuously fed by the operators of the Health Care Regional Units and managed by the National Institute of Health. People affected with diabetes were identified according to an algorithm which has been validated and shown to identify more than 80% of people with diabetes living in Tuscany [13]. Each SARS-CoV-2 positive swab was paired with a subject non-present in the whole database of SARS-CoV-2 swabs, (n = 46,152; COVID-19-), 1:1 matched for gender, age and diabetes. By this procedure we finally obtained four cohorts: (COVID-19+ Diabetes-: n = 41,555; COVID-19+ Diabetes+: n = 4,597; COVID-19- Diabetes-: n = 41,555; COVID-19- Diabetes+: n = 4,597). For each individual present in the dataset further information was obtained about prior prescription of statins (ATC C10\*), or of antiplatelet drugs (ATC B01 AC) querying the regional database of all drug prescription claims. From this database, moreover, in people identified with diabetes, the current glucose lowering therapy at baseline was identified as: oral drugs: (ATC A10BA02, A10BB\*, A10BH\*, A10BJ\*, A10BK\*, A10BG\*, A10BD\*, A10BF\*, A10BX\*), only insulin (ATC A10A\*), or oral drugs + insulin. For each subject the Charlson index [14] was recorded, regarding the hospitalizations of previous three years and coded as 0, 1 and 2. Further, the index related to individual socio-economic status (deprivation index) [15] was added and coded as low, medium or high.

## 2.2. Outcomes and statistics

The incidence rate of all-cause death, retrieved from the regional census, and of first hospitalization for myocardial infarction (ICD-9 410.xx or ICD-9: 36.01, 36.02, 36.05, 36.06, 36.1), or stroke (ICD9 430.xx, 431.xx, 432.xx, 434.xx or 436.xx) both retrieved from the regional database of all hospitalizations, were estimated for each cohort in a time-to-event analysis by Kaplan-Meier survival curves. Since the incidence rate of first hospitalizations for myocardial infarction was relatively scarce in some groups, for the purposes of this study myocardial infarction was assembled with stroke in a unique composite outcome. In each cohort the rates of incident first hospitalizations for myocardial infarction, stroke and of deaths, adjusted for all considered covariates, were analyzed by a Poisson multivariate regression model. For each subject the observation period was calculated to be 6 months or less, in case of an event (death or first hospitalization). This model was also used to calculate all incidence rate ratios (IRR) with 95% CIs of death or first hospitalization for cardiovascular events (dependent variables), adjusting for diabetes, COVID-19, gender, age class, Charlson index, socio-economic status (deprivation index) and current drug therapies including glucose lowering drugs, antiplatelets and statins (independent variables in the model). To evaluate the effect by co-presence of COVID-19 and diabetes on death or first hospitalization for cardiovascular events the interaction term COVID-19\*diabetes was added to the list of covariates in the model.

Finally, the effect of diabetes on the risk of death or of cardiovascular events in the actual cohort was compared with the risk of these outcomes in an age and gender matched cohort obtained in the pre-COVID-19 period from the regional registry of people with diabetes and retrospectively followed up for six months in pre-COVID-19 period, starting on January 1st 2019 until June 30th 2019 and adjusting for the same covariates.

Everyone was identified across all used databases by an anonymous alphanumeric unique identifier to prevent disclosure of identity as well as of any other sensitive information. Because of such formal protection, no informed consent or any approval by an Ethics Committee was required, according to current national and regional rules.

Statistical analyses were performed using Stata version 15.0 (StataCorp LLC, College Station, TX, USA).

## 3. Results

The characteristics of the population under study, stratified by presence-absence of COVID-19 and diabetes (COVID+ Diabetes-, COVID+ Diabetes+, COVID-Diabetes-, COVID- Diabetes-) are reported in Table 1. People with diabetes were more prevalent in classes with more advanced age and, as expected, were associated with more comorbidities (Charlson index 2+) as well as with higher rates of current therapy with statins or antiplatelet drugs. Women were more prevalent across all groups. About 60% of subjects with diabetes were treated with oral drugs, 18% with insulin alone or in association with oral drugs and 22% with no glucose lowering drugs. Deprivation index levels, reflecting socio-economic status were equally distributed in subjects with or without diabetes. The adjusted incidence rates of mortality were higher in people tested positive for COVID-19, independently of diabetes, while on the contrary the rates of first incident hospitalization for cardiovascular events were significantly higher in people with diabetes, independently of COVID-19 (Table 2). The analysis of time course free from the first hospitalization for CVE (myocardial infarction or stroke) or of survival, expressed by the Kaplan-Meier curves in the four groups, confirmed these results (log-rank test < 0.001) (Fig. 1). These results were, moreover, confirmed by the Poisson multiple regression model (Table 3). Further variables which increased death IRR were advanced age, presence of comorbidities (higher Charlson index scores), higher levels of the deprivation index and the use of antiplatelet drugs. Baseline therapy with insulin alone was nearly, even if not significantly, associated with all-cause mortality (IRR:1.50; 95 %CI 0.98–2.28p = 0.062). Female gender and previous statin therapy were, on the contrary, significantly inversely related with the IRR of death, by 14% and respectively by 33% (Table 3). Co-presence of diabetes and COVID-19 expressed by the interaction term COVID-19\*diabetes did not add any additional risk of death with respect to the risks singly associated with COVID-19 or diabetes (Table 3).

The six-months-incidence rate of first hospitalizations for cardiovascular events was twofold higher in people with diabetes, independently of COVID-19 (Table 2) as also suggested by the Kaplan-Meier time-course analysis (log-rank test < 0.001) (Fig. 1). Again this finding was confirmed by the adjusted multivariate model for IRRs (Table 3). Among all considered covariates, none had a measurable significant effect on the risk of first cardiovascular events, except for advanced age and male gender (both positively associated) while co-presence of COVID-19 and diabetes, as expressed by the interaction term, again didn't involve any additional risk with respect to the risks singly associated with either COVID-19 or diabetes (Table 3). Interestingly from the data of the matched historical cohort retrospectively followed up across the pre-COVID period 1st March 2019- to 31st August 2019, comparing persons with and without diabetes, this latter was associated with a significantly higher IRR of mortality and of hospitalizations for first cardiovascular events (by 17% and respectively by 67%; p < 0.05 for both) (Fig. 2).

## 4. Discussion

The main goal of the study was to test whether diabetes in COVID-19, after its recovery, is associated with an excess risk of mortality or of new cardiovascular events and, just for this purpose, the design of the study included a cohort who had no previous hospitalizations for cardiovascular diseases being these latter, by themselves, an important risk factor for mortality after COVID-19 [16,17]. The increase in mortality risk was as twice as high, in COVID-19 + subjects who recovered from viral infection, when compared with those without any prior documented exposure to SARS-CoV-2. This excess risk of mortality was, as expected, related to co-variables such as aging, lower socio-economic status, presence of co-morbidities or to male sex [1,18,19]. It is noteworthy to stress that a higher deprivation index is related with an about 20–25% increase in mortality risk: this could be due to the higher risk exposure to COVID-

**Table 1**  
Main characteristics of population under study stratified by positivity for COVID-19 and/or diabetes.

Age (yr)	COVID + Diabetes-		COVID-Diabetes+		COVID-Diabetes+		COVID + -Diabetes+		Total No.	%
	No.	%	No.	%	No.	%	No.	%		
45–54	16,499	39.7	620	13.5	16,499	39.7	620	13.5	34,238	37.1
55–64	12,598	30.3	1,135	24.7	12,598	30.3	1,135	24.7	27,466	29.8
65–74	6,533	15.7	1,287	28.0	6,533	15.7	1,287	28.0	15,640	16.9
75–84	4,130	9.9	1,078	23.5	4,130	9.0	1,078	23.5	10,416	11.3
85+	1,795	4.3	477	10.4	1,795	4.3	477	10.4	4,544	4.9
<b>Gender</b>										
Male	19,105	46.0	2,241	48.7	19,105	46.0	2,241	48.7	42,692	46.3
Female	22,450	54.0	2,356	51.3	22,450	54.0	2,356	51.3	49,612	53.7
<b>Glucose lowering therapy</b>										
None	41,555	100.0	1,028	22.4	41,555	100.0	1,027	22.3	85,028	92.1
Oral drugs only			2,798	60.9			2,779	60.5	5,708	6.2
Insulin alone			363	7.9			369	8.0	736	0.8
Insulin + oral drugs			408	8.9			422	9.2	832	0.9
<b>Previous statin therapy</b>										
No	37,060	89.2	2,544	55.3	37,017	89.1	2,657	57.8	79,278	85.9
Yes	4,495	10.8	2,053	44.7	4,538	10.9	1,940	42.2	13,026	14.1
<b>Previous antiplatelet therapy</b>										
No	38,279	92.1	3,229	70.2	38,039	91.5	3,258	70.9	82,805	89.7
Yes	3,276	7.9	1,368	29.8	3,516	8.5	1,339	29.1	9,499	10.3
<b>Charlson index</b>										
0	40,222	96.8	4,028	87.6	40,099	96.5	3,939	85.7	88,288	95.6
1	444	1.1	250	5.4	550	1.3	274	6.0	1,518	1.6
2+	889	2.1	319	6.9	906	2.2	384	8.3	2,498	2.8
<b>Deprivation index</b>										
low	13,771	33.1	1,378	30.0	14,590	35.1	1,374	29.9	31,113	33.7
medium	14,233	34.3	1,606	34.9	13,764	33.1	1,579	34.3	31,182	33.8
high	13,551	32.6	1,613	35.1	13,201	31.8	1,644	35.8	30,009	32.5

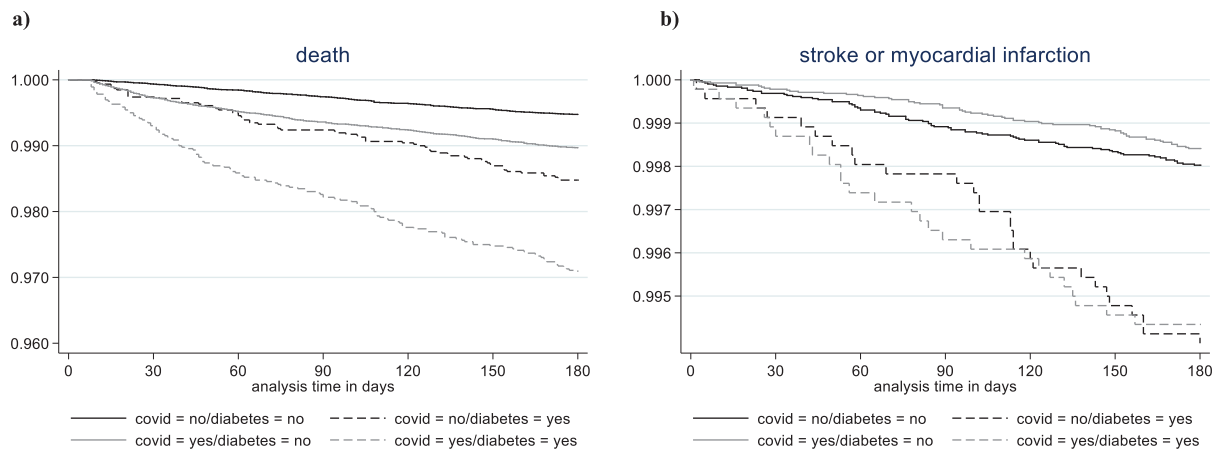
**Table 2**  
Adjusted incidence rates of first hospitalizations for myocardial infarction or for stroke (a); and of deaths or of first cardiovascular events (either myocardial infarction or stroke) (b) in the four groups under study stratified by prior COVID-19 and/or diabetes.

a)									
Groups	Incidence rate of first hospitalizations for myocardial infarction				Incidence rate of first hospitalizations for stroke				
	Events	Persons	Days	Adj. Rate (95% CI) per 100,000p-days	Events	Persons	Days	Adj. Rate (95% CI) per 100,000p-days	
COVID- Diabetes-	42	41,555	7,460,448	0.6 (0.4–0.8)	40	41,555	7,476,272	0.6 (0.4–0.7)	
COVID -Diabetes+	12	4,597	821,102	1.1 (0.1–2.1)	16	4,597	826,244	1.5 (0.4–2.5)	
COVID + Diabetes-	24	41,555	7,435,501	0.3 (0.2–0.5)	42	41,555	7,476,257	0.6 (0.4–0.8)	
COVID + Diabetes+	9	4,597	813,643	0.8 (0.0–1.6)	17	4,597	825,511	1.5 (0.5–2.5)	
b)									
Groups	All cause mortality				Incidence rate of first hospitalization for myocardial infarction or stroke				
	Deaths	Persons	Days	Adj. Rate (95% CI) per 100,000p-days	Events	Persons	Days	Adj. Rate (95% CI) per 100,000p-days	
COVID- Diabetes-	219	41,555	7,460,448	3.5 (3.0–4.0)	82	41,555	7,472,320	1.1 (0.9–1.4)	
COVID -Diabetes+	70	4,597	821,102	4.3 (2.9–5.6)	28	4,597	825,119	2.6 (1.1–4.0)	
COVID+Diabetes-	429	41,555	7,435,501	6.7 (5.9–7.4)	66	41,555	7,474,755	0.9 (0.7–1.1)	
COVID+Diabetes+	134	4,597	813,643	7.7 (5.7–9.7)	26	4,597	824,758	2.4 (1.0–3.7)	

19 in lower socio-economic strata of the population [20]. In addition, women especially in their pre-menopausal age are known to be more easily affected by COVID-19, being this partly confirmed also by the higher prevalence of women among people tested positive for COVID-19 also in our dataset, [21,22]. Nonetheless, even if more prevalent, women seem to be more protected from the incremental risk of death or of acute cardiovascular events related to COVID-19, in agreement with previous studies [23–25]. Interestingly, the current use of statins is significantly associated with reduced risk of mortality associated with COVID-19. The protective action of statins against the consequences of infectious diseases has long been known [26], even if with conflicting results about any eventual protective action by statins against mortality risk related to SARS-CoV-2 infection [27–30]. In this study, the absence of previous hospitalizations for cardiovascular events at basal suggests that statins were mainly used for primary prevention or for the treatment of dyslipidemia, possibly amplifying the protective action of statins against the

risk of mortality.

A further important finding of this study is that diabetes, independently of COVID-19 and other covariates, didn't significantly increase death incidence rate at 6-months follow up (IRR: 1.23; 95% CI 0.84–1.78; p = NS), and that the co-presence of pre-existing diabetes and COVID-19 didn't carry an additional risk of premature death as evidenced by the interaction term diabetes\*COVID-19 entering the model. The reason of this seemingly paradox could be hypothesized as due to a greater medicalization level among people with diabetes especially concerning the use of statins about four times more prevalent among people with diabetes. Interestingly examining the cohort on therapy with statins, the IRR of all-cause mortality for the interaction term prior COVID-19\*diabetes was near to statistical significance: 0.56; IC95% 0.30–1.05; p = 0.072 pointing to a protective trend, being, on the contrary, largely non-significant (1.23; 95%CI 0.80–1.89; p = 0.34) for those not on statins (data not shown). Another class of drugs,



**Fig. 1.** Kaplan-Meier curves describing cumulative survival rates at six months (a) or time course of CVE (stroke or myocardial infarction) incidence rates (b) in the four groups under study (COVID-19 + Diabetes-, COVID + Diabetes+, COVID-19-Diabetes-, COVID + Diabetes- (log-rank test < 0.001 for both).

**Table 3**

Adjusted incidence rate ratios IRR (95% CI) at six months of all-cause mortality and of first hospitalizations for myocardial infarction or stroke after positivity and recovery from prior COVID-19 and/or to diabetes after adjusting for possible confounders, by Poisson multiple regression models.

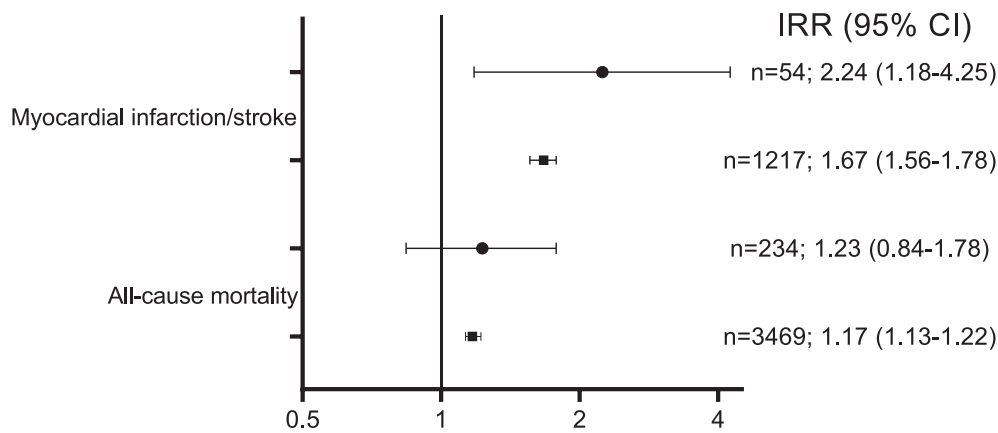
	All cause mortality		Hospitalization for myocardial infarction or stroke	
	IRR (95% CI)	p	IRR (95% CI)	p
Diabetes	1.23 (0.84–1.78)	0.283	2.24 (2.18–4.25)	0.013
COVID-19	1.92 (1.63–2.25)	0.000	0.80 (0.58–1.10)	0.172
Diabetes*COVID-19 (interaction)	0.94 (0.67–1.31)	0.716	1.15 (0.61–2.14)	0.665
<b>Age (yr)</b>				
45–54 (Ref.)	1	—		
55–64	2.56 (1.64–3.98)	0.000	2.11 (1.29–3.44)	0.003
65–74	10.35 (6.94–15.43)	0.000	3.82 (2.34–6.23)	0.000
75–84	24.02 (24.02–35.5)	0.000	5.78 (3.50–9.54)	0.000
85+	73.24 (49.68–108.00)	0.000	7.44 (4.20–13.19)	0.000
<b>Gender (F vs M)</b>	0.86 (0.75–0.99)	0.039	0.56 (0.42–0.75)	0.000
<b>Deprivation index</b>				
Low (Ref.)	1	—		
medium	1.22 (1.03–1.45)	0.024	0.84 (0.60–1.17)	0.300
High	1.26 (1.06–1.49)	0.007	0.84 (0.60–1.18)	0.323
<b>Therapy</b>				
Statins	0.67 (0.56–0.80)	0.000	0.90 (0.63–1.30)	0.574
Antiplatelets	1.23 (1.06–1.44)	0.007	1.17 (0.81–1.70)	0.394
<b>Glucose lowering drugs</b>				
None (Ref.)	1	—		
Oral drugs only	0.91 (0.65–1.28)	0.577	0.83 (0.44–1.57)	0.562
Insulin alone	1.50 (0.98–2.28)	0.062	0.92 (0.33–2.59)	0.879
Insulin + oral drugs	1.06 (0.62–1.81)	0.835	0.68 (0.22–2.09)	0.499
<b>Charlson index</b>				
(1 vs 0)	2.07 (1.59–2.68)	0.000	1.40 (0.71–2.78)	0.329
(2 + vs 0)	4.93 (4.16–5.86)	0.000	1.49 (0.85–2.61)	0.161

antiplatelets, seems, on the contrary, to be tracking a significant greater risk of mortality: IRR = 1.23 (95% CI: 1.06–1.44); p = 0.007, being probably related to the higher basal risk of cardiovascular morbidity associated with the plausible reasons for their prescription. A further hypothesis is that people with diabetes recovering from COVID-19 could reasonably represent a sort of survivors' cohort, resulting from the basal loss of the older and more complicated patients during the acute phase of the illness. This is indirectly suggested by the comparison with the matched pre-COVID-19 cohort of people with diabetes who, followed-up for six months, showed a significant 17% excess risk of mortality.

In the cohort with diabetes, a further interesting aspect is the nearly significant association between mortality IRR and the prevailing therapy with insulin at basal (1.50 (95% CI: 0.98–2.28); p = 0.062, which could be related to a prior worse metabolic control, a longer duration of diabetes, and/or to an intrinsic higher risk associated with treatment with this drug, as especially observed during the acute phase of the infection [31,32], all hypotheses which, as a limitation of this study, it is not possible to evaluate.

Furthermore, according to the present study, prior COVID-19, after its recovery, does not influence the risk of myocardial infarction or stroke, suggesting that the initial increase in thrombo-embolic risk, as observed during the acute viral disease, doesn't extend at further follow up in this population without history of previous hospitalizations for cardiovascular events.

Preexisting diabetes, however, even after recovery from SARS-CoV-2 is significantly associated with a greater risk of first hospitalization for first cardiovascular events, exactly as observed in the pre-COVID-19 matched cohort. Diabetes maintains, therefore, also after COVID-19 its expected role of risk magnifier for first hospitalizations associated with acute cardiovascular events. There is to note, however, that, as for mortality, copresence of prior COVID-19 and diabetes did not lead to any additional risk. All this suggests that people with diabetes, recovering from COVID-19 may be, at least in part, protected towards new hospitalizations for acute cardiovascular events. Perhaps this may be due to the same reasons why people with diabetes are protected from the risk of premature death i.e. from a more effective medicalization and, in this case, from the possible competitive effect of premature death (in COVID-19) impeding any future incidence of cardiovascular events. A further reason could be found in the expected overall reduction in hospitalization rate for acute cardiovascular events, as observed during the COVID-19 pandemic, [33–35] which could thereby significantly reduce the excess risk associated with diabetes.



**Fig. 2.** Effect of diabetes on six months incidence rate ratio (IRR; 95% CI) of all-cause mortality or of first CVE (myocardial infarction/stroke) after swab positivity and recovery from COVID-19 (●) or as from an antecedent similarly matched pre-COVID-19 cohort of people with diabetes (■).

#### 4.1. Limitations and strengths of the study

This study has several limitations, the most important is of being an observational retrospective study based on administrative datasets which do not permit to access to clinical data of interest. Moreover, due to its design, this study doesn't represent a real population-based study being restricted to people without prior hospitalizations for acute cardiovascular diseases, and due to its short follow up, the incidence of new first events is seemingly reduced. This study has, however also some strengths being based on large validated databases and constituting a basal cohort for further extending the observation period.

#### 4.2. Conclusions

Within six months from firstly being tested positive through a nasopharyngeal swab and having recovered from COVID-19 during the first wave of SARS-CoV-2 epidemic, the risk of all-cause mortality was as twice higher as compared with matched individuals without SARS-CoV-2 infection, without modifying the risk of being hospitalized for first cardiovascular events. People with diabetes had an about twofold greater adjusted risk of first hospitalization for stroke or myocardial infarction, without any increase in the risk of death. The co-presence of diabetes and of prior COVID-19 didn't add any excess risk of mortality, as well as of first incident hospitalizations for first cardiovascular events. This probably might be the consequence of a more prevalent use of statins among patients with diabetes, selecting a cohort of more protected survivors, as well as of the expected decrease in hospital admissions for cardiovascular diseases during SARS-CoV-2 epidemic. Across this short-term observation period, after the recovery by viral infections, a higher score of Charlson index as well as of the deprivation index and, above all, a more advanced age markedly increased the risk of death. Finally, women, independently of diabetes, were more protected against the risk of death or of new hospitalizations for cardiovascular events.

#### 5. Contribution statement

FP, GS, PF developed the study protocol, FP conducted the data analysis, PF and FP analysed the data, GS discussed and analysed the data and wrote the manuscript. FP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically discussed, revised and approved the final version of the paper.

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#### 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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