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Patterns of Health Services Utilisation after SARS-Cov-2 infection: a retrospective cohort study

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Abstract (word count: 300)

Objective: to explore the pattern of health services utilisation of people who had a documented SARS-Cov-2 infection, after becoming negative to the swab test

Design: retrospective cohort study

Setting: the Italian province of Reggio Emilia

Participants: 36,036 subjects who, after being diagnosed covid-19, did not die and were found negative during the period Sept 2020–March 2021. These were matched for age, sex and Charlson Index with an equal number of subjects never found positive at the SARS-Cov-2 swab test over the study period

Main outcome measures: hospital admissions for all medical conditions and for respiratory or cardiovascular conditions only; access to emergency room (for any cause); outpatient specialist visits (pneumology, cardiology, neurology, endocrinology, nephrology, dermatology, rehabilitation, mental health); overall cost of care

Results: within a median follow-up time of 152 days (range 1-180) previous exposure to SARS-Cov-2 infection was always associated with higher probability of needing access to hospital or ambulatory care, except for dermatology, mental health, and gastroenterology specialist visits. Post-COVID subjects with Charlson Index >=1 were hospitalized more frequently for heart disease and for non-surgical

reasons than subjects with Charlson index =0, whereas the opposite occurred for hospitalisations for respiratory diseases and pneumology visits. A previous SARS-CoV2 infection was associated with 27% higher cost of care compared to people never infected. The difference in cost was more evident among those with Charlson Index≥1. Subjects who had anti-SARS-CoV2 vaccination had lower probability of falling in the highest cost quartile.

Conclusions: our findings reflect the burden of post-COVID sequelae, providing some specific insight on their impact on the extra-use of health services according to patients' characteristics and vaccination status. Vaccination is associated with lower cost of care following covid infection, highlighting the favourable impact of vaccines on the use of health services even when they do not prevent infection.

Strengths and limitations of this study

- Our study provide insight on the extra-use of health services and cost of care by COVID patients after they have recovered, compared to people never infected by SARS-Cov-2, also considering their characteristics and vaccination status.
- To date, this is the largest study providing details on ambulatory outpatient visits and hospital admissions associated with long-covid in specific clinical areas.
- Limits in the quality of administrative data cannot be excluded, as well as the possibility of residual confounding.
- Further studies should provide longer follow-up data, also with higher numbers of vaccinated people to allow a comparison between those who developed COVID and those who do not, and to warrant the inclusion of boosted people who could not be included in our cohort yet.

Introduction

The SARS-Cov-2 pandemic forced radical changes in the organization and delivery of care, requiring a rapid expansion of health services capacity in some sectors (i.e. additional hospital beds in general and intensive care units in particular), the adoption and implementation of public health measures and interventions for efficient identification of new case and contact tracing, and the reorganization of primary care services to allow covid-19 patients to be cared for as much as possible at home. As it has been described, these changes had been at the expense of the management of other diseases, being the volume of procedures and interventions for conditions other than covid-19 drastically reduced [1].

However, the pandemic could have also long-term implications for health care systems, generating additional health care needs in individuals who have been diagnosed covid-19. Indeed, after SARS-Cov-2 infection a variable proportion of individuals experience a condition defined as “post covid-19 syndrome”, or “long covid-19”, with the persistence of signs and symptoms (or occurrence of new symptoms) after one to three months from the end of the acute phase [2,3]. In particular, cohort studies and systematic reviews have described the persistence of several symptoms including neurologic disorders (e.g. the so called “brain fog”, ageusia/anosmia), mental health disorders (e.g. anxiety, depression, sleep problems), functional impairment, respiratory, cardiac, digestive and skin disorders, etc. Although their incidence is widely variable across studies and depends on the background health status and on the initial COVID symptomatology, some of these symptoms (in particular respiratory and neurologic disorders) can affect up to half to three-quarters of recovered patients [4-8].

In this study, conducted in the Italian province of Reggio Emilia (population 539,652), we assessed the additional burden (if any) to health services due to the management of those who had a documented SARS-Cov-2 infection, exploring their pattern of health services utilisation after becoming negative to the swab test.

Methods

Study design

We conducted a retrospective cohort study in which individuals from the resident population who had a negative PCR on naso- and oropharyngeal swab test for SARS-Cov-2, after having been found positive at the same test, were followed up over time and their rates of health services utilization assessed and compared with a matched cohort of residents never found positive at the SARS-Cov-2 test .

Study population and data sources

Since the inception of the pandemic in March 2020, a surveillance database has been implemented in the province, including all the citizens undergoing SARS-Cov-2 swab test and its result.[9, 10] For this study, we identified from the SARS-Cov-2 surveillance database all those who, after being diagnosed covid-19, did not die and were found negative during the period Sept 2020 – March 2021. These individuals (n= 36,036) represented the cohort of those who previously had a documented SARS-Cov-2 infection.

Through record linkage procedures between the SARS-CoV-2 database and the administrative databases available to the Local Health Authority, we then assessed their rates of use of health services from the date of the negative swab test (index date) up to June 30, 2021.

The administrative databases include, for each resident in the province, demographic information, hospital discharge data (coded according to the International Classification of Diseases-9-CM [ICD-9-CM]) of diagnosis and procedures, admission and discharge dates, vital status at discharge, and outpatient pharmacy data at the individual prescription level, as well as access to outpatient ambulatory care. Data were anonymized, and record linkage procedures were performed according to the unique identification number which is assigned to each resident. In addition, for each individual, we searched for information on previous hospitalisations (up to preceding 10 years), as registered in these local administrative databases, in order to assess the presence of specific comorbidities individually (chronic obstructive pulmonary disease, arrhythmia, diabetes, acute myocardial infraction, heart failure, vascular diseases, obesity), and to estimate individual patients' overall degree of comorbidity (if any), according to the (not age-adjusted) Charlson index.[11]

Relying on the same data sources, we identified individuals to be included in the control group among residents alive at Jan 1st 2020 and never found positive at the SARS-Cov-2 swab test over the study period. Individuals in the control group were matched according to age, sex, and Charlson Index (in four classes: 0, 1, 2 and =>3). Each control had the same index date of the matched SARS-Cov-2 infected individual. Therefore the matching procedure made available 36,036 persons for each cohort, with equal distribution as for sex (18,481 were female, 51,3%), age (mean 43, range 1-103), comorbidities (32,561 had Charlson Index 0, while 1391, 1146 and 938 had Charlson Index 1, 2 and $\geq$3, respectively).

Outcome measures

The following items of care provided over the study period were considered, taking into account the most common symptoms persisting after the acute phase of covid-19 disease.[3]

- Hospital admissions for all medical conditions;
- Hospital admissions for respiratory or cardiovascular conditions only;
- Access to Emergency Room (for any cause);
- Outpatient specialist visits (pneumology, cardiology, neurology, endocrinology, nephrology, dermatology, rehabilitation, mental health).

The cost of individual procedures and services (according to official fees) and of drugs was taken as overall measure of the burden to the regional health care system of the care provided to individuals in both the cohorts. In cost analysis, in addition to the above reported items of care, we considered also all the outpatient diagnostic procedures and tests (i.e. blood tests, chest x-ray, etc.) and drug prescriptions.

Statistical analyses

Descriptive analysis of the items of care provided to individuals in the two cohorts are reported, as well as Poisson rates with 95% confidence intervals (95%CI). Rates have the total number of episodes of care observed as numerator, and person-months as denominator.

The strength of the association between previous SARS-Cov-2 infection and rates of use of the items of care considered was assessed through Hazard Ratios (HR). In order to better disentangle the effect of the previous SARS-Cov-2 infection, rather than of coexisting diseases, we stratified the analysis by Charlson comorbidity index, thus estimating HRs separately for convalescent covid-19 patients and control individuals with Charlson Index =0 and with Charlson Index >=1.

Mean case vs control cost differences (with 95%CI) are reported overall and according to age, sex, and Charlson Index. Total cost of care was divided in quartiles and the association between the characteristics of those who had SARS-Cov-2 infection and higher costs was assessed through a logistic regression model, with the highest costs quartile as dependent variable, and age (in categorised in four classes: ≤30, 31-50, 51-70, ≥ 71), sex, presence of symptoms at diagnosis and hospital admission for covid-19 (both proxy indicators of covid-19 severity), and pre-existence of specific comorbidities as covariates. As 986 (3%) of those who had SARS-CoV-2 infection had also received SARS-Cov-2 vaccination before testing positive at the swab test, we included SARS-Cov-2 vaccination status among the covariates.

***Patient and public involvement*:** none

Ethics approval : The study has been approved by the Area Vasta Emilia Nord Ethical Committee on 13/01/2022 n° 2022/0004443.

Results

After a median follow-up of 152 days (range 1-180), 51 and 186 individuals died, in the control and the SARS-Cov-2 positive group, respectively. Among those who had been positive at the swab test, 16,286 (45%) individuals did not use hospital care and never accessed outpatient services, vs 18,055 (50%) in the control group ($x^2_{1df} = 174,65$; $p<0,001$).

Both the proportion of individuals having at least one access at the items of care considered and the overall frequency of use was always higher in the SARS-Cov-2 positive cohort, especially for respiratory and cardiovascular hospital admissions and outpatients visits. Dermatology, mental health, and gastroenterology specialist visits has a different pattern, being the difference between the two groups negligible, if any. (table 1)

Table 1: frequency of use of hospital and ambulatory care by a cohort of 36036 convalescent covid-19 patients vs a matched control cohort, in the Province of Reggio Emilia (Italy).

		Convalescent Covid-	Matched Control	%Difference
In H for respiratory disease	Total N admissions	126	45	+180%
In H for heart disease	Total N admissions	143	76	+88%
In H for any medical reason	At least one, N (%)	724 (2.0)	538 (1.5)	
	Total N admissions	916	675	+36%
Access to Emergency Room	At least one, N (%)	3383 (9.4)	2491 (6.9)	
	Total N accesses	4299	3186	+35%
Outpatient specialist visits				

Pneumology	At least one, N (%)		766 (2.0)		310 (0.9)			
	Total N	First visits	924	572 (61.9)	380	154 (40.5)	+143	+271
Cardiology	At least one, N (%)		1588 (4.4)		1119 (3.0)			
	Total N	First visits	1708	1173 (68.7)	1198	716 (59.7)	+43	+64
Neurology	At least one, N (%)		758 (2.1)		625 (1.7)			
	Total N	First visits	939	568 (60.5)	756	424 (56.1)	+24	+34
Rheumatology	At least one, N (%)		533 (1.5)		461 (1.3)			
	Total N	First visits	670	254 (37.9)	571	181 (31.6)	+17	+40
Gastroenterology	At least one, N (%)		268 (0.7)		258 (0.7)			
	Total N	First visits	317	181 (57)	304	157 (51.6)	+4	+15
Diabetology	At least one, N (%)		1397 (3.9)		1116 (3.1)			
	Total N	First visits	1942	458 (23.6)	1500	320 (21.3)	+29	+43
Dermatology	At least one, N (%)		1470 (4.1)		1407 (3.9)			
	Total N	First visits	1670	501 (30.0)	1574	481 (30.5)	+6%	+4
Mental Health	At least one, N (%)		174 (0.5)		175 (0.5)			
	Total N	First visits	190	117 (61.6)	209	104 (49.5)	-9%	+12
Nephrology	At least one. N (%)		171 (0.5)		179 (0.5)			
	Total N	First visits	301	49 (16.3)	249	47 (18.9)	+21	

Hazard ratios, overall and by Charlson Index, are outlined in Table 2.

Table 2: Rates (x1,000 x month) of access to hospital care and outpatient specialist visits for convalescent covid-19 patients and the control group

		Rates x 1000	Rates Lower 95%CI	Rates Upper 95%CI	HR	HR Lower 95%CI	HR Upper 95%CI	HR in Charlson Index =0 (95%CI)*	HR in Charlson Index =>1 (95%CI)*
Non surgical h admissions	control	3.8	3.5	4.1	1			1	1
	covid-19 convalescent	5.2	4.9	5.5	1.38	1.25	1.52	1.11 (0.97-1.27)	1.83 (1.73-2.14)
H admissions for respiratory disease	control	0.3	0.2	0.4	1			1	1
	covid-19 convalescent	0.7	0.6	0.9	2.09	2.07	4.09	6.69 (2.84-15.7)	2.3 (.57-3.36)
H admissions for heart disease	control	0.4	0.3	0.5	1			1	1
	covid-19 convalescent	0.8	0.7	1.0	1.93	1.46	2.55	1.49 (1.37-1.62)	2.38 (1.62-3.5)
Accesses to Emergency Room	control	1	17.4	18.7	1			1	1
	covid-19 convalescent	24.4	23.7	25.1	1.36	1.29	1.42	1.32 (1.25-1.39)	1.51 (1.36-1.66)
Outpatient Specialist Visits									
Pneumology	control	2,1	1,9	2,4	1			1	1
	covid-19 convalescent	5,2	4,9	5,6	2,45	2,17	2,76	3.35 (3.09 -3.65)	1.53 (1.36-1.71)
Cardiology	control	6,8	6,4	7,2	1			1	1
	covid-19 convalescent	9,7	9,2	10,2	1,44	1,33	1,55	1.53 (1.36-1.71)	1.23 (1.07-1.41)
Neurology	control	4,8	4,5	5,2	1			1	1
	covid-19 convalescent	6	5,7	6,4	1,25	1,14	1,36	1.22 (1.1-1.35)	1.37 (1.12-1.68)
Reumathology	control	3,2	3	3,5	1			1	1
	covid-19 convalescent	3,8	3,5	4,1	1,17	1,05	1,31	1.19 (1.04 – 1.36)	1.15 (0.93- 1.42)
Gastroenterology	control	1,7	1,5	1,9	1			1	1
	covid-19 convalescent	1,8	1,6	2.0	1,04	0,89	1,22	1.0 (0.84-1.20)	1.21 (0.85 -1.73)
Mental health	control	1,2	1	1,4	1			1	1
	covid-19 convalescent	1,1	0,9	1,2	0,91	0,75	1,10	0.90 (0.73-1.11)	0.97 (0.54-1.74)
Dermatology	control	8,9	8,5	9,4	1			1	1
	covid-19 convalescent	9,5	9	9,9	1,06	0,99	1,14	1.06 (0.98 – 1.14)	1.10 (0.92-1.31)
Endocrinology	control	8,5	8,0	8,9	1			1	1
	covid-19 convalescent	11,0	10,5	11,5	1,30	1,21	1,39	1.28 (1.18 -1.40)	1.34 1.19 -1.50)

As shown, previous exposure to SARS-Cov-2 infection was always associated with a higher probability of needing access to hospital care which was more evident among those with Charlson Index >=1. The only exception were hospitalisations for respiratory diseases, whose HR associated with previous SARS-Cov-2 infection was higher among individuals without relevant comorbidities (HR:6.69 – 95%CI 2.84 – 15.7 vs HR: 2.30 – 95% 1,57 – 3,36 for those with Charlson Index >=1), and access to Emergency Room, whose HRs of the two subgroups were overlapping.

The same pattern held true for outpatient services, for whom previous exposure to SARS-Cov2 infection was always associated with higher probability of use but for gastrointestinal and mental health specialist visits.

Costs

Overall, the cost of care provided to those who had a previous SARS-CoV2 infection was 27% higher (10,357,221, mean : 287.41, range 0 – 114610.25, vs 8,149,96, mean 226,.6, range Euro). The difference in cost between the two groups was more evident (+45%) among those with relevant comorbidities (i.e. Charlson Index≥1) than among those with Charlson Index=0 (+17%) (see Table 3).

Table 3: cost of care (in Euro) for convalescent covid-19 patients and control cohort

	Convalescent covid-19					Control cohort			
	Total	**Mean**	**Median**	**Range**		**Total**	**Mean**	**Median**	**Range**
Overall	10,357,221	287.41	23.0	0 – 114,610		8,149,196	226.14	14.0	0 – 69,143
Charlson Index 0	6,318,301	194.0	18.0	0 – 114,610		5,380,207	165.23	4.0	0 – 45,510
Charlson Index >=1	4,038,919	1162.3	159.0	0 – 74,440		2,768,989	796.83	137.0	0 – 69,143

Among those in the highest quartile of total costs (i.e. ≥114,610 Euro), 9670 (54%) had previous SARS-CoV2 infection. The relationship between their individual characteristics and the likelihood of being in the highest quartile of costs is outlined in Table 4, according to the logistic regression model employed. Factors representing degree of severity of SARS-CoV2 infection were associated with higher cost of care in the following months, in particular aging and degree of comorbidity. As for COVID related factors, subjects with hospital admission for covid19 and presence of symptoms at diagnosis had 66% and 32% higher probability of higher cost of care. On the contrary, those who had anti-SARS-CoV2 vaccination had 64% lower probability of falling in the highest costs quartile.

Table 4: characteristics of individuals who had SARS-CoV-2 infection associated with higher costs of care in the following months

Covariates		Odds Ratio	95% CI
Sex	Female	1	
	Male	0,67	(0,63 to 0,71)
Age	<< 30	1	
	31-50	2,17	(2,01 to 2,34)
	51-70	3,71	(3,44 to 4,00)
	≥ 71	4,75	(4,32 to 5,23)
Charlson Index	0	1	
	1	2,09	(1,86 to 2,36)
	2	2,96	(2,60 to 3,39)
	≥3	4,00	(3,42 to 4,78)
Had anti-SARS-CoV2 vaccine			
	No	1	
	Yes	0,36	(0,30 to 0,43)
Had Symptomatic infection			
	No	1	
	Yes	1,32	(1,23 to 1,41)
Had hospital admission for covid19			
	No	1	
	Yes	1,66	(1,50 to 1,83)

Discussion

This study provides data to assess the impact of SARS-Cov-2 infection on use of health services (hospital admissions and outpatient specialist visits) and on extra costs within 6 months from recovery in an Italian province. To date, this is the largest study providing details on ambulatory outpatient visits and hospital admissions associated with long-covid in specific clinical areas. A wider UK study provided details on the complementary issue of the long-term impact of COVID on General Practitioners consultations [12].

Our data show that in the six months after recovery, out of 1000 individuals, a previous COVID infection was associated with 139 additional accesses in emergency room, eight additional non-surgical hospital admission and two hospitalizations for respiratory disease and for heart disease. As for outpatient visits, there were 19 additional pneumology visits as well as 17 cardiology, 15 endocrinology, seven neurology and four more rheumatology visits. This is highly consistent with the higher incidence of related symptoms in post-COVID patients described in several studies. On the contrary, no increase was shown in rates of mental health, gastroenterology and dermatology visits, despite related symptoms have been frequently reported among long-COVID patterns. The latter findings are unexpected, especially regarding mental health services, and warrant further qualitative analysis to explore possible determinants of the observed pattern. Overall, in six months in our province there have been extra costs for more than 2,2 million euros (about 4 euros per capita) associated with post-covid sequelae.

Subgroup analyses indicate that increase in rates of non-surgical hospital admissions, hospitalizations for heart disease and accesses to emergency room is more pronounced in people with comorbidities, whereas an opposite pattern is observed for rate of hospitalizations for respiratory disease. This

counterintuitive finding may be due to the fact that such admissions are rarer in people without comorbidities, so that their relative increase in post-COVID patients is more evident compared with people that, among their comorbidities, may have a higher background rate of respiratory problems. The same reason may hold for the less pronounced increase in rates of pneumology and cardiology outpatient visits among post-COVID patients with comorbidities. Further studies may help clarify these points.

Factors representing degree of severity of SARS-CoV2 infection (presence of symptoms at diagnosis, hospital admission for covid19) were all associated with higher cost of care in the following months, as well as age and degree of comorbidity. On the contrary, those who had anti-SARS-CoV2 vaccination were associated with lower cost of care.

Our observational data have been collected as part of patients' care: reimbursements to health services depend on their completeness, which can be assumed, and which should exclude the possibility of major biases. However, limits in the quality of administrative data cannot be excluded, as well as the possibility of residual confounding. No scientific validation of the databases used and of the record-linkage procedures is available, although the unique patient identification number present in all the databases should ensure that no data is lost. As for generalizability, incidence of COVID in our province since the start of the pandemic is similar to that in other areas of Northern Italy, although higher than the mean Italian incidence (about 5,000 cases more out of 100,000 inhabitants) [13].

In conclusion, many studies reported the frequency of post-COVID symptoms that recovered patients suffered from. Our findings also reflect the burden of post-COVID sequelae, providing some specific insight on their impact on the extra-use of health services according to patients' characteristics and

vaccination status. Vaccination is associated with lower cost of care following covid infection, highlighting the favourable impact of vaccines on the use of health services even when they do not prevent infection, in keeping with their capacity to reduce the clinical burden associated to SARS-CoV-2 infection. Further studies should provide longer follow-up data, also with higher numbers of vaccinated people to allow a comparison between those who developed COVID and those who do not, and to warrant the inclusion of boosted people who could not be included in our cohort yet.

Author contributions

GF: conception and design, interpretation of data, drafting the article

MM conception and design, data analysis, revising the article critically for important intellectual content

DF: data analysis, revising the article critically for important intellectual content

RGG: conception and design, data analysis, interpretation of data, drafting the article

All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

Competing interests: all authors declare that they do not have competing interests

Participant consent: not required (anonymised study cohort in a database, the "Area Vasta Emilia Nord" Ethics Committee waived its need)

Data sharing statement

Data will be made available upon reasonable request to the Authors and in compliance with current legislation for privacy protection. Requests should outline the objectives of the research and a protocol for the analyses in order to have the transfer of the data approved by the local Ethics Committee.

Role of the funding source

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract **Pag. 1, 3**
		Provide in the abstract an informative and balanced summary of what was done and what was found **Pag. 3,4**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pag. 6,7**
Objectives	3	State specific objectives, including any prespecified hypotheses **Pag. 6,7**
Methods		
Study design	4	Present key elements of study design early in the paper **Pag. 7**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pag. 7,8**
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pag. 7,8**
		For matched studies, give matching criteria and number of exposed and unexposed **Pag. 8**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pag. 7, 9, 10**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pag. 7 to 10**
Bias	9	Describe any efforts to address potential sources of bias **Pag. 8 to 10**
Study size	10	Explain how the study size was arrived at **No formal calculation, descriptive study. Criteria for the cohort selection and follow-up are described in pag. 7,8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pag. 9, 10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **Pag. 9, 10**
Results		
Participants	13*	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study,

		completing follow-up, and analysed **Pag. 8, 11**
		Give reasons for non-participation at each stage **Not applicable**
		(c) Consider use of a flow diagram
Descriptive data	14*	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Pag. 8**
		Indicate number of participants with missing data for each variable of interest **Not applicable**
		Summarise follow-up time (eg, average and total amount) **Pag. 11**
Outcome data	15*	Report numbers of outcome events or summary measures over time Pag. 11, 12; tables I to IV
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Tables II to IV**
		Report category boundaries when continuous variables were categorized **Not applicable**
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Pag. 13**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Tables II to IV**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pag. 13, 14**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pag. 14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pag. 14, 15**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Pag. 14**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Pag. 10**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Patterns of utilisation of specialist care after SARS-Cov-2 infection: a retrospective cohort study

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Abstract (word count: 300)

Objective: to explore the pattern of health services utilisation of people who had a documented SARS-Cov-2 infection, after becoming negative to the swab test

Design: retrospective cohort study

Setting: the Italian province of Reggio Emilia

Participants: 36,036 subjects who, after being diagnosed covid-19, did not die and were found negative during the period Sept 2020–March 2021. These were matched for age, sex and Charlson Index with an equal number of subjects never found positive at the SARS-Cov-2 swab test over the study period

Main outcome measures: hospital admissions for all medical conditions and for respiratory or cardiovascular conditions only; access to emergency room (for any cause); outpatient specialist visits (pneumology, cardiology, neurology, endocrinology, nephrology, dermatology, rehabilitation, mental health); overall cost of care

Results: within a median follow-up time of 152 days (range 1-180) previous exposure to SARS-Cov-2 infection was always associated with higher probability of needing access to hospital or ambulatory care, except for dermatology, mental health, and gastroenterology specialist visits. Post-COVID subjects with Charlson Index >=1 were hospitalized more frequently for heart disease and for non-surgical reasons than subjects with Charlson index =0, whereas the opposite occurred for hospitalisations for respiratory diseases and pneumology visits. A previous SARS-CoV2 infection was associated with 27% higher cost of care compared to people never infected. The difference in cost was more evident among

those with Charlson Index≥1. Subjects who had anti-SARS-CoV2 vaccination had lower probability of falling in the highest cost quartile.

Conclusions: our findings reflect the burden of post-COVID sequelae, providing some specific insight on their impact on the extra-use of health services according to patients' characteristics and vaccination status. Vaccination is associated with lower cost of care following covid infection, highlighting the favourable impact of vaccines on the use of health services even when they do not prevent infection.

Strengths and limitations of this study

- Our study provide insight on the extra-use of specific health services and related cost of care by COVID patients after they have recovered, compared to people never infected by SARS-Cov-2
- Subgroup analyses provide further insight on how demographic/clinical characteristics and vaccination status are associated with use of health services.
- Limits in the quality of administrative data cannot be excluded, as well as the possibility of residual confounding.
- Further studies should provide longer follow-up data, also with higher numbers of vaccinated people to allow a comparison between those who developed COVID and those who do not, and to warrant the inclusion of boosted people who could not be included in our cohort yet.

Introduction

The SARS-Cov-2 pandemic forced radical changes in the organization and delivery of care, requiring a rapid expansion of health services capacity in some sectors (i.e. additional hospital beds in general and intensive care units in particular), the adoption and implementation of public health measures and interventions for efficient identification of new case and contact tracing, and the reorganization of primary care services to allow covid-19 patients to be cared for as much as possible at home. As it has been described, these changes had been at the expense of the management of other diseases, being the volume of procedures and interventions for conditions other than covid-19 drastically reduced [1].

However, the pandemic could have also long-term implications for health care systems, generating additional health care needs in individuals who have been diagnosed covid-19. Indeed, after SARS-Cov-2 infection a variable proportion of individuals experience a condition defined as “post covid-19 syndrome”, or “long covid-19”, with the persistence of signs and symptoms (or occurrence of new symptoms) after one to three months from the end of the acute phase [2,3]. In particular, cohort studies and systematic reviews have described the persistence of several symptoms including neurologic disorders (e.g. the so called “brain fog”, ageusia/anosmia), mental health disorders (e.g. anxiety, depression, sleep problems), functional impairment, respiratory, cardiac, digestive and skin disorders, etc. Although their incidence is widely variable across studies and depends on the background health status and on the initial COVID symptomatology, some of these symptoms (in particular, respiratory and neurologic disorders) can affect up to half to three-quarters of recovered patients [4-8].

In this study, conducted in the Italian province of Reggio Emilia (population 539,652), we assessed the additional burden (if any) to health services due to the management of those who had a documented

SARS-Cov-2 infection, exploring their pattern of specific inpatient and outpatient health services utilisation after becoming negative to the swab test.

Methods

Study design

We conducted a retrospective cohort study in which individuals from the resident population who had a negative PCR on naso- and oropharyngeal swab test for SARS-Cov-2, after having been found positive at the same test, were followed up over time and their rates of health services utilization assessed and compared with a matched cohort of residents never found positive at the SARS-Cov-2 test.

Study population and data sources

Since the inception of the pandemic in March 2020, a surveillance database has been implemented in the province, including all the citizens undergoing SARS-Cov-2 swab test and its result. [9, 10] For this study, we identified from the SARS-Cov-2 surveillance database all those who, after being diagnosed covid-19, did not die and were found negative during the period Sept 2020 – March 2021. These individuals (n= 36,036) represented the cohort of those who previously had a documented SARS-Cov-2 infection.

Through record linkage procedures between the SARS-CoV-2 database and the administrative databases available to the Local Health Authority, we then assessed their rates of use of health services from the date of the negative swab test (index date) up to June 30, 2021.

The administrative databases include, for each resident in the province, demographic information, hospital discharge data (coded according to the International Classification of Diseases-9-CM [ICD-9-CM]) of diagnosis and procedures, admission and discharge dates, vital status at discharge, and outpatient pharmacy data at the individual prescription level, as well as access to outpatient ambulatory care. Data were anonymized, and record linkage procedures were performed according to the unique identification number which is assigned to each resident. In addition, for each individual, we searched for information on previous hospitalisations (up to preceding 10 years), as registered in these local administrative databases, in order to assess the presence of specific comorbidities individually (chronic obstructive pulmonary disease, arrhythmia, diabetes, acute myocardial infraction, heart failure, vascular diseases, obesity), and to estimate individual patients' overall degree of comorbidity (if any), according to the (not age-adjusted) Charlson index.[11]

Relying on the same data sources, we identified individuals to be included in the control group among residents alive at Jan 1st 2020 and never found positive at the SARS-Cov-2 swab test over the study period (either with negative tests or with no test at all). Individuals in the control group were matched according to age, sex, and Charlson Index (in four classes: 0, 1, 2 and =>3). Each control had the same index date of the matched SARS-Cov-2 infected individual. Therefore, the matching procedure made available 36,036 persons for each cohort, with equal distribution as for sex (18,481 were female, 51.3%), age (mean 43, range 1-103), comorbidities (32,561 had Charlson Index 0, while 1391, 1146 and 938 had Charlson Index 1, 2 and ≥3, respectively).

People who died before the end of study were censored at the time of death.

Outcome measures

The following items of care provided over the study period were considered, taking into account the most common symptoms persisting after the acute phase of covid-19 disease.[3]

- Hospital admissions for all medical conditions;
- Hospital admissions for respiratory or cardiovascular conditions only;
- Access to Emergency Room (for any cause);
- Outpatient specialist visits (pneumology, cardiology, neurology, endocrinology, nephrology, dermatology, rehabilitation, mental health).

The cost of individual procedures and services (according to official fees) and of drugs was taken as overall measure of the burden to the regional health care system of the care provided to individuals in both the cohorts. In cost analysis, in addition to the above reported items of care, we considered also all the outpatient diagnostic procedures and tests (i.e. blood tests, chest x-ray, etc.) and drug prescriptions.

Statistical analyses

Descriptive analysis of the items of care provided to individuals in the two cohorts are reported, as well as Poisson rates with 95% confidence intervals (95%CI). Rates have the total number of episodes of care observed as numerator, and person-months as denominator.

The strength of the association between previous SARS-Cov-2 infection and rates of use of the items of care considered was assessed through Hazard Ratios (HR). In order to better disentangle the effect of the previous SARS-Cov-2 infection, rather than of coexisting diseases, we stratified the analysis by Charlson comorbidity index, thus estimating HRs separately for convalescent covid-19 patients and control individuals with Charlson Index =0 and with Charlson Index >=1. We also calculated separate

HRs considering controls who either had negative test or no test at all, and HRs for outpatient visits, hospital and emergency room admissions in the first 90 days and after 90 days from the index date, to assess their trend over time.

Mean case vs control cost differences (with 95%CI) are reported overall and according to age, sex, and Charlson Index. Total cost of care was divided in quartiles and the association between the characteristics of those who had SARS-Cov-2 infection and higher costs was assessed through a logistic regression model, with the highest costs quartile as dependent variable, and age (in categorised in four classes: ≤30, 31-50, 51-70, ≥ 71), sex, presence of symptoms at diagnosis and hospital admission for covid-19 (both proxy indicators of covid-19 severity), and pre-existence of specific comorbidities as covariates. As 986 (3%) of those who had SARS-CoV-2 infection had also received SARS-Cov-2 vaccination before testing positive at the swab test, we included SARS-Cov-2 vaccination status among the covariates.

***Patient and public involvement*:** none

Results

After a median follow-up of 152 days (range 1-180), 51 and 186 individuals died, in the control and the SARS-Cov-2 positive group, respectively. Among those who had been positive at the swab test, 16,286 (45%) individuals did not use hospital care and never accessed outpatient services, vs 18,055 (50%) in the control group ($\chi^2_{1df} = 174.65$; $p<0.001$).

Both the proportion of individuals having at least one access at the items of care considered and the overall frequency of use was always higher in the SARS-Cov-2 positive cohort, especially for respiratory and cardiovascular hospital admissions and outpatients visits. Dermatology, mental health, and gastroenterology specialist visits have a different pattern, being the difference between the two groups negligible, if any. (Table 1)

Table 1: frequency of use of hospital and ambulatory care by a cohort of 36036 convalescent covid-19 patients vs a matched control cohort, in the Province of Reggio Emilia (Italy).

			Convalescent Covid-		Matched Control		%Difference	
In H for respiratory disease	Total N admissions		126		45		+180%	
In H for heart disease	Total N admissions		143		76		+88%	
In H for any medical reason	At least one, N (%)		724 (2.0)		538 (1.5)			
	Total N admissions		916		675		+36%	
Access to Emergency Room	At least one, N (%)		3383 (9.4)		2491 (6.9)			
	Total N accesses		4299		3186		+35%	
Outpatient specialist visits								
Pneumology	At least one, N (%)		766 (2.0)		310 (0.9)			
	Total N	First visits	924	572 (61.9)	380	154 (40.5)	+143	+271
Cardiology	At least one, N (%)		1588 (4.4)		1119 (3.0)			
	Total N	First visits	1708	1173 (68.7)	1198	716 (59.7)	+43	+64

Neurology	At least one, N (%)		758 (2.1)		625 (1.7)			
	Total N	First visits	939	568 (60.5)	756	424 (56.1)	+24	+34
Rheumatology	At least one, N (%)		533 (1.5)		461 (1.3)			
	Total N	First visits	670	254 (37.9)	571	181 (31.6)	+17	+40
Gastroenterology	At least one, N (%)		268 (0.7)		258 (0.7)			
	Total N	First visits	317	181 (57)	304	157 (51.6)	+4	+15
Diabetology	At least one, N (%)		1397 (3.9)		1116 (3.1)			
	Total N	First visits	1942	458 (23.6)	1500	320 (21.3)	+29	+43
Dermatology	At least one, N (%)		1470 (4.1)		1407 (3.9)			
	Total N	First visits	1670	501 (30.0)	1574	481 (30.5)	+6%	+4
Mental Health	At least one, N (%)		174 (0.5)		175 (0.5)			
	Total N	First visits	190	117 (61.6)	209	104 (49.5)	-9%	+12
Nephrology	At least one. N (%)		171 (0.5)		179 (0.5)			
	Total N	First visits	301	49 (16.3)	249	47 (18.9)	+21	

Hazard ratios, overall and by Charlson Index, are outlined in Table 2.

Table 2: Rates (x1,000 x month) of access to hospital care and outpatient specialist visits for convalescent covid-19 patients and the control group

		Rates x 1000	Rates Lower 95%CI	Rates Upper 95%CI	HR	HR Lower 95%CI	HR Upper 95%CI	HR in Charlson Index =0 (95%CI)*	HR in Charlson Index =>1 (95%CI)*
Non surgical h admissions	control	3.8	3.5	4.1	1			1	1
	covid-19 convalescent	5.2	4.9	5.5	1.38	1.25	1.52	1.11 (0.97-1.27)	1.83 (1.73-2.14)
H admissions for respiratory disease	control	0.3	0.2	0.4	1			1	1
	covid-19 convalescent	0.7	0.6	0.9	2.09	2.07	4.09	6.69 (2.84-15.70)	2.30 (1.57-3.36)
H admissions for heart disease	control	0.4	0.3	0.5	1			1	1
	covid-19 convalescent	0.8	0.7	1.0	1.93	1.46	2.55	1.49 (1.37-1.62)	2.38 (1.62-3.50)
Accesses to Emergency Room	control	1	17.4	18.7	1			1	1
	covid-19 convalescent	24.4	23.7	25.1	1.36	1.29	1.42	1.32 (1.25-1.39)	1.51 (1.36-1.66)
Outpatient Specialist Visits									
Pneumology	control	2,1	1,9	2,4	1			1	1
	covid-19 convalescent	5,2	4,9	5,6	2,45	2,17	2,76	3.35 (3.09 -3.65)	1.53 (1.36-1.71)
Cardiology	control	6,8	6,4	7,2	1			1	1
	covid-19 convalescent	9,7	9,2	10,2	1,44	1,33	1,55	1.53 (1.36-1.71)	1.23 (1.07-1.41)
Neurology	control	4,8	4,5	5,2	1			1	1
	covid-19 convalescent	6	5,7	6,4	1,25	1,14	1,36	1.22 (1.10-1.35)	1.37 (1.12-1.68)
Reumathology	control	3,2	3	3,5	1			1	1
	covid-19 convalescent	3,8	3,5	4,1	1,17	1,05	1,31	1.19 (1.04 – 1.36)	1.15 (0.93- 1.42)
Gastroenterology	control	1,7	1,5	1,9	1			1	1
	covid-19 convalescent	1,8	1,6	2.0	1,04	0,89	1,22	1.00 (0.84-1.20)	1.21 (0.85 -1.73)
Mental health	control	1,2	1	1,4	1			1	1
	covid-19 convalescent	1,1	0,9	1,2	0,91	0,75	1,10	0.90 (0.73-1.11)	0.97 (0.54-1.74)
Dermatology	control	8,9	8,5	9,4	1			1	1
	covid-19 convalescent	9,5	9	9,9	1,06	0,99	1,14	1.06 (0.98 – 1.14)	1.10 (0.92-1.31)
Endocrinology	control	8,5	8,0	8,9	1			1	1
	covid-19 convalescent	11,0	10,5	11,5	1,30	1,21	1,39	1.28 (1.18 -1.40)	1.34 1.19 -1.50)

As shown, previous exposure to SARS-Cov-2 infection was always associated with a higher probability of needing access to hospital care which was more evident among those with Charlson Index >=1. The only exception were hospitalizations for respiratory diseases, whose HR associated with previous SARS-Cov-2 infection was higher among individuals without relevant comorbidities (HR:6.69 – 95%CI 2.84 – 15.70 vs HR: 2.30 – 95% 1.57 – 3.36 for those with Charlson Index >=1), and access to Emergency Room, whose HRs of the two subgroups were overlapping.

The same pattern held true for outpatient services, for whom previous exposure to SARS-Cov2 infection was always associated with higher probability of use but for gastrointestinal and mental health specialist visits.

Risk of hospital and emergency room accesses and outpatient visits were highest for covid subjects compared to controls who did not have swab tests (Figure 1 and Table 3). A decline in HRs after 90 days from the index date was observed, although this decline was statistically significant only for hospital admissions when covid subjects were compared to controls who did not have swab tests (Figure 1). Subjects with higher Charlson index are more likely to have been tested. At the same time younger people are more likely to have been tested (Table 4).

Table 3. HRs (from Poisson regression) comparing rates of occurrence of the events considered between Covid19 convalescents and matched controls who had no swab test and who had at least one (negative) swab test.

	Covid convalescents vs Controls who never had swab test		Covid convalescents vs Controls who had swab test (negative)		Overall	
	HR	95%CI	HR	95%CI	HR	95%CI
H admissions	1.34	1.23 to 1.45	1.09	0.96 to 1.23	1.25	1.17 to 1.34
AE access	1.42	1.34 to 1.50	1.17	1.08 to 1.26	1.33	1.27 to 1.39
Outpatient visits	1.23	1.21 to 1.23	1.09	1.08 to 1.11	1.18	1.17 to 1.19

Table 4. Odds ratios of being tested for covid within the control cohort (logistic model)

Covariates	Odds Ratio	(95% Conf. Int.)
Age <30	1	
31-50	0.61	(0.58 to 0.64)
51-70	0.43	(0.40 to 0.45)
>71	0.36	(0.33 to 0.40)
Charlson Index 0	1	
1	1.32	(1.17 to 1.49)
2	1.22	(1.07 to 1.39)
3	1.37	(1.17 to 1.59)
Sex female	1	
male	0.93	(0.89 to 0.97)

We checked pattern of accesses in the year before the index date as well, focusing on those outpatient visits occurring more frequently, to strengthen the comparability of the two cohorts in terms of health-seeking behavior. No differences were observed (Table 5).

Table 5. *% of access to the main outpatient specialist visits for convalescent covid-19 patients and the control group in the year preceding the index date*

Outpatient specialist visits*	**Covid cohort (n=36,036)**	**Control cohort (n=36,036)**
Pneumology	5.97%	5.64%
Cardiology	5.48%	5.73%
Neurology	3.28%	3.33%
Mental health	0.72%	0.90%

**No statistically significant differences (p<0.05) were found*

Costs

Overall, the cost of care provided to those who had a previous SARS-CoV2 infection was 27% higher (10,357,221 Euro, mean: 287.41, range 0 – 114,610, vs 8,149,196, mean 226.14, range 0 – 69,143). The difference in cost between the two groups was more evident (+45%) among those with relevant comorbidities (i.e. Charlson Index≥1) than among those with Charlson Index=0 (+17%) (Table 6).

Table 6: cost of care (in Euro) for convalescent covid-19 patients and control cohort

	Convalescent covid-19					**Control cohort**			
	Total	**Mean**	**Median**	**Range**		**Total**	**Mean**	**Median**	**Range**
Overall	10,357,221	287.41	23.0	0 – 114,610		8,149,196	226.14	14.0	0 – 69,143
Charlson Index 0	6,318,301	194.0	18.0	0 – 114,610		5,380,207	165.23	4.0	0 – 45,510
Charlson Index >=1	4,038,919	1162.3	159.0	0 – 74,440		2,768,989	796.83	137.0	0 – 69,143

Among those in the highest quartile of total costs (i.e. ≥114,610 Euro), 9,670 (54%) had previous SARS-CoV2 infection. The relationship between their individual characteristics and the likelihood of being in the highest quartile of costs is outlined in Table 7, according to the logistic regression model employed. Factors representing degree of severity of SARS-CoV2 infection were associated with higher cost of care in the following months, in particular aging and degree of comorbidity. As for COVID related factors, subjects with hospital admission for covid19 and presence of symptoms at diagnosis had 66% and 32% higher probability of higher cost of care. On the contrary, those who had anti-SARS-CoV2 vaccination had 64% lower probability of falling in the highest costs quartile.

Table 7: characteristics of individuals who had SARS-CoV-2 infection associated with higher costs of care in the following months

Covariates		Odds Ratio	95% CI
Sex	Female	1	
	Male	0.67	(0.63 to 0.71)
Age	<< 30	1	
	31-50	2.17	(2.01 to 2.34)
	51-70	3.71	(3.44 to 4.00)
	≥ 71	4.75	(4.32 to 5.23)
Charlson Index	0	1	
	1	2.09	(1.86 to 2.36)
	2	2.96	(2.60 to 3.39)
	≥3	4.00	(3.42 to 4.78)
Had anti-SARS-CoV2 vaccine			
	No	1	
	Yes	0.36	(0.30 to 0.43)
Had Symptomatic infection			
	No	1	
	Yes	1.32	(1.23 to 1.41)
Had hospital admission for covid19			
	No	1	
	Yes	1.66	(1.50 to 1.83)

Discussion

This study provides data to assess the impact of SARS-Cov-2 infection on use of specific specialist care (hospital admissions and outpatient specialist visits) and on related extra costs within 6 months from recovery on a large cohort from an Italian province. Unfortunately, we could not include data on primary care encounters since in Italy they are not traceable.

Our data show that in the six months after recovery, out of 1,000 individuals, a previous COVID infection was associated with 139 additional accesses in emergency room, eight additional non-surgical hospital admission and two hospitalizations for respiratory disease and for heart disease. As for outpatient visits, there were 19 additional pneumology visits as well as 17 cardiology, 15 endocrinology, seven neurology and four more rheumatology visits. This is highly consistent with the higher incidence of related symptoms in post-COVID patients described in several studies. On the contrary, no increase was shown in rates of mental health, gastroenterology and dermatology visits, despite related symptoms have been frequently reported among long-COVID patterns. The latter findings may be unexpected, especially regarding mental health services, although also studies carried out in Norway did not find a higher use of these services in the post-covid period. [12,13] Further qualitative analyses are warranted to explore possible determinants of the observed pattern, also considering accessibility to services.

HRs related to people who had never tested are higher than HRs related to people with at least one negative test. The latter may be at higher risk for clinical sequelae and this may be the reason why they are more likely to be tested. This hypothesis is also supported by a logistic model using the subjects in the control cohort: those with higher Charlson index are more likely to have been tested. At the same time younger people are more likely to have been tested (they are more likely to be

socially involved), while older people are less (they are more likely to have been kept isolated in those months). For covid patients, risk of outpatient visits and of hospital or emergency room accesses was (or tended to be) lower after 90 days from the negative test. Overall, in six months in our province there have been extra costs for more than 2.2 million euros (about 4 euros per capita) associated with post-covid sequelae.

Subgroup analyses indicate that increase in rates of non-surgical hospital admissions, hospitalizations for heart disease and accesses to emergency room is more pronounced in people with comorbidities, whereas an opposite pattern is observed for rate of hospitalizations for respiratory disease. This counterintuitive finding may be due to the fact that such admissions are rarer in people without comorbidities, so that their relative increase in post-COVID patients is more evident compared with people that, among their comorbidities, may have a higher background rate of respiratory problems. The same reason may hold for the less pronounced increase in rates of pneumology and cardiology outpatient visits among post-COVID patients with comorbidities. Further studies may help clarify these points.

Factors representing degree of severity of SARS-CoV2 infection (presence of symptoms at diagnosis, hospital admission for covid19) were all associated with higher cost of care in the following months, as well as age and degree of comorbidity. On the contrary, those who had anti-SARS-CoV2 vaccination were associated with lower cost of care.

Our hypothesis is that it was the covid that brought the positives to a subsequent greater use of services, but we cannot assume (only through the adjustment for age, sex and Charlson Index) that they were comparable in this regard also before: those who do not have a positive test may be more careful in lifestyles (and more likely to be able to avoid covid, as well as be more likely to be visited) or

vice versa avoid tampons and visits. Therefore, we did an additional analysis confirming that the two cohorts did not differ in terms of ambulatory visits, so that their health-seeking behavior could be considered comparable.

We acknowledge potential risks of misclassification, although in Italy an exit test was mandatory and the risk of having "non-recovered" positives is extremely low. In any case, all people in the "positive test" cohort have been included if they did have a subsequent negative test. Also, we did not use a time window but started the follow-up from the negative test. The assumption is that those who have been negativized cannot be in an acute phase (or that it is unlikely to do a further test during the acute phase to check if one has been negativized). This may bring a risk of misclassification too, although we consider it very small and not higher than the risk of missing cases which could occur within a time window.

Our observational data have been collected as part of patients' care: reimbursements to health services depend on completeness of these data, which can be assumed, and which should exclude the possibility of major biases. However, limits in the quality of administrative data cannot be excluded, as well as the possibility of residual confounding. No scientific validation of the databases used and of the record-linkage procedures is available, although the unique patient identification number present in all the databases should ensure that no data is lost. As for generalizability, incidence of COVID in our province since the start of the pandemic is similar to that in other areas of Northern Italy, although higher than the mean Italian incidence (about 5,000 cases more out of 100,000 inhabitants) [14].

In conclusion, many studies reported the frequency of post-COVID symptoms that recovered patients suffered from. Our findings also reflect the burden of post-COVID sequelae, providing some specific

insight on their impact on the extra-use of health services according to patients' characteristics and vaccination status. Vaccination is associated with lower cost of care following covid infection, highlighting the favourable impact of vaccines on the use of health services even when they do not prevent infection, in keeping with their capacity to reduce the clinical burden associated to SARS-CoV-2 infection. We plan to expand these data in a further paper using longer follow-up periods, also with higher numbers of vaccinated people to allow a comparison between those who developed COVID and those who do not, and to warrant the inclusion of boosted people who could not be included in our cohort yet.

Author contributions

RG, GF and MM conceived the study; MM and DF extracted the data; RG and MM analysed the data; GF and RG interpreted its results and drafted the paper; GF revised the final version. All the authors revised the article critically for important intellectual content.

All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

Competing interests: all authors declare that they do not have competing interests

Participant consent: not required (anonymised study cohort in a database, the "Area Vasta Emilia Nord" Ethics Committee waived its need)

Data sharing statement

Data will be made available upon reasonable request to the Authors and in compliance with current legislation for privacy protection. Requests should outline the objectives of the research and a protocol for the analyses in order to have the transfer of the data approved by the local Ethics Committee.

Role of the funding source

The study did not receive any external funding. It was entirely supported by the Azienda Unità Sanitaria Locale-IRCCS of Reggio Emilia, Reggio Emilia (Italy).

Ethics approval : The study has been approved by the Area Vasta Emilia Nord Ethics Committee on 13/01/2022 n° 2022/0004443.

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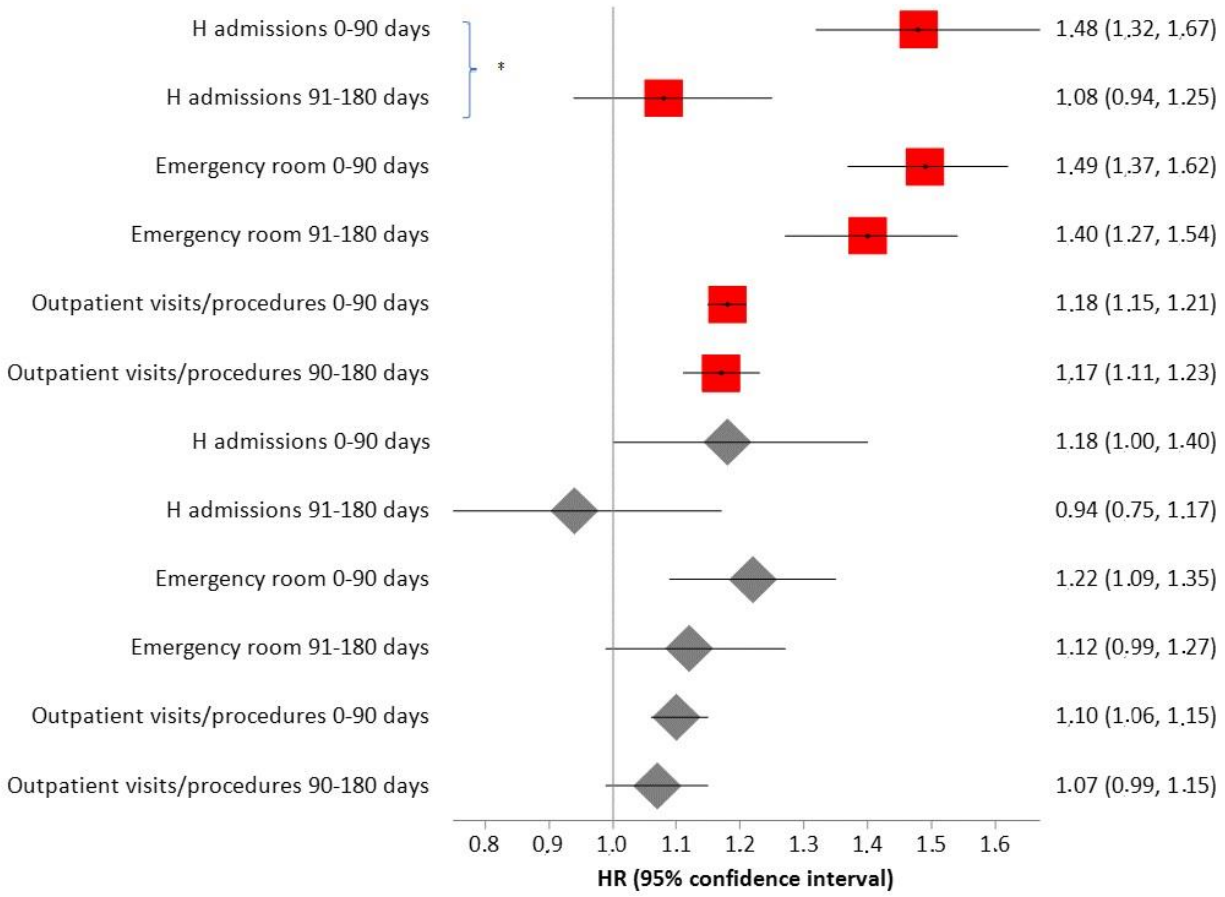

Figure 1: HRs (from Poisson regression) comparing rates of occurrence of the events considered between Covid19 convalescents and matched controls who had no swab test (red squares) and who had at least one (negative) swab test (grey diamonds). *P<0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract **Pag. 1, 3**
		Provide in the abstract an informative and balanced summary of what was done and what was found **Pag. 2,3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pag. 4,5**
Objectives	3	State specific objectives, including any prespecified hypotheses **Pag. 4,5**
Methods		
Study design	4	Present key elements of study design early in the paper **Pag. 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pag. 5,6**
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pag. 5,6**
		For matched studies, give matching criteria and number of exposed and unexposed **Pag. 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pag. 7, 8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pag. 5 to 8**
Bias	9	Describe any efforts to address potential sources of bias **Pag. 6 to 8**
Study size	10	Explain how the study size was arrived at **No formal calculation, descriptive study. Criteria for the cohort selection and follow-up are described in pag. 5,6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pag. 7,8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **Pag. 7,8**
Results		
Participants	13*	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study,

		completing follow-up, and analysed **Pag. 5,6**
		Give reasons for non-participation at each stage **Not applicable**
		(c) Consider use of a flow diagram
Descriptive data	14*	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Pag. 6**
		Indicate number of participants with missing data for each variable of interest **Not applicable**
		Summarise follow-up time (eg, average and total amount) **Pag. 8**
Outcome data	15*	Report numbers of outcome events or summary measures over time Pag**. 9 to 16**
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Pag. 9 to 11, 14,15**
		Report category boundaries when continuous variables were categorized **Not applicable**
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Pag. 17**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Pag. 12 to 16**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pag. 17,18**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pag. 19**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pag. 19,20**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Pag. 19**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Pag. 22**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Patterns of utilisation of specialist care after SARS-Cov-2 infection: a retrospective cohort study

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Patterns of utilisation of specialist care after SARS-Cov-2 infection: a retrospective cohort study

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Abstract (word count: 287)

Objective: to explore the pattern of health services utilisation of people who had had a documented SARS-Cov-2 infection.

Design: retrospective cohort study.

Setting: the Italian province of Reggio Emilia.

Participants: 36,036 subjects who recovered from SARS-CoV-2 infection during the period Sept 2020–May 2021. These were matched for age, sex and Charlson Index with an equal number of subjects never found positive at the SARS-Cov-2 swab test over the study period.

Main outcome measures: hospital admissions for all medical conditions and for respiratory or cardiovascular conditions only; access to emergency room (for any cause); outpatient specialist visits (pneumology, cardiology, neurology, endocrinology, gastroenterology, rheumatology, dermatology, mental health); overall cost of care.

Results: within a median follow-up time of 152 days (range 1-180) previous exposure to SARS-Cov-2 infection was always associated with higher probability of needing access to hospital or ambulatory care, except for dermatology, mental health, and gastroenterology specialist visits. Post-COVID subjects with Charlson Index >=1 were hospitalized more frequently for heart disease and for non-surgical reasons than subjects with Charlson index =0, whereas the opposite occurred for hospitalisations for respiratory diseases and pneumology visits. A previous SARS-CoV2 infection was associated with 27% higher cost of care compared to people never infected. The difference in cost was more evident among

those with Charlson Index≥1. Subjects who had anti-SARS-CoV2 vaccination had lower probability of falling in the highest cost quartile.

Conclusions: our findings reflect the burden of post-COVID sequelae, providing some specific insight on their impact on the extra-use of health services according to patients' characteristics and vaccination status. Vaccination is associated with lower cost of care following SARS-CoV-2 infection, highlighting the favourable impact of vaccines on the use of health services even when they do not prevent infection.

Strengths and limitations of this study

- Our study provide insight on the extra-use of specific health services and related cost of care by COVID patients after they have recovered, compared to people never infected by SARS-Cov-2.
- Subgroup and sensitivity analyses provide further insight on how demographic/clinical characteristics, vaccination status, time to recovery, recent hospital and emergency room admissions and subsequent admissions due to COVID are associated with use of health services.
- Limits in the quality of administrative data cannot be excluded, as well as the possibility of residual confounding.
- Further studies should provide longer follow-up data, also with higher numbers of vaccinated people to allow a comparison between those who developed COVID and those who do not, and to warrant the inclusion of boosted people who could not be included in our cohort yet.

Introduction

The SARS-Cov-2 pandemic forced radical changes in the organization and delivery of care, requiring a rapid expansion of health services capacity in some sectors (i.e. additional hospital beds in general and intensive care units in particular), the adoption and implementation of public health measures and interventions for efficient identification of new case and contact tracing, and the reorganization of primary care services to allow COVID-19 patients to be cared for as much as possible at home. As it has been described, these changes had been at the expense of the management of other diseases, being the volume of procedures and interventions for conditions other than COVID-19 drastically reduced [1].

However, the pandemic could have also long-term implications for health care systems, generating additional health care needs in individuals who have been diagnosed with SARS-CoV-2 infection. Indeed, after infection a variable proportion of individuals experience a condition defined as “post COVID-19 syndrome”, or “long COVID-19”, with the persistence of signs and symptoms (or occurrence of new symptoms) after one to three months from the end of the acute phase [2,3]. In particular, cohort studies and systematic reviews have described the persistence of several symptoms including neurologic disorders (i.e. the so called “brain fog”, ageusia/anosmia), mental health disorders (e.g. anxiety, depression, sleep problems), functional impairment, respiratory, cardiac, digestive and skin disorders, etc. Although their incidence is widely variable across studies and depends on the background health status and on the initial COVID symptomatology, some of these symptoms (in particular, respiratory and neurologic disorders) can affect up to half to three-quarters of recovered patients [4-8].

In this study, conducted in the Italian province of Reggio Emilia (population 539,652), we assessed the additional burden (if any) to health services due to the management of those who had a documented

SARS-Cov-2 infection, exploring their pattern of specific inpatient and outpatient health services utilisation after recovering from the infection.

Methods

Study design

We conducted a retrospective cohort study in which individuals from the resident population who had a negative PCR on naso and oropharyngeal swab test for SARS-Cov-2 after having been found positive at the same test, or who were asymptomatic after 21 days from the positive test, were followed up over time and their rates of health services utilization assessed and compared with a matched cohort of residents never found positive at the SARS-Cov-2 test.

Study population and data sources

Since the inception of the pandemic in March 2020, a surveillance database has been implemented in the province, including all the citizens undergoing SARS-Cov-2 swab test and its result, as well as time of recovery. [9, 10] For this study, we identified from the SARS-Cov-2 surveillance database all those who, after being diagnosed with SARS-Cov-2 infection, recovered during the period Sept 2020 – May 2021. These individuals (n= 36,036) represented the cohort of those who previously had a documented SARS-Cov-2 infection.

Through record linkage procedures between the SARS-CoV-2 database and the administrative databases available to the Local Health Authority, we then assessed their rates of use of health services from the date of recovery indicated in the COVID database (index date) up to June 30, 2021.

The administrative databases include, for each resident in the province, demographic information, hospital discharge data (coded according to the International Classification of Diseases-9-CM [ICD-9-CM]) of diagnosis and procedures, admission and discharge dates, vital status at discharge, and outpatient pharmacy data at the individual prescription level, as well as access to outpatient ambulatory care. Data were anonymized, and record linkage procedures were performed according to the unique identification number which is assigned to each resident. In addition, for each individual, we searched for information on previous hospitalisations (up to preceding 10 years), as registered in these local administrative databases, in order to assess the presence of specific comorbidities individually (chronic obstructive pulmonary disease, arrhythmia, diabetes, acute myocardial infraction, heart failure, vascular diseases, obesity), and to estimate individual patients' overall degree of comorbidity (if any), according to the (not age-adjusted) Charlson Index.[11]

Relying on the same data sources, we identified individuals to be included in the control group among residents alive at Jan 1st 2020 and never found positive at the SARS-Cov-2 swab test over the study period (either with negative tests or with no test at all). Individuals in the control group were matched according to age, sex, and Charlson Index (in four classes: 0, 1, 2 and =>3). Each control had the same index date of the matched SARS-Cov-2 infected individual. Therefore, the matching procedure made available 36,036 persons for each cohort, with equal distribution as for sex (18,481 were female, 51.3%), age (mean 43, range 1-103), comorbidities (32,561 had Charlson Index 0, while 1391, 1146 and 938 had Charlson Index 1, 2 and ≥3, respectively).

People who died during the follow-up were censored at the time of death.

Outcome measures

The following items of care provided over the study period were considered, taking into account the most common symptoms persisting after the acute phase of COVID-19 disease:[3]

- hospital admissions for all medical conditions;
- hospital admissions for respiratory or cardiovascular conditions only;
- access to Emergency Room (for any cause);
- outpatient specialist visits (pneumology, cardiology, neurology, endocrinology, gastroenterology, dermatology, rheumatology, mental health).

The cost of individual procedures and services (according to official fees) and of drugs was taken as overall measure of the burden to the regional health care system of the care provided to individuals in both the cohorts. In cost analysis, in addition to the above reported items of care, we considered also all the outpatient diagnostic procedures and tests (i.e. blood tests, chest x-ray, etc.) and drug prescriptions.

Statistical analyses

Descriptive analysis of the items of care provided to individuals in the two cohorts are reported, as well as Poisson rates with 95% confidence intervals (95%CI). Rates have the total number of episodes of care observed as numerator, and person-months as denominator.

The strength of the association between previous SARS-Cov-2 infection and rates of use of the items of care considered was assessed through Hazard Ratios (HR). In order to better disentangle the effect of the previous SARS-Cov-2 infection, rather than of coexisting diseases, we stratified the analysis by Charlson comorbidity index, thus estimating HRs separately for convalescent COVID-19 patients and control individuals with Charlson Index =0 and with Charlson Index >=1. We also calculated separate

HRs considering COVID convalescents who were hospitalized and not hospitalized (vs controls), controls who either had negative test or no test at all (vs COVID convalescents), HRs according to quartiles of time to recovery and HRs for outpatient visits, hospital and emergency room admissions in the first 90 days and after 90 days from the index date, to assess their trend over time. A sensitivity analysis adjusting for imbalances in hospital and emergency room admissions in the year before the index date was also performed, to limit the possible influence of recent acute health problems on the risk of subsequent use of health services.

Mean case vs control cost differences (with 95%CI) are reported overall and according to age, sex, and Charlson Index. Total cost of care was divided in quartiles and the association between the characteristics of those who had SARS-Cov-2 infection and higher costs was assessed through a logistic regression model, with the highest costs quartile as dependent variable, and age (in categorised in four classes: ≤30, 31-50, 51-70, ≥ 71), sex, presence of symptoms at diagnosis and hospital admission for COVID-19 (both proxy indicators of COVID-19 severity), and pre-existence of specific comorbidities as covariates. As 986 (3%) of those who had SARS-CoV-2 infection had also received SARS-Cov-2 vaccination before testing positive at the swab test, we included SARS-Cov-2 vaccination status among the covariates.

***Patient and public involvement*:** none

Results

Seventy-seven percent of people in the SARS-Cov-2 cohort recovered within 21 days from a positive test and had a negative exit test; the remaining 23% were asymptomatic (without an exit test) after 21 days. After a median follow-up of 152 days (range 1-180), 51 and 186 individuals died, in the control and the SARS-Cov-2 positive group, respectively. Among those who had been positive at the swab test, 16,286 (45%) individuals did not use hospital care and never accessed outpatient services, vs 18,055 (50%) in the control group ($\chi^2_{1df} = 174.65$; $p<0.001$).

Both the proportion of individuals having at least one access at the items of care considered and the overall frequency of use was always higher in the SARS-Cov-2 positive cohort, especially for respiratory and cardiovascular hospital admissions and outpatients visits. Dermatology, mental health, and gastroenterology specialist visits have a different pattern, being the difference between the two groups negligible, if any. (Table 1)

***Table 1**. Frequency of use of hospital and ambulatory care by a cohort of 36,036 convalescent COVID-19 patients vs a matched control cohort, in the Province of Reggio Emilia (Italy).*

		Convalescent COVID-	Matched Control	%Differenc
In H for respiratory disease	Total N admissions	126	45	+180%
In H for heart disease	Total N admissions	143	76	+88%
In H for any medical reason	At least one, N (%)	724 (2.0)	538 (1.5)	
	Total N admissions	916	675	+36%
Access to Emergency Room	At least one, N (%)	3383 (9.4)	2491 (6.9)	
	Total N accesses	4299	3186	+35%
Death		186	51	+264%
Outpatient specialist visits				
	At least one, N (%)	766 (2.0)	310 (0.9)	

Pneumology	Total N	First visits	924	572 (61.9)	380	154 (40.5)	+143	+271
Cardiology	At least one, N (%)		1588 (4.4)		1119 (3.0)			
	Total N	First visits	1708	1173 (68.7)	1198	716 (59.7)	+43	+64
Neurology	At least one, N (%)		758 (2.1)		625 (1.7)			
	Total N	First visits	939	568 (60.5)	756	424 (56.1)	+24	+34
Rheumatology	At least one, N (%)		533 (1.5)		461 (1.3)			
	Total N	First visits	670	254 (37.9)	571	181 (31.6)	+17	+40
Gastroenterology	At least one, N (%)		268 (0.7)		258 (0.7)			
	Total N	First visits	317	181 (57)	304	157 (51.6)	+4	+15
Endocrinology	At least one, N (%)		1397 (3.9)		1116 (3.1)			
	Total N	First visits	1942	458 (23.6)	1500	320 (21.3)	+29	+43
Dermatology	At least one, N (%)		1470 (4.1)		1407 (3.9)			
	Total N	First visits	1670	501 (30.0)	1574	481 (30.5)	+6%	+4
Mental Health	At least one, N (%)		174 (0.5)		175 (0.5)			
	Total N	First visits	190	117 (61.6)	209	104 (49.5)	-9%	+12

Hazard ratios, overall, by Charlson Index and by COVID related hospitalization are outlined in Table 2.

***Table 2**. Rates (x1,000 x month) and hazard ratios of access to hospital care, outpatient specialist visits, and death for convalescent COVID-19 patients and the control group, overall and according to Charlson Index and hospitalization for COVID-19*

		Rates x 1000 (95%CI)	**HR (95%CI)**	**HR in Charlson Index =0 (95%CI)***	**HR in Charlson Index =>1 (95%CI)***	**HR hospitalised COVID19 vs control (95%CI)**	**HR non hospitalised COVID19 vs control (95%CI**
Non-surgical h admissions	**control**	3.8 (3.5-4.1)	1	1	1	1	1
	COVID-19	5.2 (4.9-5.5)	1.38 (1.25-1.52)	1.11 (0.97-1.27)	1.83 (1.73-2.14)	3.16 (2.53-3.95)	1.12 (1.0-1.29)
H admissions for respiratory disease	**control**	0.3 (0.2-0.4)	1	1	1	1	1
	COVID-19	0.7 (0.6-0.9)	2.09 (2.07-4.09)	6.69 (2.84-15.7)	2.3 (1.57-3.36)	4.19 (2.41-7.30)	1.91 (1.27-2.89)
H admissions for heart disease	**control**	0.4 (0.3-0.5)	1	1	1	1	1
	COVID-19	0.8 (0.7-1.0)	1.93 (1.46-2.55)	1.49 (1.37-1.62)	2.38 (1.62-3.5)	3.56 (2.02-6.25)	1.44 (1.04-1.97)
Accesses to Emergency Room	**control**	7.4 (7.1-7.7)	1	1	1	1	1
	COVID-19	9.5 (9.2-9.8)	1.36 (1.29-1.42)	1.32 (1.25-1.39)	1.51 (1.36-1.66)	2.05 (1.79-2.35)	1.23 (1.18-1.29)
Death	**control**	0.19 (0.16-0.22)	1	1	1	1	1
	COVID-19	0.41 (0.35-0.47)	3.69 (2.73-4.98)	3.07 (1.73-5.47)	3.68 (2.59-5.23)	6.20 (3.50-10.10)	2.87 (2.01-4.11)
Outpatient Specialist Visits							
Pneumology	**control**	2.1 (1.9-2.4)	1	1	1	1	1
	COVID-19	5.2 (4.9-5.6)	2,45 (2.17-2.76)	3.35 (3.09 -3.65)	1.53 (1.36-1.71)	4.44 (3.36-5.86)	1.83 (1.61-2.09)
Cardiology	**control**	6.8 (6.4-7.2)	1	1	1	1	1
	COVID-19	9.7 (9.2-10.2)	1.44 (1.33-1.55)	1.53 (1.36-1.71)	1.23 (1.07-1.41)	1.72 (1.43-2.06)	1.28 (1.18-1.39)
Neurology	**control**	4.8 (4.5-5.2)	1	1	1	1	1

	COVID-19	6.0 (5.7-6.4)	1,25 (1.14-1.36)	1.22 (1.1-1.35)	1.37 (1.12-1.68)	1.46 (1.10-1.92)	1.17 (1.06-1.28)
Rheumatology	**control**	3.2 (3.0-3.5)	1	1	1	1	1
	COVID-19	3.8 (3.5-4.1)	1,17 (1.05-1.31)	1.19 (1.04 – 1.36)	1.15 (0.93- 1.42)	1.09 (0.78-1.51)	1.23 (1.09-1.38)
Gastroenterology	**control**	1.7 (1.5-1.9)	1	1	1	1	1
	COVID-19	1.8 (1.6-2.0)	1,04 (0.89-1.22)	1.0 (0.84-1.20)	1.21 (0.85 -1.73)	1.25 (0.68-2.32)	0.97 (0.82-1.14)
Mental health	**control**	1.2 (1.0-1.4)	1	1	1	1	1
	COVID-19	1.1 (0.9-1.2)	0,91 (0.75-1.10)	0.90 (0.73-1.11)	0.97 (0.54-1.74)	1.38 (0.59-3.24)	0.93 (0.76-1.14)
Dermatology	**control**	8.9 (8.5-9.4)	1	1	1	1	1
	COVID-19	9.5 (9.0-9.9)	1,06 (0.99-1.14)	1.06 (0.98 – 1.14)	1.10 (0.92-1.31)	0.95 (0.72-1.26)	1.07 (1.00-1.15)
Endocrinology	**control**	8.5 (8.0-8.9)	1	1	1	1	1
	COVID-19	11.0 (10.5-11.5)	1,30 (1.21-1.39)	1.28 (1.18 -1.40)	1.34 (1.19 -1.50)	2.05 (1.74-2.41)	1.11 (1.03-1.20)

As shown, previous exposure to SARS-Cov-2 infection was always associated with a higher probability of needing access to hospital care which was more evident among those with Charlson Index >=1. The only exception were hospitalizations for respiratory diseases, whose HR associated with previous SARS-Cov-2 infection was higher among individuals without relevant comorbidities (HR:6.69 – 95%CI 2.84 – 15.70 vs HR: 2.30 – 95% 1.57 – 3.36 for those with Charlson Index >=1), and access to Emergency Room, whose HRs of the two subgroups were overlapping.

The same pattern held true for outpatient services, for whom previous exposure to SARS-Cov2 infection was always associated with higher probability of use but for gastrointestinal and mental health specialist visits.

Subsequent use of these services was higher for people who had been hospitalized for COVID-19, except for rheumatology and dermatology visits (higher risk of subsequent visits for people not hospitalized for COVID-19).

Risk of hospital and emergency room accesses and outpatient visits were highest for SARS-CoV-2 positive subjects compared to controls who did not have swab tests (Figure 1). Looking more closely to each specific outcome, this specific pattern was significantly shown only for accesses to emergency room and for pneumology and gastroenterology visits (Table 3). A decline in HRs after 90 days from the index date was observed, although this decline was statistically significant only for hospital admissions when SARS-CoV-2 positive subjects were compared to controls who did not have swab tests (Figure 1). Subjects with higher Charlson index were more likely to have been tested. At the same time younger people were more likely to have been tested (Table 4).

Table 3. *HRs (from Poisson regression) comparing rates of occurrence of the events considered between COVID19 convalescents and matched controls who had no swab test (N= 22,820) and who had at least one (negative) swab test (N=13,216).*

	COVID19 convalescents vs Controls who never had swab test		COVID19 convalescents vs Controls who had (negative) swab test	
	HR	**95%CI**	**HR**	**95%CI**
Non surgical h admissions				
• control	1		1	
• COVID19 convalescents	1.46	1.30-1.64	1.21	1.06-1.40
H admissions for respiratory disease				
• control	1		1	
• COVID19 convalescents	2.66	1.82-3.89	2.15	1.31-3.53
H admissions for heart disease				
• control	1		1	
• COVID19 convalescents	1.76	1.30-2.39	1.78	1.15-2.75
Accesses to Emergency Room				
• control	1		1	
• COVID19 convalescents	1.39	1.32-1.47	1.14	1.06-1.21
OUTPATIENT SPECIALIST VISITS				
Pneumology				
• control	1		1	
• COVID19 convalescents	2.50	2.17-2.88	1.71	1.45-2.02
Cardiology				
• control	1		1	
• COVID19 convalescents	1.32	1.21-1.43	1.33	1.19-1.49
Neurology				
• control	1		1	
• COVID19 convalescents	1.22	1.10-1.35	1.09	0.96-1.24
Rheumatology				
• control	1		1	
• COVID19 convalescents	1.16	1.03-1.32	1.25	1.05-1.47
Gastroenterology				
• control	1		1	
• COVID19 convalescents	0.83	0.70-0.99	1.39	1.08-1.78
Mental health				
• control	1		1	
• COVID19 convalescents	0.88	0.71-1.10	1.01	0.77-1.33
Dermatology				
• control	1		1	
• COVID19 convalescents	1.04	0.96-1.12	1.09	0.99-1.21
Endocrinology				
• control	1		1	
• COVID19 convalescents	1.19	1.11-1.29	1.18	1.07-1.30

Table 4. *Odds ratios of being tested for SARS-CoV-2 infection within the control cohort (logistic model)*

Covariates	**Odds Ratio**	**(95% Conf. Int.)**
Age <30	1	
31-50	0.61	(0.58 to 0.64)
51-70	0.43	(0.40 to 0.45)
>71	0.36	(0.33 to 0.40)
Charlson Index 0	1	
1	1.32	(1.17 to 1.49)
2	1.22	(1.07 to 1.39)
3	1.37	(1.17 to 1.59)
Sex female	1	
male	0.93	(0.89 to 0.97)

We checked patterns of access to health services in the year before the index date as well, to verify the comparability of the two cohorts in terms of health-seeking behavior. Compared to control patients, COVID convalescent patients had had more emergency room accesses (24% vs 14%), non-surgical hospital admissions (9% vs 3%) and admissions for respiratory problems (included in the former: 5% vs 0.2%) in the 365 days before the index date. This was somehow expected, considering that respiratory patients may be at higher risk of getting covid [12]. Results of a sensitivity analysis adjusting for age, sex, and occurrence of hospital admissions and/or accesses to emergency room over the 365 days before the index date are presented in Table 5, where results are also stratified for time to recovery. The risk of hospital admissions for respiratory disease and heart disease, accesses to emergency room, pneumology, cardiology, rheumatology and endocrinology visits and the risk of death remained higher for COVID convalescent patients than controls, in particular for those with longer time to recovery,

except for endocrinology visits (in the latter case, the higher risk does not seem to be related to time to recovery).

***Table 5**. Hazards ratios (HR) representing the risk of death and of requiring hospital care and outpatients specialist visits for COVID-19 convalescent patients vs controls, adjusting for age, sex, and occurrence of hospital admissions and/or accesses to emergency room over the 365 days before the index date. HRs are reported also according to time to swab test negativity (or otherwise certified end of disease.*

	HR (overall)	**HR (according to time to recovery)**			
		1-14 days (n=10,469)	**15-19 days (n=10,022)**	**20-21 days (n=7,235)**	**>21 days (n=8,310)**
Non surgical h admissions	1.04 (0.94-1.15)	0.93 (0.78-1.10)	0.85 (0.72-1.01)	0.88 (0.74-1.06)	1.06 (0.92-1.21)
H admissions for respiratory disease	1.42 (1.02-2.00)	1.41 (0.78-2.53)	0.74 (0.37-1.48)	0.94 (0.51-1.76)	1.98 (1.32-2.95)
H admissions for heart disease	1.43 (1.07-1.88)	1.43 (0.92-2.25)	1.11 (0.69-1.78)	1.45 (0.93-2.28)	1.62 (1.13-2.33)
Accesses to Emergency Room	1.13 (1.08-1.19)	1.05 (0.98-1.13)	1.16 (1.08-1.24)	1.12 (1.03-1.21)	1.27 (1.19-1.36)
Death	2.50 (1.83-3.42)	1.45 (0.81-2.58)	0.88 (0.45-1.69)	2.03 (1.25-3.30)	3.89 (2.73-5.55)
Outpatient specialist visits					
Pneumology	1.79 (1.59-2.01)	1.44 (1.20-1.73)	1.77 (1.49-2,10)	1.58 (1.30-1.93)	2.90 (2.49-3.37)
Cardiology	1.19 (1.11-1.29)	1.22 (1.09-1.37)	1.23 (1.08-1.39)	1.18 (1.03-1.34)	1.39 (1.25-1.54)
Neurology	1.07 (0.97-1.17)	1.00 (0.87-1.15)	1.04 (0.90-1.19)	1.14 (0.98-1.33)	1.23 (1.09-1.41)
Reumathology	1.16 (1.03-1.30)	1.09 (0.92-1.30)	1.11 (0.93-1.31)	1.09 (0.90-1.33)	1.16 (1.00-1.38)
Gastroenterology	0.88 (0.76-1.04)	0.75 (0.58-0.98)	0.96 (0.75-1.22)	1.06 (0.82-1.38)	0.97 (0.76-1.25)
Mental health	0.87 (0.72-1.07)	0.77 (0.57-1.04)	0.86 (0.63-1.16)	0.86 (0.61-1.21)	0.81 (0.58-1.14)
Dermatology	1.06 (0.99-1.13)	1.04 (0.94-1.16)	1.07 (0.97-1.19)	1.07 (0.95-1.21)	1.01 (0.90-1.13)
Endocrinology	1.09 (1.02-1.17)	1.11 (1.00-1.24)	1.17 (1.05-1.29)	1.07 (0.95-1.21)	1.12 (1.01-1.23)

Costs

Overall, the cost of care provided to those who had a previous SARS-CoV2 infection was 27% higher (10,357,221 Euro, mean: 287.41, range 0 – 114,610, vs 8,149,196, mean 226.14, range 0 – 69,143). The difference in cost between the two groups was more evident (+45%) among those with relevant comorbidities (i.e. Charlson Index≥1) than among those with Charlson Index=0 (+17%) (Table 6).

Table 6*. Cost of care (in Euro) for convalescent COVID-19 convalescents and control cohort*

	Convalescent COVID-19					**Control cohort**			
	Total	**Mean**	**Median**	**Range**		**Total**	**Mean**	**Median**	**Range**
Overall	10,357,221	287.41	23.0	0 – 114,610		8,149,196	226.14	14.0	0 – 69,143
Charlson Index 0	6,318,301	194.0	18.0	0 – 114,610		5,380,207	165.23	4.0	0 – 45,510
Charlson Index >=1	4,038,919	1162.3	159.0	0 – 74,440		2,768,989	796.83	137.0	0 – 69,143

Among those in the highest quartile of total costs (i.e. ≥114,610 Euro), 9,670 (54%) had previous SARS-CoV2 infection. The relationship between their individual characteristics and the likelihood of being in the highest quartile of costs is outlined in Table 7, according to the logistic regression model employed. Factors representing degree of severity of SARS-CoV2 infection were associated with higher cost of care in the following months, in particular aging and degree of comorbidity. As for COVID related factors, subjects with hospital admission for COVID19 and presence of symptoms at diagnosis had 66% and 32% higher probability of higher cost of care. On the contrary, those who had anti-SARS-CoV2 vaccination had 64% lower probability of falling in the highest costs quartile.

***Table 7**. Characteristics of individuals who had SARS-CoV-2 infection associated with higher costs of care in the following months*

Covariates		Odds Ratio	95% CI
Sex	Female	1	
	Male	0.67	(0.63 to 0.71)
Age	<< 30	1	
	31-50	2.17	(2.01 to 2.34)
	51-70	3.71	(3.44 to 4.00)
	≥ 71	4.75	(4.32 to 5.23)
Charlson Index	0	1	
	1	2.09	(1.86 to 2.36)
	2	2.96	(2.60 to 3.39)
	≥3	4.00	(3.42 to 4.78)
Had anti-SARS-CoV2 vaccine			
	No	1	
	Yes	0.36	(0.30 to 0.43)
Had Symptomatic infection			
	No	1	
	Yes	1.32	(1.23 to 1.41)
Had hospital admission for COVID19			
	No	1	
	Yes	1.66	(1.50 to 1.83)

Discussion

This study provides data to investigate the possible impact of SARS-Cov-2 infection on use of specific specialist care (hospital admissions and outpatient specialist visits) and on related extra costs within 6

months from recovery on a large cohort from an Italian province. Unfortunately, we could not include data on primary care encounters since in Italy they are not traceable.

Our data show that in the six months after recovery, out of 1,000 individuals, a previous SARS-CoV-2 infection was associated with 139 additional accesses in emergency room, eight additional non-surgical hospital admission and two hospitalizations for respiratory disease and for heart disease. As for outpatient visits, there were 19 additional pneumology visits as well as 17 cardiology, 15 endocrinology, seven neurology and four more rheumatology visits. This is highly consistent with the higher incidence of related symptoms in post-COVID patients described in several studies. On the contrary, no increase was shown in rates of mental health, gastroenterology and dermatology visits, despite related symptoms have been frequently reported among long-COVID patterns. The latter findings may be unexpected, especially regarding mental health services, although also studies carried out in Norway did not find a higher use of these services in the post-COVID period. [13,14] Further qualitative analyses are warranted to explore possible determinants of the observed pattern, also considering accessibility to services.

The sensitivity analysis performed adjusting also for the occurrence of hospital admissions and/or accesses to emergency room over the 365 days before the index date provided lower HRs but confirmed the statistical significance of these results (except for subsequent non-surgical admissions and neurological visits), mostly led by COVID convalescents who had longer time to recovery.

Subgroup analyses indicate that increase in rates of non-surgical hospital admissions, hospitalizations for heart disease and accesses to emergency room is more pronounced in people with comorbidities (Charlson Index $\geq$1), whereas an opposite pattern is observed for rate of hospitalizations for respiratory disease. This counterintuitive finding may be due to the fact that such admissions are

rarer in people without comorbidities, so that their relative increase in post-COVID patients is more evident compared with people that, among their comorbidities, may have a higher background rate of respiratory problems. The same reason may hold for the less pronounced increase in rates of pneumology and cardiology outpatient visits among post-COVID patients with comorbidities. Further studies may help clarify these points.

As expected, subsequent use of health services was higher for people who had been hospitalized for COVID-19, except for rheumatology and dermatology visits (higher risk of subsequent visits for people not hospitalized for COVID). The latter findings are unexpected and difficult to explain, although their relevance may be limited since the corresponding confidence intervals related to hospitalized and non-hospitalized patients are widely overlapping.

Hazard Ratios of emergency room accesses, pneumology and gastroenterology visits comparing COVID convalescents to controls who had never tested were significantly higher than HRs vs controls with at least one negative test. The latter may be more likely to be tested for having higher health risks (this would explain why the corresponding HRs are lower). This hypothesis is also supported by a logistic model using the subjects in the control cohort: those with higher Charlson Index are more likely to have been tested. At the same time younger people are more likely to have been tested (they are more likely to be socially involved), while older people are less (they are more likely to have been kept isolated in those months). For SARS-CoV-2 infected subjects, risk of outpatient visits and of hospital or emergency room accesses was (or tended to be) lower after 90 days from the negative test. Overall, in six months in our province there have been extra costs for more than 2.2 million euros (about 4 euros per capita) associated with post-COVID sequelae.

Factors representing degree of severity of SARS-CoV2 infection (presence of symptoms at diagnosis, hospital admission for COVID19) were all associated with higher cost of care in the following months, as well as age and degree of comorbidity. On the contrary, those who had anti-SARS-CoV2 vaccination were associated with lower cost of care.

Our hypothesis is that COVID19 brought the positives to a subsequent greater use of services, but we cannot assume (only through various adjustments and stratifications) that they were comparable in this regard also before: those who do not have a positive test may be more careful in lifestyles (and more likely to be able to avoid SARS-CoV-2 infection, as well as be more likely to be visited) or vice versa avoid tampons and visits. Residual confounding cannot be excluded.

We acknowledge potential risks of misclassification, although the risk of having “non-recovered” positives in the COVID database is extremely low: three-quarters of former SARS-CoV-2 infected subjects had a negative exit test within 21 days from a positive test, and one quarter of them were asymptomatic (after 21 days from a positive test). As for the latter, a surveillance system with daily phone calls and interviews with all cases cared for in outpatient settings was into place. In addition, we did not use a time window but started the follow-up from the date of recovery. The assumption is that those who have been confirmed as recovered cannot be in an acute phase. This may bring a risk of misclassification too, although we consider it very small and not higher than the risk of missing cases which could occur within a time window.

Our observational data have been collected as part of patients’ care: reimbursements to health services depend on completeness of these data, which can be assumed, and which should exclude the possibility of major biases. However, limits in the quality of administrative data cannot be excluded., The adjustment for imbalances in hospital and emergency room admissions in the year before the

index date, performed as sensitivity analysis and stratification for Charlson Index to better disentangle the effect of the previous SARS-Cov-2 infection, rather than of coexisting diseases may limit, but of course not eliminate, the possibility of residual confounding. No scientific validation of the databases used and of the record-linkage procedures is available, although the unique patient identification number present in all the databases should ensure that no data is lost. As for generalizability, incidence of SARS-CoV-2 infection in our province since the start of the pandemic is similar to that in other areas of Northern Italy, although higher than the mean Italian incidence (about 5,000 cases more out of 100,000 inhabitants) [15].

In conclusion, many studies reported the frequency of post-COVID symptoms that recovered patients suffered from. Our findings also suggest an extra burden for patients and health services due to post-COVID sequelae, providing some specific insight on association of SARS-CoV-2 infection with extra-use of health services after the acute phase, according to patients' characteristics and vaccination status. Vaccination is associated with lower cost of care following SARS-CoV-2 infection, highlighting the possibly favourable impact of vaccines on the use of health services even when they do not prevent infection, in keeping with their capacity to reduce the clinical burden associated to SARS-CoV-2 infection. We plan to expand these data in a further paper using longer follow-up periods, also with higher numbers of vaccinated people to allow a comparison between those who developed COVID and those who do not, and to warrant the inclusion of boosted people who could not be included in our cohort yet.

Author contributions

RG, GF and MM conceived the study; MM and DF extracted the data; RG and MM analysed the data; GF and RG interpreted its results and drafted the paper; GF revised the final version. All the authors revised the article critically for important intellectual content.

All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

Competing interests: all authors declare that they do not have competing interests

Participant consent: not required (anonymised study cohort in a database, the "Area Vasta Emilia Nord" Ethics Committee waived its need)

Data sharing statement

Data will be made available on request to researchers who meet the criteria for access to confidential data. Requests should outline the objectives of the research and a protocol for the analyses. In order to obtain data, approval must be obtained from the Area Vasta Emilia Nord (AVEN) Ethics Committee, who would then authorize us to provide aggregated or anonymized data. Data access requests should

be addressed to the Ethics Committee at CEReggioemilia@ausl.re.it as well as to the corresponding author.

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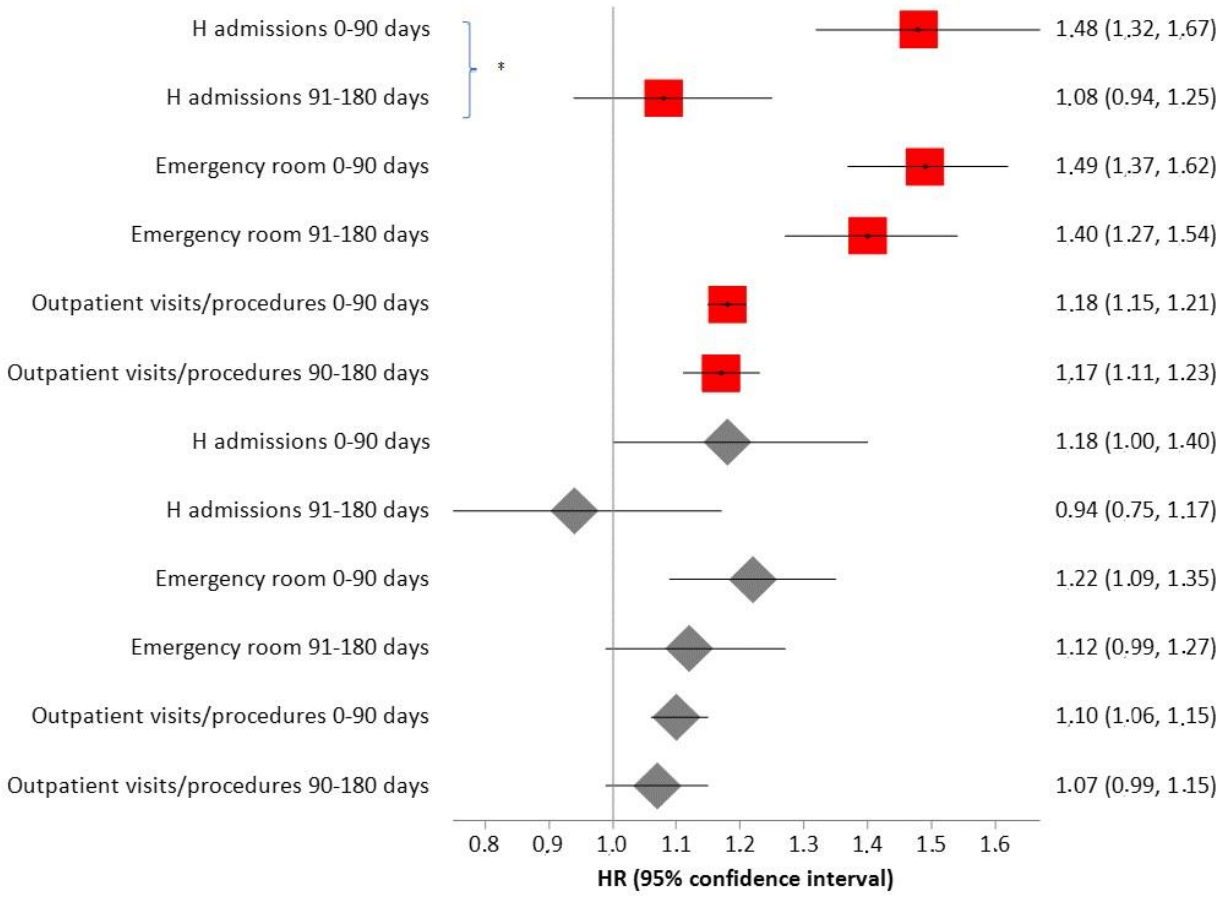

Figure 1: HRs (from Poisson regression) comparing rates of occurrence of the events considered between Covid19 convalescents and matched controls who had no swab test (red squares) and who had at least one (negative) swab test (grey diamonds). *P<0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract **Pag. 1 to 3**
		Provide in the abstract an informative and balanced summary of what was done and what was found **Pag. 2,3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pag. 4,5**
Objectives	3	State specific objectives, including any prespecified hypotheses **Pag. 4,5**
Methods		
Study design	4	Present key elements of study design early in the paper **Pag. 5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pag. 5,6**
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pag. 5,6**
		For matched studies, give matching criteria and number of exposed and unexposed **Pag. 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pag. 6 to 8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Pag. 5 to 8**
Bias	9	Describe any efforts to address potential sources of bias **Pag. 6 to 8**
Study size	10	Explain how the study size was arrived at **No formal calculation, descriptive study. Criteria for the cohort selection and follow-up are described in pag. 5,6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pag. 7,8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **Pag. 7,8**
Results		
Participants	13*	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study,

		completing follow-up, and analysed **Pag. 6**
		Give reasons for non-participation at each stage **Not applicable**
		(c) Consider use of a flow diagram
Descriptive data	14*	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Pag. 6**
		Indicate number of participants with missing data for each variable of interest **Not applicable**
		Summarise follow-up time (eg, average and total amount) **Pag. 8**
Outcome data	15*	Report numbers of outcome events or summary measures over time Pag**. 8 to 18**
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Pag. 8 to 18**
		Report category boundaries when continuous variables were categorized **Not applicable**
		If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Pag. 19**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Pag. 11 to 18**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pag. 19,20**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pag. 19**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Pag. 19 to 21**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Pag. 22**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Pag. 25**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.