Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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ORIGINAL ARTICLE

Change in healthcare during Covid-19 pandemic was assessed through observational designs

Giovanni Corrao[a,b], Anna Cantarutti[a,b], Matteo Monzio Compagnoni[a,b], Matteo Franchi[a,b], Federico Rea[a,b,*]

[a] *National Centre for Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy*

[b] *Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy*

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Abstract

Objective: Methodological challenges for investigating the changes in healthcare utilization during COVID-19 pandemic must be considered for obtaining unbiased estimates.

Study design and setting: A population-based study in the Lombardy region (Italy) measured the association between the level of epidemic restrictions (increasing exposure during pre-epidemic, post-lockdown, and lockdown periods) and the recommended healthcare (outcome) for patients with schizophrenia, heart failure, chronic obstructive pulmonary disease, breast cancer, and pregnancy women. Two designs are applied: the self-controlled case series (SCCS) and the usual cohort design. Adjustments for between-patients unmeasured confounders and seasonality of medical services delivering were performed.

Results: Compared with pre-epidemic, reductions in delivering recommended healthcare during lockdown up to 73% (95% confidence interval: 63%–80%) for timeliness of breast cancer surgery, and up to 20% (16%–23%) for appropriated gynecologic visit during pregnancy were obtained from SCCS and cohort design, respectively. Healthcare provision came back to pre-epidemic levels during the post-lockdown, with the exception of schizophrenic patients for whom the SCCS showed a reduction in continuity of care of 11% (11%–12%).

Conclusion: Strategies for investigating the changes in healthcare utilization during pandemic must be implemented. Recommendations for taking into account sources of systematic uncertainty are discussed and illustrated by using motivating examples.

Keywords: Cohort; Covid-19; Healthcare utilization database; Indirect burden; Self-controlled case series; Recommendations

Conflicts of interest: GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (ie, Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche. The other authors report no conflicts.

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Data availability: The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Lombardy Region upon reasonable request.

* Corresponding author. Tel.: +39.02.64485859.

E-mail address: federico.rea@unimib.it (F. Rea).

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What is new?

Key findings

- Compared to the prepandemic period, a reduction in the delivery of recommended healthcare was observed in several medical fields (schizophrenic disorders, heart failure, chronic obstructive pulmonary disease, breast cancer, and pregnancy) during the COVID-19 pandemic

What this adds to what is known?

- Several sources of biases could affect studies aiming to investigate the changes in healthcare utilization during a pandemic. This manuscript provides some recommendations for taking into account sources of systematic uncertainty

What is the implication, what should change now?

- Policy-makers should take into account these findings for planning the management of resources in order to get back the delivery of recommended healthcare
- Strategies for investigating the changes in healthcare utilization during a pandemic must be considered for obtaining unbiased estimates

1. Introduction

Although the direct burden of the coronavirus disease 2019 (COVID-19) has been worldwide substantial [1–4], concerns have arisen about the indirect effects of the pandemic on patients with chronic medical conditions. A recent systematic review reports major changes in the utilization of healthcare services because of such restrictions as lockdowns and stay-at-home orders [5]. These changes included large reductions in services, particularly in places hit harder by the pandemic "first wave."

A major methodological challenge for suitably investigating the changes in healthcare utilization is the choice of the observational unit. The more popular approach is of observing volume trends of specific types of care delivered to a given population during the pandemic period, possibly compared with those delivered to the same population during nonpandemic periods [6]. However, it should be considered that the number of individuals who experience the variation of health services delivered, and their structural characteristics, remains unknown by investigating aggregated volume trends. For example, the reduction in the dispensed drug therapy is alarming in itself, but does not tell us who experiences this reduction, for example, whether it regards all patients to the same extent (eg a dose reduction uniformly distributed among patients), or just some patients who fully discontinued the treatment. Yet, in the latter circumstance, who interrupted the usual/recommended healthcare? Is it regard mainly patients with a severe clinical profile, that is, those who strongly need continuous and intensive care, or patients with a less critical profile? It has been also emphasized that reduction in healthcare volume is not necessarily a negative signal, since the pandemic may also have resulted in some people being spared unnecessary or inappropriate care, which can cause harm [7,8], but this cannot be directly investigated by an approach based on the volumes trend analysis. All these considerations together suggest that person-level analysis should be used for properly and carefully investigating changes in recommended healthcare during the pandemic.

Finally, a relevant amount of literature consistently reported reduced volumes of emergency medical care worldwide. For example, relevant declines in admissions due to acute coronary syndrome [9] and cancer surgery [10], and delayed time to hip fracture intervention [11], were noticed. However, recommended outpatients healthcare (eg, scheduled analytic, radiologic and clinical controls, uninterrupted drug therapy) has received little attention, likely because of unavailable or limited data on out-of-hospital services in many jurisdictions. Because at our best knowledge the impact of the pandemic on usual outpatient healthcare has never been systematically measured with a person-level approach, new methodological challenges should be faced for investigating this issue.

Recognizing the challenges and complications that we must face for carefully measuring out-of-hospital healthcare reduction for patients affected by chronic conditions during the COVID-19 pandemic, this paper proposes some person-level analysis taking into account informative needs and systematic uncertainty sources.

2. Observing and modeling healthcare changes during pandemic

2.1. Preliminary remarks

The usual exposure outcome association was of interest, where "exposure" and "outcome" respectively refer to the level of epidemic restrictions and the recommended use healthcare. The following factors affecting study design and data processing should be careful considered defined.

First, we must evaluate whether cohort members may be identified in a given time-point prior the epidemic starts (eg, prevalent hypertensive patients identified in a specific day) or dynamically as a certain origin event occurs (eg, women identified at the date when they were underwent to breast cancer surgery). In the latter situation, we must decide whether cohort members must to be included before the epidemic start, and/or over the epidemic period.

Second, increasing levels of exposure to restriction measures must to be considered. The Italian Government imposed a generalized lockdown on March 9th, 2020 (ie, from this date citizens could leave their homes only for medical needs, grocery or pharmacy shopping, and com-

muting to work for essential jobs [12]) and those restrictions were lifted since May 18th, 2020. This implies that in our setting a generic cohort member was considered exposed to none, light and strong restriction according whether his/her observation period respectively falls before March 8th, between May 19th and the end-point of observation (according to the current data availability, see below), and between March 9th and May 18th.

Third, the outcome may be regarded as a given service recommended to be continuously offered in an uninterrupted way (eg, glucose-lowering drugs to patients with diabetes) or performed once, or however few times, during the observation period (eg, periodic echocardiography examination of patients discharged with diagnosis of heart failure).

Fourth, we must understand whether a long- or short-term observational period is of interest. Long-term follow-up is required for measuring continuity of care (eg, lipid-lowering drug therapy of patients suffering of dyslipidemia) or providing a service expected to be delivered at last once within a long period after entry (eg, at least a pneumologic visit within 1 year after discharge for chronic obstructive pulmonary disease, COPD). Short-term follow-up is instead required for evaluating whether a service is provided as soon as possible after entry (eg, starting recommended drug therapy after discharge for acute coronary syndrome). Every cohort member generally experiences all the investigated levels of exposure if long-term follow-up is designed, while only one or two levels are experienced for short-term follow-up.

Finally, because the intensity of healthcare may vary along calendar time not only for the epidemic restrictions but also for seasonality of medical services, a proper comparison between healthcares provided during the epidemic period with that provided one year before is recommended.

2.2. Possible scenarios

Fig. 1, **scenario A**, implies the inclusion of a prevalent cohort. During their period of observation, every cohort member switches from one exposure status to another, and experiences all the considered exposure levels. In these setting, we can compare the incidence rates (IR) of healthcare supplied during person-days spent on each exposure status (eg, the number of drug prescriptions, of specialist visits, of control examinations delivered during person-days covered by none, light and strong restrictive measures). The most proper way for modeling the association of interest is to fit a conditional Poisson regression model estimating the incidence rate ratio (IRR), and corresponding 95% confidence interval (CI), associated with a given exposure status (ie, exposure to light or strong restrictions) compared to the status of exposure to none restriction. The comparison of incidence rates within each cohort member (ie, the choice of a within-person design), is the main advantage provided by this approach. The corresponding design, which has been labeled as self-controlled case series (SCCS) by Farrington et al. [13,14], provides implicit adjustment of time-invariant between-person confounding. It should be emphasized that at least three key assumptions should be fulfilled for obtaining valid estimates from SCCS, nominally (i) two consecutive outcomes should be independent if they are recurrent; (ii) the probability of further exposure should not be affected by an outcome onset; and (iii) the outcome should not affect the short-term mortality probability. Because healthcare (the outcome of interest in our application) (i) may be either unique or recurrent; in the latter case there are not reasons to believe that a supplied service affects the probability that the following one is provided), (ii) does not affect the future risk of exposure to restriction measures, (iii) should not affect short-term mortality (at least there are not reasons for believe that); the key assumptions are likely fulfilled, so the SCCS design may provide robust and nonbiased estimates in our setting [15]. By repeating the analyses on patient cohorts recruited with a one-year delay with respect to the above-described ones, seasonality-adjusted estimates of IRR may be obtained by dividing estimates from epidemic and referent patient cohorts.

Fig. 1, **scenario B**, implies the inclusion of a cohort whose members dynamically enter into follow-up prior the epidemics onset. Because the observation always starts before the epidemic begins, and a long-term follow-up is of interest, also in this setting the choice of a seasonality-adjusted SCCS approach, should generate unbiased estimates.

Fig. 1, **scenario C**, implies again the inclusion of a cohort whose members dynamically enter into follow-up (as well as for scenario B). Several differences should however be noticed. First, in this case, we are interested in verifying whether a given service is supplied within a short time-window after the observation starts. In this condition, because cohort members do not experience all the considered exposure levels, but at most two, a within-patient comparison is not enforceable, and a between-person design is unavoidable. Moreover, as we are interested to verify whether a given medical service is supplied within a given amount of time, it follows that every observation must be censored whenever the outcome occurs. Finally, as the outcome of interest concerns the time between study entry and the provision of a given service, a time-to-failure approach (the Cox proportional hazard model estimating hazard ratio [HR], and corresponding 95% CI) should be indicated in this situation. Two main cautions should be taken into account, however. First, as exposure change over time, assessment of its effect requires consideration of its varying nature. This may be done by fitting a model including exposure categories expressed as a time-dependent covariate [16]. Second, as for the previously described scenarios, seasonality-adjusted HR may be obtained by comparing estimates from epidemic and referent patient cohorts. Because in this scenario cohort members

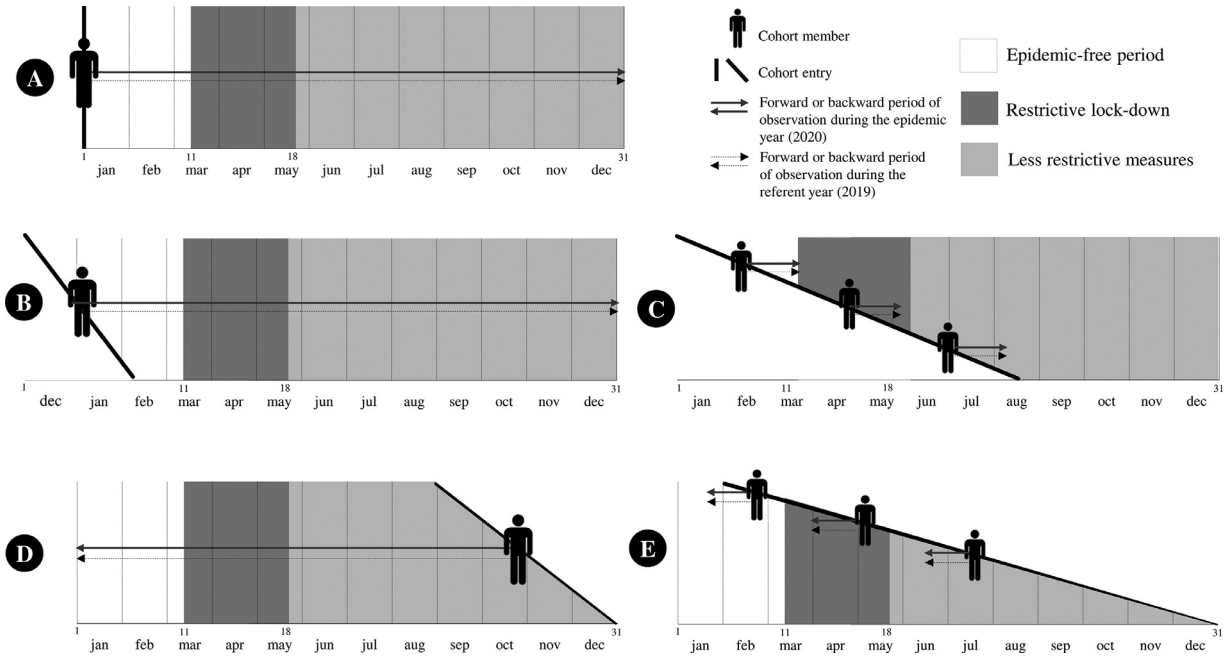

Fig. 1. Graphical representation of five situations useful for investigating the relationship between exposure (level of epidemic restrictions) and outcome (the recommended use of outpatient service) by means of person-level approaches.
(A) The observation starts on a given day before pandemic begun (eg, patients known to be affected by the considered condition/disease on January 1, 2020) and purses forward for recording recommended healthcare (outcome) supplied during a period so long to cover all the considered levels of exposure (eg, specialist visits, instrumental controls or drug prescriptions received until December 31, 2020). (B) The observation starts dynamically over time when an origin event occurred prior pandemic begun (eg, patients who were discharged from hospital for the considered disease from December 2019 to February 2020) and purses forward for recording recommended healthcare supplied during a period so long to cover all the considered exposure levels (as for the situation A). (C) The observation starts dynamically over time when an origin event occurred either before or after pandemic begun (eg, patients who were discharged from hospital for the considered disease from January to August 2020) and purses forward for recording healthcare expected to occur at once after the origin event (eg, drug therapy started within two months after the index discharge). For the latter situation, cohort members do not experience all the considered exposure levels (as in the situations A and B), at most two. (D) The observation starts dynamically over time when an origin event occurred after pandemic begun (eg, patients who received a medical or surgical therapy from October to December 2020), and does on backward for assessing when that therapy was prescribed along a period so long to cover all the considered exposure levels (ie, for measuring the timeliness of yielded therapy along several months before its supplying). (E) The observation starts dynamically over time when an origin event occurred either before or after pandemic begun (eg, patients who received the considered service from February to December 2020), and does on backward for recording healthcare expected to occur at once before the origin event (eg, specialist visits, instrumental controls within three weeks before the origin event occurred). For all the situations, the outcomes observed during the epidemic period (continuous line) were compared with those that occurred 1 year before (dotted line).

enters when the epidemic was already started, validity of estimates are based on the assumption that clinical features of patients entered during epidemic did not differ from those of referent patients. As accessibility to medical care change over time, however, this assumption is likely violated. For example, because during epidemics, cancer surgery might be mostly reserved to patients with more severe disease, patients included in epidemic and referent periods may substantially differ for their clinical features. This implies that some additional precautionary devices should be adopted to avoid confounding. Among these, the high-dimensional propensity-score (HDPS) matching design may be employed to make comparable epidemic and referent cohorts. The HDPS algorithm empirically identifies and prioritizes covariates that are believed proxies for unmeasured confounders [17]. In our setting, the predicted probability of entering the study during the epidemic periods was estimated by covariates available from healthcare utilization databases. Candidate predictors were all the possible causes of hospital discharge and drug dispensed in the 5-year period prior to the index date of cohort entry. Candidate predictors were regarded as covariates in a logistic regression model. The 200 most predictive covariates were selected. For each cohort member entering into observation during the epidemic year, one cohort member entering one year before was randomly selected to be 1:1 matched for gender, age, the number of previous contacts with National Health Service (NHS), and HDPS through the nearest neighbor matching algorithm [18].

Fig. 1, **scenarios D** and **E**, shows situations in which patients are dynamically recruited for the occurrence of a given event, but rather than follow these patients forward (as for scenarios B and C), we are interested to verify backward when the recommended healthcare was previously occurred. Again, SCCS or usual cohort designs should be respectively adopted when each cohort member

experiences all the considered exposure levels (Scenario D) or only one or at most two of them (Scenario E). Finally, an HDPS matching design may be appropriate when epidemic cohort members start follow-up during the epidemic period and there are reasons for suspecting that epidemics affect the event triggering the start of the observation.

Finally, although follow-up of cohort members was designed according to different rules based on the above-described scenarios, a common assumption is that observation should be censored whenever SARS-CoV-2 infection (positivity to the oropharyngeal swamp), hospital admission with diagnosis of COVID-19, death or end-point of follow-up occurs.

3. Applications

Motivating applications of the above-described situations have been drawn from the setting of epidemic spread that severely hit the population of the Italian region of Lombardy.

Data sources. All Italian citizens have equal access to health care services as part of the NHS. An automated system of healthcare utilization (HCU) databases allows each Italian region to manage the NHS at local level. HCU data include a variety of information on residents who receive NHS assistance, diagnosis on discharge from public or private hospitals, outpatient drug prescriptions, specialist visits and diagnostic exams reimbursable by the NHS. Since the starting of the COVID-19 pandemic, all Italian Regions established, under the coordination of the National Health Institute, a population-based registry of patients with a confirmed diagnosis of infection with the SARS-CoV-2 virus. As a unique identification code is systematically used for all the above reported databases, records can be linked to enable searches on the complete care pathways of NHS beneficiaries. In order to preserve privacy, individual identification codes are automatically anonymized, the inverse process being allowed only to the Regional Health Authority on request from judicial authorities.

Setting. The COVID-19 epidemic spread to and increased exponentially in Italy earlier than in any other Western country. During the first wave of COVID-19 epidemic, the most severely hit part of Italy was Lombardy, a northern region with just over 10 million people (approximately 16% of the entire Italian population) in which SARS-CoV-2 has infected thousands of patients and has been associated with a high incidence of hospitalization for intensive care and a high mortality [19].

Motivating examples and designs. With the aim to supply motivating examples of the above-reported situations, we estimated the effect of epidemic light and strong restrictions (exposure) on (i) continuity in mental health service attendance of patients taken in care for schizophrenic disorder, as an example of the situation depicted in Fig. 1, Scenario A); (ii) echocardiographic control of patients discharged with a diagnosis of heart failure, as an example of the situation depicted in Fig. 1, scenario B; (iii) starting medical therapy with long-term inhaled bronchodilators after discharge for chronic obstructive pulmonary disease, as an example of the situation depicted in Fig. 1, scenario C; (iv) surgery timeliness after diagnosis of breast cancer, as an example of the situation depicted in Fig. 1, scenario D; (v) prepartum gynecologic visit in the same structure where the woman will give birth, as an example of the situation depicted in Fig. 1, scenario E.

Table 1 reports some details about the adopted design for each of the examples. Briefly, the effect of restrictions on the healthcare provided for schizophrenia, heart failure, and breast cancer patients was investigated by the SCCS design, while the usual cohort design was used for investigating chronic obstructive pulmonary disease and pregnancy. Seasonality of medical services supply was taken into account for all the considered situations by including a referent cohort. Finally, an HDPS matching design was adopted for comparing epidemic and referent cohorts of chronic obstructive pulmonary disease and breast cancer patients.

Results. Compared with no epidemic periods, significant reductions in delivering recommended healthcare during periods on strong restrictive measures were observed for all the considered settings (**Fig. 2**). In particular, reductions regarded timeliness in starting drug therapy with inhaled bronchodilators of patients discharged for COPD (-12%; 95% CI, 1% to 22%), prepartum visit at the same structure where the woman will give birth (-20%; 16% to 23%), continuity in mental health service attendance of patients taken in care for schizophrenia (-28%; 27% to 29%), echocardiographic controls after discharge for heart failure (-64%; 57% to 70%), and surgery timeliness after diagnosis of breast cancer (-73%; 63% to 80%). With the exception of continuity in mental health service attendance (which had -11% significant reduction during the light exposure period), all other healthcare services were restored during periods with less restrictive measures.

4. Discussion

Measuring and characterizing the unprecedented recent changes in healthcare utilization may help health systems to optimize the post-pandemic management of resources. However, investigating the impact of changes in healthcare utilization during the pandemic has major methodological challenges. First, disentangling populations who have missed necessary care from those who have avoided unnecessary care requires careful analysis. For this reason, we only investigated guidelines recommended healthcare. For example, reaching the continuity with territorial interventions of patients with schizophrenic disorders [20,21], performing at least one echocardiographic control every year of patients with heart failure [22], timely starting therapy with inhaled bronchodilators after discharge for COPD [23], surgery timeliness after diagnosis of breast cancer

Table 1. Details on study design and data analysis of the five motivating examples for estimating the association between restrictive measures during the COVID-19 pandemic and failure of delivering outpatient services

Scenario (ref. Fig. 1)	Cohort definition	Epidemic cohort		Referent cohort		Outcome	Design	Model	Association measure
		Entry (starting follow-up)	Exit (stopping follow-up)	Entry (starting follow-up)	Exit (stopping follow-up)				
A	Patients taken in care for schizophrenic disorder who had at least a visit in a public mental health service during the observational period	January 1, 2020 ($N = 30,584$)	September 30, 2020	January 1, 2019 ($N = 29,961$)	September 30, 2019	Rate: months covered by a visit in a public mental health service on months spent on a given level of epidemic restriction (exposure)	Self-controlled case series	Conditional Poisson regression	Ratio between incidence rate ratios of epidemic and referent cohorts
B	Patients discharged with diagnosis of heart failure who had at least an echocardiographic control during the observational period	From October to December 2019 ($N = 7,542$)	December 31, 2020	From October to December 2018 ($N = 7,540$)	December 31, 2019	Rate: number of echocardiographic controls on months spent on a given level of epidemic restriction (exposure)	Self-controlled case series	Conditional Poisson regression	Ratio between incidence rate ratios of epidemic and referent cohorts
C	Patients discharged with diagnosis of COPD	From January to July 2020 ($N = 2,252$ [a])	The earliest between the date of starting drug therapy and two months after index discharge	From January to July 2019 ($N = 2,252$ [a])	The earliest between the date of starting drug therapy and two months after index discharge	Time to failure: time to starting drug therapy with inhaled long-acting bronchodilators during a given level of epidemic restriction (exposure)	Conventional cohort and Propensity score matching of epidemic and referent cohort members[a]	Cox proportional hazard	Ratio between hazard ratios of epidemic and referent cohorts
D	Women underwent to breast cancer surgery who had at least a mammographic examination within nine months before surgery	From September to December 2020 ($N = 2,276$[b])	Nine months before entry	From September to December 2019 ($N = 2,276$[b])	Nine months before entry	Rate: mammographic examination during a given level of epidemic restriction (exposure)	Self-controlled case series and Propensity score matching of epidemic and referent cohort members[b]	Conditional Poisson regression	Ratio between incidence rate ratios of epidemic and referent cohorts
E	In-hospital occurred deliveries	From February to November 2020 ($N = 52,312$)	Twenty one days before deliver	From February to November 2019 ($N = 53,551$)	Twenty one days before deliver	Proportion of women who had at least a gynecology visit in the same structure where the woman delivers within twenty one days before deliver during a given level of epidemic restriction (exposure)	Conventional cohort	Cox proportional hazard	Ratio between hazard ratios of epidemic and referent cohorts

COPD, chronic obstructive pulmonary disease; *N*, cohort size at entry.

Exposure levels were indexed as 0 (ie, no exposure, periods without restrictive measures), 1 (ie, light exposure, periods with light restrictive measures), and 2 (ie, strong exposure, periods imposing generalized lockdown).

[a] Because a 1:1 matching design was adopted, epidemic and referent cohorts had a by-design equal size; really, original cohorts had sizes of 2,591 and 4,510 patients

[b] Because a 1:1 matching design was adopted, epidemic and referent cohorts had a by-design equal size; really, original cohorts had sizes of 2,512 and 2,857 patients

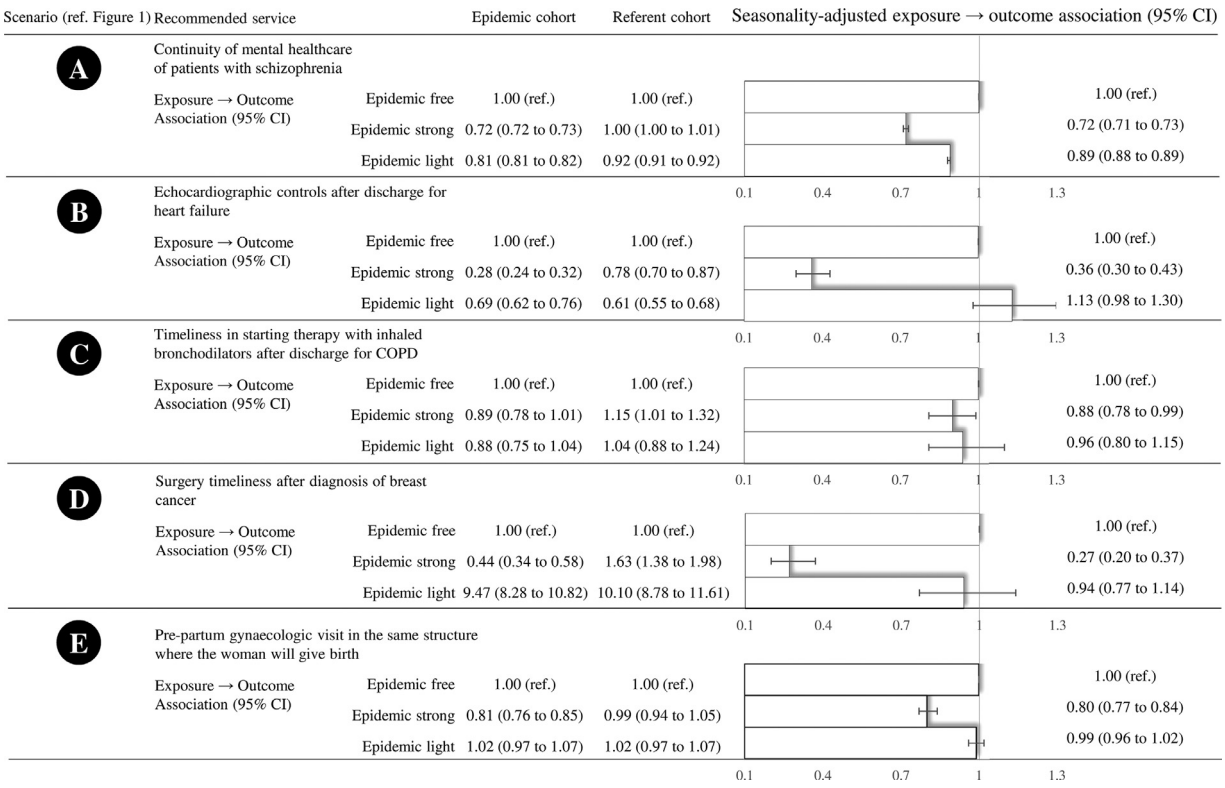

Fig. 2. Effect of restriction measures during epidemics (exposure) on adherence with recommendations (outcomes) in five clinical settings.

[24,25], and prepartum gynecologic visit in the same structure where the woman will give birth [26,27], should be considered as "core" interventions of community care, so that failure of adherence with each of them must be regarded with concerns. Second, approaches investigating trends in the aggregated volume of specific types of healthcare must be considered reductive, as it only informs on the entirety of procedures that are delivered, not on individual patients who received them. For example, observing a reduction of drug prescribed (such as inhaled bronchodilators), procedures supplied (such as breast surgery), or services delivered (such as psychological community care interventions, echocardiographic and gynecologic visit) during the epidemic shock with respect to no epidemic periods, does not necessarily negatively impact on health; on the contrary, it could instead point out the reduction of unnecessary care. Again, limiting investigation of recommended healthcare (ie, those that offered evidence of benefit on health outcomes of patients who receive them) allows overcoming this limitation but it requires using a person-level analysis. It should be finally considered that person-level approach (ie, observational designs based on a set of patients of whom are recorded individual information on relevant characters, including received healthcare) requires careful considerations about their vulnerability to biases.

At first sight, a simple cohort design investigating the association between time-varying exposure to restrictive measures and healthcare delivered should be adopted. However, as patient's clinical characters likely differ according to the level of epidemic restrictions (eg, hospital admission with a diagnosis of heart failure or COPD more rarely occur during the lockdown, unless the severity of the patient's condition does not offer alternatives to hospitalization), and because relevant clinical data are not measured in a study based on HCU data, a cohort approach likely generates estimates affected by between-person confounding. For this reason, a within-patient SCCS design aimed at eliminating time-invariant between-person confounding is recommended, provided that the assumptions necessary for its application are met [13–15]. Two main restrains however limit the applicability of such an approach. First, because the design restricts analysis to patients who experience the outcome at least once, both selection bias and power limitations may be of concern. For example, among the nearly thirty thousand patients discharged for heart failure, more than two-thirds of them who did not receive any echocardiographic control during the observational period were excluded. Second, because the design assumes that patients must cross all the exposure levels of interest, it cannot be applied when we are interested in verifying whether a service occurs shortly after the cohort entry. For example, because we were interested to ascertain drug dispensing within two months after hospital discharge for COPD, the SCCS design cannot be applied. This insinuates a problem because, to investigate the effect of expo-

sure to restrictions, we are forced to include patients who enter (say) between February 2020 (each of whom can go through both an epidemic-free and severely restricted period) and April 2020 (each of which can go through both a heavily restricted and a less tightly restricted period). As accessibility to hospital admission likely changes over time (ie, severe patients are expected to be admitted more in April than in February), comparability of patients according to the time of inclusion is not ensured. For this reason, adequate tools to take into account unmeasured confounders should be used. In the specific application under consideration, an HDPS matching design was adopted. However, because HDPS not always showed proper ability for between group balancing [28], alternative algorithms should be explored. For example, comparing results derived from administrative data with an approach of selecting covariates through HDPS and according with expert opinion [29], might be an adequate way for giving consistence to results. Of course, confounding control does not need to be taken into account when considering an origin event not subjected to selective pressure over time such as childbirth.

Another caution for the considered field of investigation is disentangling the effect of restriction measures from that of seasonality in healthcare delivery. For example, because many medical treatments are issued less frequently during the summer months, the latter seasonal reduction, rather than the relaxing of restrictive measures, may explain the reduction in the delivery of care observed after the rigid lockdown that occurred until May 2020. The simplest way to consider this is to compare the cohort of patients whose care is expected to be provided during the pandemic period with a cohort recruited exactly one year earlier in order to take into account any seasonality in the provision of care and adjusting the current estimates accordingly. It should be considered, however, that using the previous year for a historical control may be reasonable when studying pandemic effects during the first 12 months of the pandemic as for the current applications, but becomes a problem when the interest is for the subsequent effects. For example, to study healthcare supplied in the spring/summer of 2021, control period should be chosen set at least two years earlier (ie, 2019, or even multiple periods such as 2017-2019 to obtain more stable estimates).

Not always our approach generates directly interpretable results. For example, the reduction in the proportion of patients who starts pharmacological treatment early after discharge for COPD should be considered a negative signal of the functioning of the treatment system during pandemics, independently from the epidemiological setting in which the observation is carried out. In fact, the substantial reduction in admissions for COPD exacerbations during the COVID-19 pandemic period, likely associated with a reduction in respiratory viral infections that trigger exacerbations [30], is expected to be independent from (ie, of not affecting) the need of starting drug therapy with inhaled long-acting bronchodilators as early as possible after discharge. Conversely, the reduction in the average number of echocardiograms in the year following discharge for heart failure may not be a negative sign but a saving in excess tests performed the year before the epidemic one. The empirical verification of the impact of the reduction of examinations on the occurrence of clinical outcomes subsequent to the index one (hospitalizations, deaths, etc) is a challenge that should be met by overcoming difficulties inherent the changing of epidemiological framework during the epidemic waves. A future methodological research direction should go in this direction.

Our study has a number of potential limitations other than those above discussed. First, because information about outpatient facilities supplied by private organizations are not available from our databases, we cannot exclude that the observed reduced healthcare for free delivered from public services may have been wholly or partially replaced by out-of-pocket health expenditure [31]. Second, the validity of our estimates is based on the assumption that the prescription of a drug or a medical control corresponds to medicament using or control performing. There is, however, no guarantee that this is always the case, and indeed it is likely that in a number of patients medical prescription may not hesitate in healthcare exposure. Finally, although we censured information whenever occurred an event potentially modifying the likelihood of receiving outpatient healthcare (eg, when the SARS-CoV-2 infection was detected), not all events of this type have been recorded (for example, many infections that occurred at the beginning of the epidemic were easily escaped).

5. Conclusions

In conclusion, we described several common situations for measuring the effect of epidemic restrictions on the use of recommended outpatient healthcare by means of person-level analyses. Recommendations for avoiding, or at least taking into account, common sources of systematic uncertainty are discussed and illustrated by using motivating examples.

Credit authorship contribution statement

Giovanni Corrao: Conceptualization, Methodology, Writing – Original Draft, Supervision, Funding acquisition

Anna Cantarutti: Methodology, Software, Formal analysis, Writing – Review & Editing

Matteo Monzio Compagnoni: Methodology, Software, Formal analysis, Writing – Review & Editing

Matteo Franchi: Methodology, Software, Formal analysis, Writing – Review & Editing

Federico Rea: Methodology, Software, Formal analysis, Writing – Review & Editing

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