

ORIGINAL ARTICLE

People exposed to proton-pump inhibitors shortly preceding COVID-19 diagnosis are not at an increased risk of subsequent hospitalizations and mortality: A nationwide matched cohort study

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Aims: To assess whether exposure to proton-pump inhibitors (PPIs) shortly preceding COVID-19 diagnosis affected the risk of subsequent hospitalizations and mortality.

Methods: This population-based study embraced first COVID-19 episodes in adults diagnosed up to 15 August 2021 in Croatia. Patients were classified based on exposure to PPIs and burden of PPI-requiring morbidities as *nonusers* (no issued prescriptions, no recorded treatment-requiring conditions between 1 January 2019 and COVID-19 diagnosis), *possible users* (no issued prescriptions, but morbidities present; self-medication possible) and *users* (≥ 1 prescription within 3 months prior to the COVID-19 diagnosis; morbidities present). Subsets were mutually exactly matched for pre-COVID-19 characteristics. The contrast between *users* and *possible users* informed about the effect of PPIs that is separate of the effect of PPI-requiring conditions.

Results: Among 433 609 patients, *users* and *possible users* were matched 41 195 (of 55 098) to 17 334 (of 18 170) in the primary and 33 272 to 16 434 in the sensitivity analysis. There was no relevant difference between them regarding mortality (primary: relative risk [RR] = 0.93 [95% confidence interval 0.85–1.02; absolute risk difference [RD] = -0.34% [-0.73, 0.03]; sensitivity: RR = 0.88 [0.78–0.98]; RD = -0.45% [-0.80, -0.11]) or hospitalizations (primary: RR = 1.04 [0.97–1.13]; RD = 0.29% [-0.16, 0.73]; sensitivity: RR = 1.05 [0.97–1.15]; RD = 0.32% [-0.12, 0.75]). The risks of both were slightly higher in *possible users* or *users* than in *nonusers* (absolutely by ~0.4–1.6%) indicating the effect of PPI-requiring morbidities.

Conclusion: Premorbid exposure to PPIs does not affect the risk of death or hospitalization in adult COVID-19 patients, but PPI-requiring morbidities seemingly slightly increase the risk of both.

KEYWORDS

COVID-19 disease, hospitalization, mortality, proton-pump inhibitors

1 | INTRODUCTION

When used rationally, proton-pump inhibitors (PPIs) are well tolerated and safe^{1–3} and are commonly available over-the-counter (OTC).⁴

Long-term PPI use (continuous or intermittent), as required in some peptic acid disorders,^{2,3} has been suggested associated with a range of untoward health outcomes,^{5,6} but evidence of a causal PPI effect is highly questionable.^{2,7} Concerns were also raised that PPI use might

be an unfavourable factor in respect to COVID-19, by analogy to previously reported associations with other respiratory viral infections.⁸ At the same time, their antiviral effects and potential use *against* SARS-CoV-2 were also discussed.^{9–11} Biological plausibility for the presumed PPI–COVID-19 relationship is based on reduced antiviral resistance due to prolonged gastrointestinal hypochlorhydria and subsequently increased pulmonary colonization.^{5,6,8} Two questions about pre-COVID PPI use seem to naturally arise from this mechanistic rationale: 1 pertaining to the risk of infection and the other to the risk of severe COVID-19.⁸ Four recent systematic reviews^{12–15} identified a number of observational studies dealing with these questions. Among them, as reviewed,¹² 5 low risk of bias community-based case-control studies referring to periods before mass vaccination consistently showed no association between PPI use and odds of COVID-19 infection. In addition to being medically relevant, this fact informs also about applicable methods in studies focused on PPI exposure and the risk of unfavourable COVID-19 course: they may validly include only COVID-19 infected patients. Otherwise, such studies would need to embrace both infected and noninfected people; by inclusion of only COVID-19 infected patients, they would (in such a case) condition (by selective inclusion) on a variable that is on a path between the exposure (PPIs) and the outcome (COVID-19 course), and this would introduce bias.¹⁶ As reviewed,^{12–15} most of the studies assessing the relationship between PPI use and COVID-19 outcomes included only hospitalized patients, thus suffering from this very type of bias, as well as from selection bias (the effect in nonhospitalized patients remained unknown).¹⁶ Three community-based (hence, devoid of such limitations) studies formed matched cohorts (propensity score-based) of *PPI current users* and *never users* among COVID-19 positive patients. In a Danish study,¹² *current users* (at least 1 PPI prescription within 90 days prior to the index COVID-19 diagnosis) and *never users* (no such prescriptions over the preceding 15 y; 3955 current vs. 3955 never users) had closely similar risk of a severe disease or death, while the risk of hospitalization was marginally and irrelevantly¹² higher in *current users* (RR = 1.13; 1.03–1.24). In a UK study,¹⁷ mortality was closely similar in *regular users* and *nonusers* (1516 vs. 1516 patients, no definitions provided). In a South Korean study,¹⁸ the risk of several unfavourable outcomes was higher in *current users* (at least 1 PPI prescription within 30 days prior to the index COVID-19 diagnosis) than in *never users* (no prescriptions within 1 year): point odds ratios between 1.63 and 1.90 for 267 vs. 267 patients. In an additional analysis, the odds were particularly higher in *current users* prescribed with PPIs twice daily, and not (or less so) in those with once daily prescriptions.¹⁹

Owing to these somewhat inconsistent reports, we aimed to address the same question. In doing so, we adopted the following logic: PPIs are not prescribed to treat/prevent COVID-19, but to treat peptic acid disorders and are not prescribed when such conditions are absent. If identification of exposure to PPIs is based only on issued prescriptions, *current users* and *never users* differ in respect to presence/absence of PPI-requiring conditions. No method of confounding control (regression, matching, weighting) can ascertain balance: even if matched on a practically identical propensity score, a *current user*

What is already known about this subject

- It appears biologically plausible that premorbid exposure to proton-pump inhibitors (PPIs) might contribute to an unfavourable course of COVID-19 disease.
- Two population-based studies in the early pandemics stage indicated no effect of PPIs, while 1 suggested a higher risk of death/severe COVID-19 disease in PPI pre-exposed subjects.

What this study adds

- Exposure to PPIs directly preceding SARS-CoV-2 infection has no effect on the risk of subsequent hospitalizations and mortality.
- Conditions requiring PPI treatment seem to mildly increase the risk of both.

and a *never user* are likely to differ in this respect.²⁰ Moreover, a complete *nonexposure* to PPIs/PPI-requiring conditions shortly preceding COVID-19 diagnosis is difficult to assume: milder forms of gastrointestinal reflux disease or functional dyspepsia may remain underdiagnosed²¹ and might be self-medicated (OTC PPIs). To discern the risk attributable to specifically PPIs from the risk attributable to PPI-requiring conditions, COVID-19 patients prescribed with (and presumably exposed to) PPIs shortly preceding the COVID-19 diagnosis and their nonprescribed peers (controls) should come from the same target population of people suffering peptic acid disorders.

Having this in mind, using a nationwide cohort of adults and adolescents diagnosed with COVID-19 up to 15 August 2021, we aimed to estimate whether those prescribed with PPIs shortly preceding the COVID-19 diagnosis differed from their nonprescribed peers regarding subsequent mortality and hospitalizations.

2 | METHODS

2.1 | Study outline

Anonymized routinely collected data were linked into a database including all subjects in Croatia diagnosed with COVID-19 between start of the pandemic (25 February 2020) and 15 August 2021. Linked were data on: date and mode of COVID-19 diagnosis; demographics and COVID-19 vaccination status at diagnosis; medical histories from 1 January 2019 to 31 October 2021, including comorbidities (International Classification of Diseases [ICD-10] codes), all issued prescriptions (Anatomical Therapeutic Chemical codes [ATC]) and other medical care, hospital admissions and diagnoses and dates and causes of death.

Having in mind certain country specifics (OTC availability of pantoprazole 20 × 20 mg tablets, of H₂ receptor antagonists [extremely rarely prescribed, i.e. <3000 prescriptions issued between 1 January 2019 and 31 October 2021 in the present cohort comprising ~15% of total population aged ≥16 y]), and of most of the classical nonsteroidal anti-inflammatory drugs (NSAIDs),²² as well as inability to link OTC purchases to specific individuals and our views on the problem of confounding control in the present setting, we defined patient subsets based on timing of issuance of PPI prescriptions as well as the burden of PPI-treatment-requiring conditions. The subsets were mutually exactly matched and compared regarding mortality and hospitalizations subsequent to the index COVID-19 diagnosis.

Since anonymized administrative data standardly collected on routine procedures were used in this observational study, ethical approval was waived by the Ethics Committee of the Zagreb University School of Medicine and Croatian Institute for Public Health.

2.2 | Patient subsets regarding PPI exposure and comparisons of interest

We defined 3 patient subsets (details in Table 1): *PPI users*—(i) patients issued at least 1 prescription for PPIs within 3 months¹² prior to the index COVID-19 diagnosis (with different number of prescriptions issued over 12 months; Table 1) and (ii) burdened with respective morbidities/exposure to NSAIDs (Table 1); *PPI possible users*—(i) no PPI/H₂ receptor antagonist prescriptions issued between 1 January and the index COVID-19 diagnosis, but (ii) burdened with respective morbidities/exposure to NSAIDs (Table 1); hence, PPI OTC self-medication shortly preceding COVID-19 diagnosis cannot be absolutely excluded; and *PPI nonusers*—(i) no PPI/H₂ receptor antagonist prescriptions issued within 12 months prior to the index COVID-19 diagnosis, (ii) no burden of respective morbidities/exposure to NSAIDs (Table 1). Considering the subset characteristics, the most informative about the *effect* of PPIs (i.e. of the fact of being prescribed PPIs)—hence, comparison of primary interest—is that between *PPI users* and *possible users* (Table 1). Other comparisons provide supportive information (Table 1).

2.3 | Potential problem of misclassification of possible users

We were aware that not all patients would be classifiable into categories of interest and deemed it reasonable to assume that at least some of the *nonclassifiable* subjects might have suffered—at certain points between 1 January 2019 and the index COVID-19 diagnosis—milder and commonly underdiagnosed forms of acid peptic disorders. By this virtue, such conditions would remain unregistered, and even if these patients were issued (occasional) PPI prescriptions (and would not meet criteria for *nonusers*), they would not qualify for the *possible users* subset—although they could bear similar risks as subjects in the

TABLE 1 Subsets of patients diagnosed with COVID-19 (up to 15 August 2021) in respect to issuance and timing of proton-pump inhibitor (PPI) prescriptions up to the date of the index COVID-19 diagnosis, and contrasts of interest

- **PPI users** with different levels of exposure: (i) at least 1 prescription for PPIs issued within 3 mo prior to the index COVID-19 diagnosis,¹² further subclassified as those with 1–3, 4–7 and ≥8 prescriptions within 12 mo before the diagnosis; (ii) have ICD-10 entries for conditions requiring anti-secretory treatment at any time between 1 January 2019 and the index COVID-19 diagnosis or ≥3 prescriptions for NSAIDs issued within 6 mo prior to COVID-19 diagnosis
- **PPI possible users** (i.e. OTC self-medication cannot be excluded): have no PPI or H₂ receptor antagonist prescriptions issued between 1 January 2019 and the date of the index COVID-19 diagnosis, but have (i) ICD-10 entries for conditions requiring anti-secretory treatment at any time between 1 January 2019 and the date of diagnosis or (ii) ≥3 prescriptions for NSAIDs issued within 6 mo prior to COVID-19 diagnosis
- **PPI nonusers**: no prescriptions for PPIs or H₂ receptor antagonists issued during the period of 12 mo prior to diagnosis of COVID-19 + no ICD-10 code entries for conditions requiring anti-secretory treatment between 1 January 2019 and the date of the index COVID-19 diagnosis + no prescriptions issued for NSAIDs within 6 mo prior to COVID-19 diagnosis
- **Users vs. possible users**: the 2 subsets differ primarily in respect to exposure to PPIs shortly preceding the COVID-19 diagnosis (it is considered certain for *users* (with different intensity) and some minor exposure cannot be completely excluded for *possible users*), while burden of conditions requiring anti-secretory treatments may be reasonably considered as fairly similar. The contrast quantifies primarily the effect of exposure to PPIs
- **Users vs. nonusers**: the 2 subsets differ regarding the burden of conditions requiring antisecretory treatments and regarding pre-COVID exposure to PPIs. The contrast quantifies a joint effect of conditions requiring antisecretory treatments and of PPIs
- **Possible users vs. nonusers**: the 2 subsets differ primarily regarding the burden of conditions requiring anti-secretory treatments, and to minor extent (if at all) in the extent of pre-COVID exposure to PPIs. The contrast primarily quantifies effect of conditions that require antisecretory treatments

ATC, anatomical, therapeutic, chemical classification; ICD, International Classification of Disease; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over-the-counter.

category of *possible users*. Therefore, we generated also a matched comparison between *PPI users* and *unclassified* patients.

2.4 | Data sources and curation

Raw data were prepared by the Croatian Institute for Public Health (CIPH) from nationwide databases on: (i) COVID-19 laboratory test results (polymerase chain reaction-based or rapid antigen tests) and COVID-19 patients diagnosed on clinical/epidemiological criteria (without laboratory tests); (ii) COVID-19 vaccinations; (iii) all hospitalizations; (iv) deceased individuals; and (v) Central Health Information

System (CEZIH)—primary healthcare database maintained by the Ministry of Health.

All subjects diagnosed with COVID-19 (any means) between 25 February 2020 and 15 October 2021 were identified, and data were linked to the hospitalizations database and database of deceased persons and to their primary healthcare data (1 January 2019 to 31 October 2021 for all; Figure 1A). We received anonymized merged database (Figure 1B) and excluded patients aged <16 years, those for whom data on sex, date of birth, COVID-19 testing date/result/date of diagnosis or vaccination status/dates were missing or were erroneously entered. We identified subjects with more than 1 COVID-19 episode: we considered that positive polymerase chain reaction-based or rapid antigen tests or ICD-10 code U07.1/U07.2 entries or hospitalizations related to COVID-19 that were ≥ 30 days apart indicated 2 separate COVID-19 episodes. Only the first documented COVID-19 episode for each subject was included. We set the cut-off date for COVID-19 diagnosis at 15 August 2021 to allow for a follow-up period long enough for outcomes to occur (until October 31). We identified patient

subsets, comorbidities and treatments needed for matching as well as the outcomes of interest (Figure 1B).

2.5 | Identification of treatments and comorbidities and of vaccination status

Exposure to PPIs, H₂ antagonists and NSAIDs was identified on their respective ATC codes (A02BC, A02BA, M01A). All identified treatments are detailed in Table A1. Subjects were considered burdened with anti-secretory treatment-requiring morbidities based on any of the following ICD-10 entries between 1 January 2019 and date of COVID-19 diagnosis: R12, K20, K21, K22, K23, K24, K25, K26, K27, K28, K29, K30, K31. Identification of all other comorbidities is detailed in Tables A2–A4, and section on immunocompromised and diabetic patients. Regarding vaccination, patients were classified as *not vaccinated*—or as (i) vaccinated with a single-dose vaccine; (ii) received first dose of a 2-dose vaccine; or (iii) received second (full) dose of a 2-dose vaccine—and were further sub-classified based on

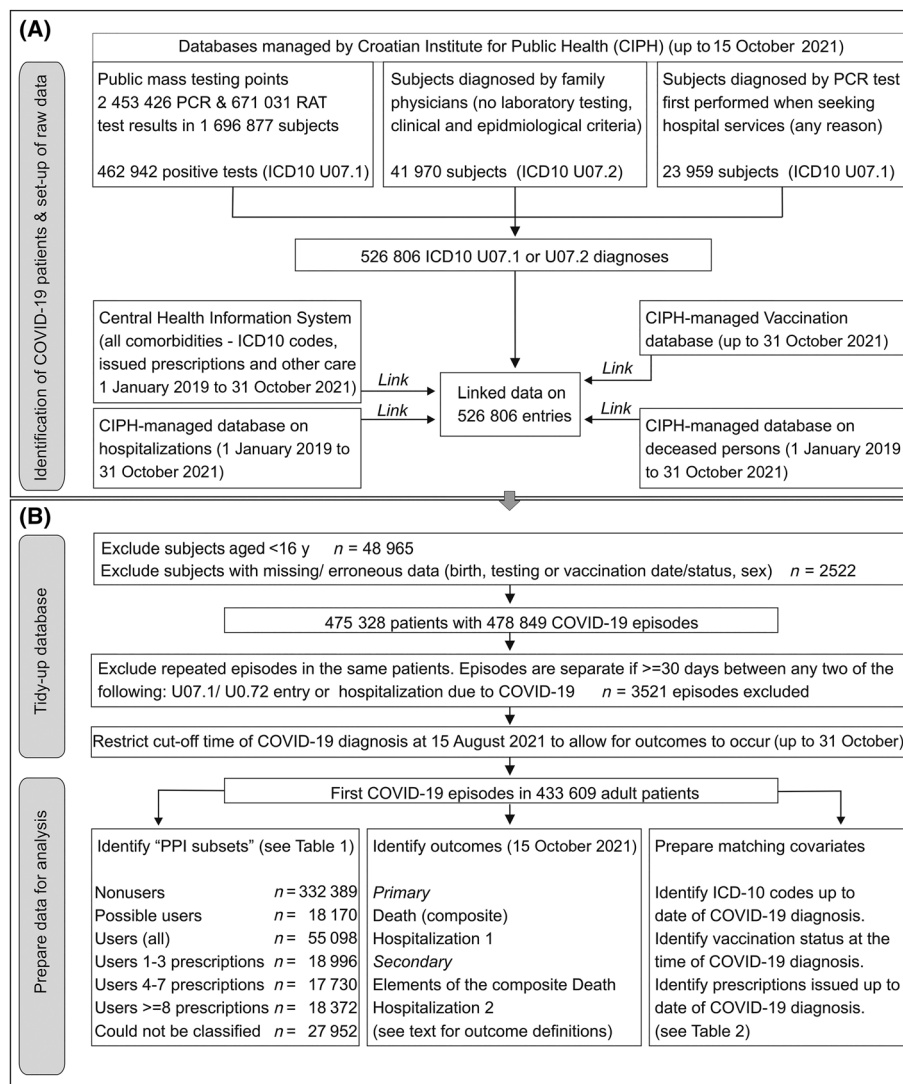


FIGURE 1 Data sources and curation (see text for details). (A) Raw data were prepared by the Croatian Institute for Public Health from several databases that it maintains. COVID-19 patients were identified based on positive polymerase chain reaction (PCR) or rapid antigen testing (RAT) performed at dedicated public testing points or hospitals (ICD-10 code U07.1) or based on epidemiological/clinical criteria (ICD-10 code U07.2), and individual data were linked to databases on vaccination, deceased persons, hospitalizations and Central Health Information System. (B) Anonymized data were tidied up by exclusion of subjects younger than 16 years and those with missing/erroneous entries on key variables. Also, repeated COVID-19 episodes were excluded, and cut-off date for index COVID-19 diagnosis was set at 15 August 2021. Based on International Classification of Disease version 10 (ICD-10) code entries, Anatomical Therapeutic Chemical (ATC) code entries and COVID-19 vaccination status between 1 January 2019 and date of COVID-19 diagnosis, subsets of patients in respect to exposure to proton-pump inhibitors (PPIs) and health/treatment data relevant for covariate matching were identified. Data on hospitalizations and registry of deceased persons up to 31 October 2021 were used to identify outcomes of interest for each subject.

time elapsed between the last vaccine administration and the index COVID-19 diagnosis (<14, 14–90 and >90 d).

2.6 | Outcomes

We defined 2 *primary outcomes*: *Death* as a composite of (i) death occurring after the index COVID-19 diagnosis with U07.1 or U07.2 as the cause of death, regardless of the time elapsed since the COVID-19 diagnosis (minimum follow-up window is 77 days for those diagnosed on 15 August 2021; Death 1); (ii) death in hospital, where hospitalization followed within 45 days since the index COVID-19 diagnosis with U07.1/U07.2 was the leading diagnosis, or within 30 days of the index COVID-19 diagnosis and U07.1/U07.2 were listed among discharge diagnoses (regardless of immediate cause of death or elapsed time; Death 2); or (iii) all-cause death within 14 days since the index COVID-19 diagnosis (Death 3); and *Hospitalization 1*, hospitalized within 45 days since the index COVID-19 diagnosis with U07.1/U07.2 as the leading diagnosis, or hospitalized within 30 days since the index COVID-19 diagnosis and U07.1/U07.2 is listed among diagnoses. We considered elements of the composite Death outcome and all-cause hospitalization within 14 days since the index COVID-19 diagnosis (*Hospitalization 2*) as secondary outcomes.

2.7 | Matching and data analysis

We implemented exact matching in package *MatchIt*²³ in R²⁴ with average treatment effect as the estimand. Two matched sets were generated for each contrast—one for *primary analysis* and 1 for a *sensitivity analysis* with some shared and some different covariates used for matching (Table 2). Matched data were analysed by fitting weighted generalized linear models (distribution = binary) with robust sandwich variance estimator to generate relative risks (RR; link = log) and risk differences (link = identity). To assess susceptibility of effects of PPI exposure to unmeasured confounding, we calculated E-values (package *Evalue* in R).²⁵ Confidence intervals were not adjusted for multiplicity—we considered this a more conservative approach in order not to miss possible untoward effects of exposure to PPIs. In a sensitivity analysis to account for potential misclassification of *possible users*, we applied exact (primary) matching between *users* and *unclassified* patients. Differences between *users* and *unclassified* patients were meta-analytically pooled with the differences between *users* and *possible users* to illustrate the effect of exposure to PPIs. We used random-effects pooling in package *meta*²⁶ in R.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org> and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.²⁷

TABLE 2 Covariates used for exact matching in primary and sensitivity analysis (see Appendix A for details: Table A1 for ATC codes of pharmacological treatments, Tables A2–A4 for ICD-10 codes of comorbidities, Section 3 and Section 4 on identification of immunocompromised patients and patients with diabetes)

Matching variables common for primary and sensitivity analysis		
Age	As 5-y bins between 16 and 111 y	
Sex	Male or female	
Vaccination status	Not vaccinated; received a single-dose vaccine (i) <14 d before diagnosis; (ii) 14–90 d before or (iii) >90 d before; received the first dose of a 2-dose vaccine (i) <14 d before; (ii) 14–90 d before or (iii) >90 d before; received the second dose of a 2-dose vaccine (i) <14 d before; (ii) 14–90 d before or (iii) >90 d before	
Time period	Up to 10 January 2020: still no vaccination, alpha strain(s) prevailing; 10 January to 15 July 2021: alpha strain(s) prevailing, mass vaccination in progress; after 15 July 2021: delta strain starts to prevail, mass vaccination in progress	
Comorbidities	Congestive heart failure; malignant disease; renal disease ^a	
Matching variables specific for primary and sensitivity analysis		
	Primary analysis	Sensitivity analysis
Comorbidities	Charlson comorbidity index with 4 levels: 0, 1–2, 3–4 or ≥5; and additionally: atrial fibrillation; autoimmune disease; chronic obstructive pulmonary disease; ischemic heart disease or cerebrovascular disease; immunocompromised status (by disease or pharmacologically)	Acute myocardial infarction; peripheral vascular disease; cerebrovascular disease; Alzheimer dementia; other dementia; mild liver disease; moderate to severe liver disease; diabetes without complications; diabetes with complications; metastatic cancer; human immunodeficiency virus infection/AIDS
Co-treatments	RAAS inhibitors (includes angiotensin converting enzyme inhibitors, AT1 receptor antagonists, aliskiren, mineralocorticoid receptor antagonists)	RAAS inhibitors, β-blockers, diuretics, systemic corticosteroids, other immunosuppressants, antineoplastic drugs, antivirals

ATC, anatomical, therapeutic and chemical classification; ICD, International Classification of Disease; RAAS, renin–angiotensin–aldosterone system.

^aRenal disease is included in Charlson comorbidity index (CCI) with extensive codes. In the primary analysis, matching based on CCI levels was supplemented also by exact matching in respect to chronic kidney disease (ICD-10 code N18) and dependence on renal dialysis (ICD-10 code Z99.2). In the sensitivity analysis, renal disease included all individual ICD-10 codes included in CCI.

3 | RESULTS

3.1 | Patients

Raw data (Figure 1A) pertained to 526 806 COVID-19 diagnoses (U07.1/U07.2) verified during the index period, eventually resulting in a dataset comprising first COVID-19 episodes in 433 609 adults diagnosed up to 15 August 2021 (Figure 1B): 332 389 qualified as PPI *nonusers*, 18 170 were *possible users*, and 55 098 qualified as *users*, while 27 952 (6.4%) could not be classified. The vast majority of the subjects were not even partially vaccinated (Table 3). Age, Charlson comorbidity index and prevalence of all individual comorbidities and treatments used for matching in the primary and sensitivity analysis were the lowest in *nonusers* (no PPI exposure, no respective conditions) and increased in *possible users* and *users* (overall; Table 3), as well as across subsets of *users* with increasing number of issued PPI prescriptions (Table 3). Identical pattern was seen regarding all outcomes (Table 4): mortality and hospitalizations were the lowest in *nonusers*, increased in *possible users* and *users*, and across subsets of *users* with increasing number of issued PPI prescriptions (Table 4).

Appendix B provides tabulated data on all covariates used in matching in all comparisons—before and after matching, as well as data on all outcomes (Tables B1–B9 for primary analysis; Tables B10–B18 for sensitivity analysis).

3.2 | Primary outcomes: Analysis in matched sets

Relative risks (RR) and absolute risk differences (RD) of *Death (composite)* were mildly higher in *possible users* and *users vs. nonusers* (Figure 2A), but in the comparison of *users (all)* to *possible users*, RR and RD were tightly around 1.0/0.0 or were <1.0/0.0 (Figure 2A), and there was no indication of a *dose* effect (Figure 2A).

RR and RD of *Hospitalization 1* were mildly higher in *possible users* and *users vs. nonusers* (Figure 2B), but in the comparison of *users (all)* to *possible users*, RR and RD were tightly around 1.0/0.0 (Figure 2B), and there was no indication of a *dose* effect (Figure 2B).

3.3 | Secondary outcomes: Analysis in matched sets

RR and RD of all secondary outcomes were mildly higher in *possible users* and *users vs. nonusers* (Figure 3A), but in the comparison of *users* to *possible users*, all RR and RD were tightly around 1.0/0.0 or were <1.0/0.0 (Figure 3A).

3.4 | Sensitivity analysis to account for a potential misclassification of possible users

Table B19 provides tabulated data before and after matching for *users* (all) vs. unclassified patients. In this comparison, RR for the primary

and secondary outcomes somewhat differed from those in the *users vs. possible users* comparison (Figure 3B). Due to this heterogeneity, pooled estimates of the *users vs. unclassified* and *users vs. possible users* RR were somewhat imprecise (wide confidence intervals), but also did not indicate any obvious/relevant effect of exposure to PPIs regarding any of the primary or secondary outcomes (Figure 3B).

4 | DISCUSSION

As recently reviewed,^{12–15} 3 out of many studies addressing potential effect of pre-morbid exposure to PPIs on the risk of unfavourable outcomes in COVID-19 patients were population based^{12,17–19} and thus devoid of biases common to studies restricted to hospitalized patients.¹⁶ The present population-based analysis was motivated primarily by their somewhat discrepant results, that is, increased risk of poorer outcomes (Korean study^{18,19}) or no increased risk (Danish study,¹² UK study¹⁷) in people issued prescriptions for PPIs shortly before the index COVID-19 diagnosis. Next, all 3 studies^{12,17–19} pertained to the period before vaccine availability, and vaccination could modify the relationship between any potential risk factor and course of the COVID-19 disease. We deemed that observations from different cultural and healthcare settings should contribute to the overall body of evidence on the topic.²⁸ In respect to the Danish¹² and Korean^{18,19} studies, the present analysis is limited in that we focused on relatively *crude* outcomes and did not pursue in detail the issue of a possibly dose-dependent effect of exposure to PPIs (suggested in the Korean study¹⁹). On the other hand, we believe that the strength of the present analysis is in the use of combined criteria of prescription (non)issuance and presence/history of conditions requiring PPI treatment to define patients *exposed* and *nonexposed* to the presumed risk factor, that is, treatment with PPIs shortly preceding the COVID-19 diagnosis. Consequently, naming of the patient subsets somewhat differed from the common classification into *current* and *never* users, and, although this might not be immediately intuitive, the comparison of primary interest was that between *users* (at least 1 PPI prescription within 90 days prior to the index COVID-19 episode,¹² suffer peptic acid disorders/exposure to NSAIDs) and *possible users* (no PPI/H₂ antagonist prescriptions within 12 months prior to the index COVID-19 episode, suffer peptic acid disorders/exposure to NSAIDs). We adopted this approach for several reasons. First, the addressed question is not relevant for all COVID-19 patients—focus is on those who, at this critical time preceding the COVID-19 diagnosis, suffer from conditions that need PPI treatment (should it be withheld/postponed?). Thus, both *exposed* (treated) and *nonexposed* (control) patients should come from this target population. In the present setting, this cannot be achieved when the 2 subsets are identified solely on prescription (non)issuance. Next, if latter is the case, confounding (by indication) is likely to occur and might not be controllable. *Current users* would be suffering from acid peptic disorders, while all or most of their *nonuser* controls would not: no exact matching in this respect would be feasible; there would be insufficient overlap between the subsets for any sensible regression modelling, including that for

TABLE 3 Subject characteristics (n, %) across subsets based on exposure to PPIs shortly preceding the index COVID-19 diagnosis (see Table 1 for definitions)

	Nonusers	Possible users	Users (all)	Users, 1-3	Users, 4-7	Users, ≥8
n	332 389	181 770	55 098	18 996	17 730	18 372
Age (y), mean ± SD (range)	44.7 ± 17.1 (16-108)	53.2 ± 17.9 (16-101)	61.6 ± 16.4 (16-103)	55.7 ± 16.8 (16-98)	62.8 ± 15.6 (16-100)	66.6 ± 14.8 (16-103)
Men	162 983 (49.0)	7582 (41.7)	22 645 (41.1)	7707 (40.6)	7472 (42.1)	7466 (40.6)
Vaccination status						
1/1, >90 d	2 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)
1/1, 14-90 d	47 (0.0)	1 (0.0)	12 (0.0)	2 (0.0)	2 (0.0)	8 (0.0)
1/1, <14 d	48 (0.0)	0 (0.0)	5 (0.0)	2 (0.0)	2 (0.0)	1 (0.0)
No vaccination	322 899 (97.1)	17 347 (95.5)	51 111 (92.8)	18 000 (94.8)	16 370 (92.3)	16 741 (91.1)
1/2, >90 d	35 (0.0)	7 (0.0)	22 (0.0)	7 (0.0)	8 (0.0)	7 (0.0)
1/2, 14-90 d	3549 (1.1)	295 (1.6)	1121 (2.0)	332 (1.7)	367 (2.1)	422 (2.3)
1/2, <14 d	3880 (1.2)	355 (2.0)	1791 (3.3)	431 (2.3)	621 (3.5)	739 (4.0)
2/2, >90 d	363 (0.1)	30 (0.2)	239 (0.4)	36 (0.2)	76 (0.4)	127 (0.7)
2/2, 14-90 d	420 (0.1)	44 (0.2)	242 (0.4)	56 (0.3)	89 (0.5)	97 (0.5)
2/2, <14 d	1146 (0.3)	91 (0.5)	553 (1.0)	129 (0.7)	194 (1.1)	230 (1.3)
Before 10 January 2021	192 599 (57.9)	10 566 (58.2)	32 317 (58.7)	10 627 (55.9)	10 501 (59.2)	11 189 (60.9)
10 January to 15 July 2021	132 866 (40.0)	7257 (39.9)	22 102 (40.1)	8105 (42.7)	7015 (39.6)	6982 (38.0)
After 15 July 2021	6924 (2.1)	347 (1.9)	679 (1.2)	264 (1.4)	214 (1.2)	201 (1.1)
Weighted Charlson index						
0	270 536 (81.4)	11 868 (65.3)	23 477 (42.6)	10 660 (56.1)	7204 (40.6)	5613 (30.6)
1-2	53 673 (16.1)	5248 (28.9)	21 575 (39.2)	6259 (32.9)	7253 (40.9)	8063 (43.9)
3-4	6652 (2.0)	845 (4.7)	7228 (13.1)	1527 (8.0)	2393 (13.5)	3308 (18.0)
≥5	1528 (0.5)	209 (1.2)	2818 (5.1)	550 (2.9)	880 (5.0)	1388 (7.6)
Atrial fibrillation	6300 (1.9)	661 (3.6)	5687 (10.3)	1163 (6.1)	1854 (10.5)	2670 (14.5)
Autoimmune diseases	19 580 (5.9)	2270 (12.5)	10 034 (18.2)	2987 (15.7)	3420 (19.3)	3627 (19.7)
Malignant diseases	10 142 (3.1)	978 (5.4)	6253 (11.3)	1873 (9.9)	2040 (11.5)	2340 (12.7)
Metastatic cancer	375 (0.1)	52 (0.3)	611 (1.1)	183 (1.0)	208 (1.2)	220 (1.2)
Congestive heart failure	3380 (1.0)	462 (2.5)	4234 (7.7)	783 (4.1)	1353 (7.6)	2098 (11.4)
COPD	21 520 (6.5)	1979 (10.9)	9700 (17.6)	2626 (13.8)	3152 (17.8)	3922 (21.3)
IHD or CVD	12 849 (3.9)	1518 (8.4)	11 683 (21.2)	2437 (12.8)	3861 (21.8)	5385 (29.3)
Acute myocardial infarct.	198 (1.1)	2103 (0.6)	2830 (5.1)	515 (2.7)	934 (5.3)	1381 (7.5)
Cerebrovascular disease	5189 (1.6)	604 (3.3)	4552 (8.3)	980 (5.2)	1451 (8.2)	2121 (11.5)
Renal disease (primary) ^a	1710 (0.5)	230 (1.3)	2580 (4.7)	409 (2.2)	864 (4.9)	1307 (7.1)

(Continues)

TABLE 3 (Continued)

	Nonusers	Possible users	Users (all)	Users, 1–3	Users, 4–7	Users, ≥8
Renal disease (sensitivity) ^a	1904 (0.6)	230 (1.3)	2580 (4.7)	409 (2.2)	864 (4.9)	1307 (7.1)
Immunocompromised	1463 (0.4)	132 (0.7)	1873 (3.4)	266 (1.4)	620 (3.5)	987 (5.4)
Peripheral vasc. disease	2579 (0.8)	301 (1.7)	2238 (4.1)	476 (2.5)	748 (4.2)	1014 (5.5)
Alzheimer dementia	2294 (0.7)	249 (1.4)	1540 (2.8)	266 (1.4)	461 (2.6)	813 (4.4)
Other dementia	21 520 (6.5)	1979 (10.9)	9700 (17.6)	2626 (13.8)	3152 (17.8)	3922 (21.3)
Mild liver disease	3363 (1.0)	340 (1.9)	1724 (3.1)	502 (2.6)	578 (3.3)	644 (3.5)
Moderate/severe liv. dis.	66 (0.0)	7 (0.0)	127 (0.2)	33 (0.2)	43 (0.2)	51 (0.3)
Diabetes w/o complic.	21 896 (6.6)	2449 (13.5)	11 803 (21.4)	2729 (14.4)	3888 (21.9)	5186 (28.2)
Diabetes with complic.	1735 (0.5)	202 (1.1)	1499 (2.7)	304 (1.6)	450 (2.5)	745 (4.1)
HIV/AIDS	21 (0.0)	1 (0.0)	8 (0.0)	2 (0.0)	4 (0.0)	2 (0.0)
RAAS inhibitors	43 193 (13.0)	4841 (26.6)	23 376 (42.4)	5450 (28.7)	7861 (44.3)	10 065 (54.8)
Beta blockers	22 235 (6.7)	2450 (13.5)	16 969 (30.8)	3309 (17.4)	5842 (32.9)	7818 (42.6)
Diuretics	14 387 (4.3)	1872 (10.3)	13 757 (25.0)	2567 (13.5)	4586 (25.9)	6604 (35.9)
Systemic corticosteroids	617 (0.2)	72 (0.4)	2535 (4.6)	539 (2.8)	920 (5.2)	1076 (5.9)
Other immunosuppress.	800 (0.2)	75 (0.4)	1454 (2.6)	203 (1.1)	560 (3.2)	691 (3.8)
Antineoplastic drugs	1241 (0.4)	118 (0.6)	975 (1.8)	233 (1.2)	337 (1.9)	405 (2.2)
Antiviral agents	215 (0.1)	16 (0.1)	417 (0.8)	80 (0.4)	150 (0.8)	187 (1.0)

Shown are all covariates used in primary and sensitivity matching (see Table 2). Vaccination status refers to number of doses received/number for full vaccination and time since the last vaccine dose. COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IHD, ischaemic heart disease; RAAS, any of the inhibitors of the renin-angiotensin-aldosterone system.

^aSee footnote to Table 2 for renal disease in primary and sensitivity analysis.

TABLE 4 Crude incidence (n, %) of primary and secondary outcomes across patient subsets based on exposure to PPIs shortly preceding the index COVID-19 diagnosis (see Table 1 for definitions)

	Nonusers	Possible users	Users (all)	Users, 1–3	Users, 4–7	Users, ≥8
n	332 389	18 170	55 098	18 996	17 730	18 372
Death (composite)	5594 (1.7)	801 (4.4)	4375 (7.9)	1064 (5.6)	1392 (7.9)	1889 (10.3)
Hospitalization 1	10 905 (3.3)	1160 (6.4)	5824 (10.6)	1646 (8.8)	1830 (10.3)	2348 (12.8)
Death 1	4321 (1.3)	581 (3.2)	3196 (5.8)	760 (4.0)	1028 (5.8)	1415 (7.7)
Death 2	3656 (1.1)	527 (2.9)	2865 (5.2)	703 (3.7)	922 (5.2)	1213 (5.2)
Death 3	4653 (1.4)	672 (3.7)	3692 (6.7)	893 (4.7)	1170 (6.6)	1598 (8.7)
Hospitalization 2	26 924 (8.1)	2671 (14.7)	12 728 (23.1)	3628 (19.1)	4096 (23.1)	5016 (27.3)

Death (composite)—composite of Death 1 (death occurring after the index COVID-19 diagnosis with U07.1 or U07.2 as a cause of death, regardless of elapsed time); Death 2 (death in hospital, where hospitalization followed within 45 d since the index COVID-19 diagnosis with U07.1/U07.2 as the leading diagnosis, or within 30 d since the index COVID-19 diagnosis and U07.1/U07.2 are listed among diagnoses, regardless of the immediate cause of death or elapsed time); and Death 3 (all-cause death within 14 d since the index COVID-19 diagnosis); Hospitalization 1 (hospitalization within 45 d since the index COVID-19 diagnosis with U07.1/U07.2 as the leading diagnosis, or within 30 d since the index COVID-19 diagnosis and U07.1/U07.2 are listed among diagnoses); Hospitalization 2 (all-cause hospitalization within 14 d since the index COVID-19 diagnosis).

calculation of a propensity score—weighted or matched (on propensity score) *exposed* and *nonexposed* subjects would still differ in this respect.^{20,29}

It is not medically implausible to consider that peptic acid disorders could be proxies (or descendants) of unmeasured confounders or that they could on their own impact the course of the COVID-19 disease. The present data support such a view: crude incidence of all outcomes was higher in older and more comorbid *possible users* than in *nonusers* (no PPI/H₂ prescriptions and no conditions requiring anti-secretory treatment within 14 months prior to the index COVID-19 episode; Tables 3 and 4), and the difference was still present after matching (primary, sensitivity) on a range of covariates (Figures 2 and 3). Similarly, the suggested dose-dependent effect of PPI exposure with propensity-score matched *current* and *never* PPI users¹⁹ might be largely due to confounding by indication. Odds ratio for a composite of hypoxaemia, intensive care admission, invasive ventilation or death for *current users* prescribed with once-daily PPIs within 30 days prior to the index COVID-19 diagnosis vs. *never users* was 1.49 (0.87–2.50), and it was 2.36 (1.08–5.10) if *current users* were prescribed with twice-daily PPIs.¹⁹ It is not unreasonable to assume that the observed could have been largely due to the fact that *twice-daily users* suffered more severe peptic acid disorders than those with once-daily prescriptions (while *never users* suffered no such conditions).

A small confounder effect (e.g. due to bias by indication) of only RR = 1.33 would suffice to largely explain away the observed effect (e.g. move the lower limit of confidence interval to 0.95).²⁵ To the extent to which *intensity* of issued prescriptions over a 12-month period preceding the COVID-19 diagnosis is indicative of a *PPI burden*, present data support such a view: (i) crude incidence of all outcomes was progressively higher in *users* with increasing number of issued prescriptions vs. *nonusers*, and less so vs. *possible users* (Table 4); and (ii) after matching, the risk of death (composite) or hospitalization was mildly higher in *users* vs. *nonusers*, but similarly across subsets with increasing numbers of issued prescriptions (Figure 3), while all RR for *users* vs. *possible users* were closely around 1.0 (Figure 3). Finally, when

exposed and *nonexposed* are (in the present setting) identified only based on prescription issuance, an attempt to control for (underlying) peptic acid disorders (e.g. by their inclusion in propensity score calculation) might not only fail to reduce bias, but might worsen it: peptic acid disorders are the main driver for PPI prescription issuance; if they have no impact (or have a very weak impact) on the outcome (apart from that exerted *through* the impact on PPI treatment), then they qualify as instrumental (or near-instrumental) variables—conditioning on them introduces new or amplifies existing bias.^{30,31} Overall, with the method used for patient subsets definition and with exact matching on 2 comprehensive sets of relevant covariates (taking care to avoid post-baseline variables), we believe that we achieved a reasonable control of confounding. Under these conditions, all comparisons between *users* and *possible users* yielded relative risks for all outcomes that were consistently closely around or lower than unity thus strongly indicating no untoward effect of exposure to PPIs shortly preceding COVID-19 diagnosis on subsequent mortality and hospitalizations.

We used routinely collected administrative data and not a dedicated preplanned database; hence, some inaccuracies in identification of exposures, comorbidities and outcomes cannot be excluded. In this respect, the following is of notion: (i) although data originated from databases regularly maintained by professional organizations (CIPH), we re-checked them using entries on key variables such as dates of birth, sex, vaccination status, dates of COVID-19 test/test results or diagnosis as proxies—only 0.47% of the original entries had missing/erroneous entries, suggesting that inaccuracies/chance errors were sporadic; and (ii) in the national system, prescriptions are issued exclusively within the primary healthcare network, and each prescription bears an ATC code/ICD-10 code. Moreover, for specialist consultations and work-up, patients need to be referred by the primary healthcare physicians who need to record the feedback information. All such activities are automatically entered into the Central Health Information System (CEZIH). We left a period of a minimum 14 months (from 1 January 2019 to the first COVID-19

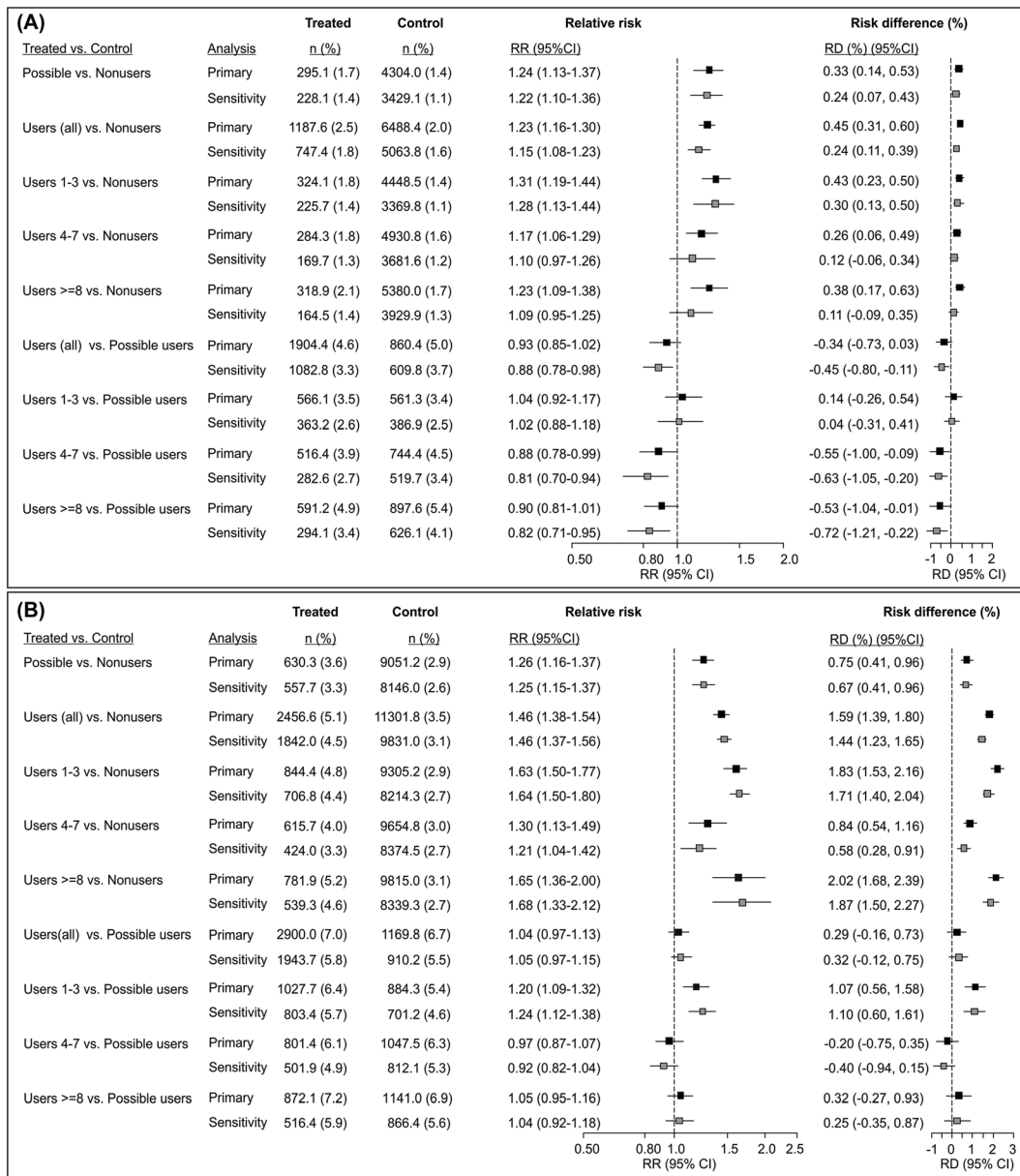


FIGURE 2 Analysis of the primary outcomes in matched sets: (a) death (composite) and (b) hospitalization 1 (see Methods for outcome definitions). Contrasts between different patient subsets defined in respect to exposure to proton-pump inhibitors (PPIs) and burden of diseases requiring anti-secretory treatments (*nonusers*, *possible users* and *users* with different numbers of issued prescriptions [1–3, 4–7 or ≥8]) inform on different effects (elaborated in Table 1)—the contrast between *users* and *possible users* is the 1 most informative about the potential effect of exposure to PPIs. Data are weighted counts (%) from matched sets in primary and sensitivity analysis (matching variables are elaborated in Table 2). The numbers of exactly matched patients were (for contrasts displayed from top to bottom): *possible users* vs. *nonusers* 17 466–316 168 in the primary and 16 795–307 785 in the sensitivity analysis; *users* (all) vs. *nonusers* 48 453–325 005 in the primary and 40 653–317 678 in the sensitivity analysis; *users* with 1–3 prescriptions vs. *nonusers* 17 734–318 312 in the primary and 16 157–308 555 in the sensitivity analysis; *users* with 4–7 prescriptions vs. *nonusers* 15 569–316 577 in primary and 12 812–306 627 in the sensitivity analysis; *users* with ≥8 prescriptions vs. *nonusers* 15 150–313 399 in the primary and 11 684–303 530 in the sensitivity analysis; *users* (all) vs. *possible users* 41 195–17 334 in the primary and 33 272–16 343 in the sensitivity analysis; *users* with 1–3 prescriptions vs. *possible users* 15 998–16 517 in the primary and 14 205–15 405 in the sensitivity analysis; *users* with 4–7 prescriptions vs. *possible users* 13 115–16 594 in the primary and 10 315–15 414 in the sensitivity analysis; *users* with ≥8 prescriptions vs. *possible users* 12 082–16 564 in the primary and 8752–15 337 in the sensitivity analysis. Differences are expressed as relative risks (RR) and as absolute risk (percentage) differences (RD). Estimates (confidence intervals, CI) based on matched data were generated in generalized linear models with robust sandwich variance estimation. Confidence intervals were not adjusted for multiplicity.

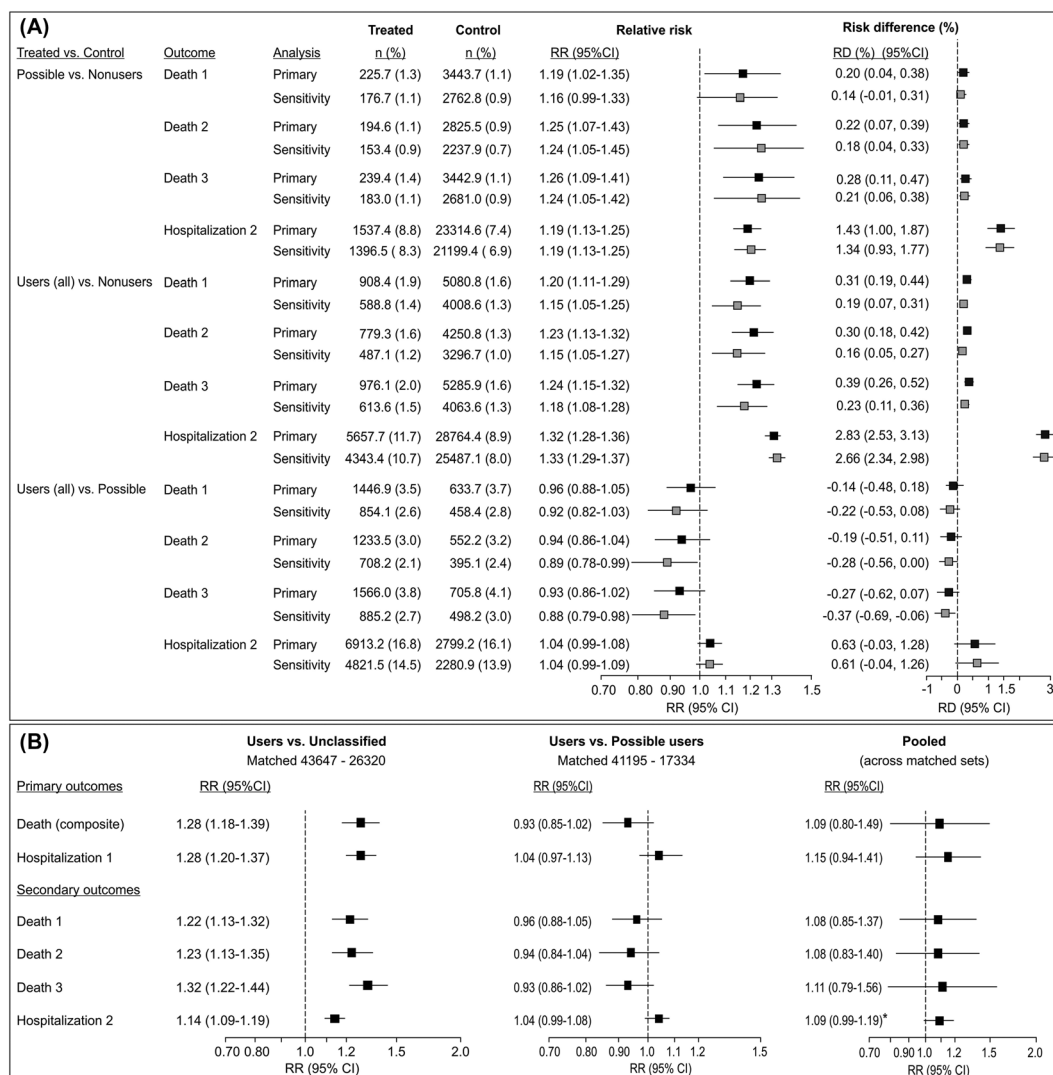


FIGURE 3 (A) Analysis of the secondary outcomes in matched sets (see Methods for outcome definitions). Contrasts between different patient subsets defined in respect to exposure to proton-pump inhibitors (PPIs) and burden of diseases requiring anti-secretory treatments (*nonusers*, *possible users* and *users*) inform on different effects (elaborated in Table 1)—the contrast between *users* and *possible users* is the most informative about the potential effect of exposure to PPIs. Data are weighted counts (%) from matched sets in primary and sensitivity analysis (matching variables are elaborated in Table 2). The numbers of exactly matched patients in subset-to-subset comparisons are depicted in footnote to Figure 2. Differences are expressed as relative risks (RR) and as absolute risk (percentage) differences (RD). Estimates (confidence intervals, CI) based on matched data were generated in generalized linear models with robust sandwich variance estimation. B. Differences (as relative risks) between *users* and *unclassified* patients in exactly matched subsets (as for the primary analysis, see Table 2 for covariates) along with differences between *users* and *possible users* in respect to primary and secondary outcomes (see Methods for outcome definitions). Pooled estimates were generated by random-effects pooling (restricted maximum likelihood variance estimator) of the 2 estimates. Confidence intervals were not adjusted for multiplicity. *Numerically, this estimate indicated a trend towards a mildly higher risk in *users*, but already a mild effect (RR = 1.25) of unmeasured (and, actually, unknown) confounding would suffice to push the point estimate to 1.04 and lower limit of the CI to 0.95.

case in February 2020) to precede the index COVID-19 diagnosis not to miss entries related to comorbidities that did not require recent prescriptions or other medical procedures. Hence, it is likely that no relevant comorbidity or treatment was missed; (iii) having in mind clinical effectiveness of the on-demand PPI use,³² we considered that at least 1 prescription for a 30-tablet pack within 90 days prior to the index COVID-19 diagnosis indicated exposure¹² in the sense of a reduced gastric acidity at the time of SARS-CoV-2 virus

infection; and (iv) outcomes were defined in respect to medical relevance, but also in respect to probability of not remaining unrecorded/erroneously recorded, and we left a reasonable period of observation for outcomes to occur (a minimum of 77 days for subjects diagnosed with COVID-19 on 15 August 2021). The observed crude incidence of hospitalizations subsequent to the index COVID-19 diagnosis across the patient subsets were in line with published expected probabilities of hospitalization for people of similar age

and comorbidity diagnosed with COVID-19,^{33,34} thus providing a form of external validation of the present data. The overall crude mortality (all subsets and unclassified patients) of 3.0% is in line with the ratio of cumulative COVID-19-confirmed deaths and COVID-19 confirmed cases in Croatia up to 31 October 2021.³⁵ Overall, it seems plausible to consider that we reasonably accurately captured relevant exposures, confounders and outcomes and that inaccuracies/missing data were minor and not prejudiced in respect to the exposure and outcomes of interest.

In conclusion, in the present population-based matched cohort study, we observed no signal that people prescribed with PPIs shortly preceding the COVID-19 diagnosis are at increased risk of subsequent mortality or hospitalizations compared to their nonprescribed peers.

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COMPETING INTERESTS

Authors declare that they have no financial or nonfinancial conflict of interest.

CONTRIBUTORS

Ivan Kodvanj, Jan Homolak and Vladimir Trkulja conceived and designed the study. Material preparation, data collection and analysis were performed by Ivan Kodvanj and Vladimir Trkulja. The first draft was written by Ivan Kodvanj and Vladimir Trkulja. All authors commented on previous versions of the manuscripts, read and approved the final version.

DATA AVAILABILITY STATEMENT

Data can be obtained upon a reasonable request directly from the CIPH.

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APPENDIX A

A.1 | Lists of ATC codes and ICD-10 codes used to identify exposure to pharmacological treatments and comorbidities

A.1.1 | Identification of drug prescriptions

TABLE A1 ATC codes used for identification of prescribed drugs (issued prescriptions)

Drug	ATC ^a
Proton-pump inhibitors	A02BC
H2-receptor inhibitors	A02BA
Oral antidiabetic drugs	A10B
Insulin	A10A
Anticoagulants	BO1AA, B01AB, B01AE, B01AF
RAAS inhibitors	C09
Beta blocking agents	C07
Diuretics	C03, C07B, C07C, C09DA, C09DX01, C09DX03
Systemic corticosteroids	H02
Antivirals	J05A
Antineoplastic agents	L01, L02, L03
Immunosuppressants	L04
NSAID	M01A

^aIncludes all children codes.

A.1.2 | Identification of comorbidities

TABLE A2 Charlson comorbidity index codes

Charlson comorbidity components	ICD10 codes ^a
Myocardial infarction	I21, I22, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45, G46, H34.0, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69
Dementia	F00, F01, F02, F03, F05.1, G30, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68.4, J70.1, J70.3
Rheumatic disease	M05, M06, M31.5, M32, M33, M34, M35.1, M35.3, M36.0
Peptic ulcer disease	K25, K26, K27, K28

(Continues)

TABLE A2 (Continued)

Charlson comorbidity components	ICD10 codes ^a
Mild liver disease	B18, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.7, K73, K74, K76.0, K76.2, K76.3, K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	E10.2, E10.3, E10.4, E10.5, E10.7, E11.2, E11.3, E11.4, E11.5, E11.7, E12.2, E12.3, E12.4, E12.5, E12.7, E13.2, E13.3, E13.4, E13.5, E13.7, E14.2, E14.3, E14.4, E14.5, E14.7
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0, G83.1, G83.2, G83.3, G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N18, N19, N25.0, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2
Malignancy	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumour	C77, C78, C79, C80
AIDS	B20, B21, B22, B24

^aAll subcodes are included when subcode is not specified.

TABLE A3 Weights used for calculation of the Charlson comorbidity index

Charlson comorbidity components	Weights
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatic disease	1

TABLE A3 (Continued)

Charlson comorbidity components	Weights
Peptic ulcer disease	1
Mild liver disease	1
Diabetes without chronic complications	1
Diabetes with chronic complications	2
Hemiplegia or paraplegia	2
Renal disease	2
Malignancy	2
Moderate or severe liver disease	3
Metastatic solid tumour	6
AIDS	6

TABLE A4 Additional comorbidities (ICD10 codes) used for matching

Covariates for matching	ICD10 codes ^a
Atrial fibrillation or undulation	I48
Autoimmune diseases	D86, G35, K50, K52, K73, K74.3, K90.0, L10, L40, L93, L94, M05, M06, M07, M08, M09, M30, M32, M33, M34, M35, M36, M45, M51, N00, N01, N03, N04, N05
Cancer	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Chronic obstructive pulmonary disease, asthma, pneumoconiosis	I27.8, I27.9, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68.4, J70.1, J70.3
Ischaemic or cerebrovascular disease	G45, G46, H34.0, I20, I21, I22, I23, I24, I25, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69
Renal disease	N18, Z99.2

^aAll subcodes are included when subcode is not specified.

A.1.3 | Identification of immunocompromised patients

Patients were considered immunocompromised when meeting any of the following: (i) were diagnosed with HIV/AIDS (ICD10 codes: B20, B21, B22, B24); (ii) within 12 months before COVID-19 diagnoses were issued at least 6 prescriptions for antineoplastic drugs, at least 9 prescriptions for immunosuppressive drugs or at least 9 prescriptions for systemic corticosteroids; (iv) received solid organ or stem cells transplants (ICD codes: Z94.0, Z94.1, Z94.2, Z94.3, Z94.4, Z94.6, Z94.8); (v) were maintained on dialysis (ICD10 codes found in primary care records or in hospital records: N18.5, Z99.2); (vi) where hospitalized due to cancer (ICD10 codes for cancer used for Charlson comorbidity index in hospital records); or (vii) had any of the following diagnoses: D45, D46, D47. Exact codes used to detect prescriptions

of antineoplastic, immunosuppressive and systemic corticosteroid drugs are displayed in Table 1.

A.1.4 | Identifications of patients suffering from diabetes

Due to specific rules related to diagnosing diabetes mellitus (DM), patients were assigned diagnosis of diabetes (only) when undergoing measurement of HbA1c. We considered that a patient suffered from diabetes any of the following was met: (i) At least 2 entries of DM diagnosis could be identified between 1 January 2019 and the index COVID-19 diagnosis; or (ii) 1 entry of DM diagnosis was identified over the designated period and at least 1 prescription was issued for either insulin preparations or for oral antidiabetics (for ATC codes, see Table 1).

APPENDIX B

B.1 | Tabulated data on covariates used for matching in comparisons between patient subsets—before matching (counts, [%]) and after matching (weighted counts [%]), with standardized mean differences (d)

B.1.1 | Primary analysis

TABLE B1 Primary analysis: possible users vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 170	332 389		17 466	316 168	
Age (5-y bins)						
16–21	540 (3.0)	22 054 (6.6)	−0.172	1166.6 (6.7)	21 117.4 (6.7)	0.000
21–26	759 (4.2)	27 711 (8.3)	−0.172	1468.3 (8.4)	26 578.7 (8.4)	0.000
26–31	981 (5.4)	31 607 (9.5)	−0.157	1673.8 (9.6)	30 298.2 (9.6)	0.000
31–36	1142 (6.3)	34 524 (10.4)	−0.149	1839.2 (10.5)	33 292.8 (10.5)	0.000
36–41	1425 (7.8)	37 047 (11.1)	−0.113	1973.8 (11.3)	35 729.2 (11.3)	0.000
41–46	1644 (9.0)	35 359 (10.6)	−0.053	1899.7 (10.9)	34 388.3 (10.9)	0.000
46–51	1775 (9.8)	30 711 (9.2)	0.018	1656.3 (9.5)	29 982.7 (9.5)	0.000
51–56	1833 (10.1)	28 177 (8.5)	0.056	1517.0 (8.7)	27 461.0 (8.7)	0.000
56–61	1886 (10.4)	25 009 (7.5)	0.100	1344.4 (7.7)	24 335.6 (7.7)	0.000
61–66	1664 (9.2)	19 809 (6.0)	0.121	1046.0 (6.0)	18 934.0 (6.0)	0.000
66–71	1332 (7.3)	14 082 (4.2)	0.133	708.9 (4.1)	12 833.1 (4.1)	0.000
71–76	1010 (5.6)	9476 (2.9)	0.135	449.6 (2.6)	8139.4 (2.6)	0.000
76–81	831 (4.6)	6813 (2.0)	0.141	308.2 (1.8)	5578.8 (1.8)	0.000
81–86	755 (4.2)	5529 (1.7)	0.149	246.5 (1.4)	4462.5 (1.4)	0.000
86–91	430 (2.4)	3158 (1.0)	0.111	126.6 (0.7)	2292.4 (0.7)	0.000
91–96	135 (0.7)	1101 (0.3)	0.056	36.1 (0.2)	652.9 (0.2)	0.000
96–101	28 (0.2)	214 (0.1)	0.027	5.0 (0.0)	91.0 (0.0)	0.000

(Continues)

TABLE B1 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
101–106	0 (0.0)	7 (0.0)	−0.006	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7582 (41.7)	162 983 (49.0)	−0.147	8457.4 (48.4)	153 095.6 (48.4)	0.000
F	10 588 (58.3)	169 406 (51.0)	0.147	9008.6 (51.6)	163 072.4 (51.6)	0.000
Vaccination status						
1/1, >90 d	0 (0.0)	2 (0.0)	−0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	1 (0.0)	47 (0.0)	−0.009	0.1 (0.0)	1.9 (0.0)	0.000
1/1, 14–90 d	0 (0.0)	48 (0.0)	−0.017	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	17 347 (95.5)	322 899 (97.1)	−0.089	17189.8 (98.4)	311168.2 (98.4)	0.000
1/2, >90 d	7 (0.0)	35 (0.0)	0.018	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	295 (1.6)	3549 (1.1)	0.048	129.1 (0.7)	2337.9 (0.7)	0.000
1/2, 14–90 d	355 (2.0)	3880 (1.2)	0.063	124.1 (0.7)	2246.9 (0.7)	0.000
2/2, >90 d	30 (0.2)	363 (0.1)	0.015	1.2 (0.0)	21.8 (0.0)	0.000
2/2, <14 d	44 (0.2)	420 (0.1)	0.027	5.1 (0.0)	91.9 (0.0)	0.000
2/2, 14–90 d	91 (0.5)	1146 (0.3)	0.024	16.5 (0.1)	299.5 (0.1)	0.000
Period						
Before 10.01.2021	10 566 (58.2)	192 599 (57.9)	0.004	10304.3 (59.0)	186527.7 (59.0)	0.000
10.01.2021 to 15.07.2021	7257 (39.9)	132 866 (40.0)	−0.001	6866.2 (39.3)	124290.8 (39.3)	0.000
After 15.07.2021	347 (1.9)	6924 (2.1)	−0.012	295.5 (1.7)	5349.5 (1.7)	0.000
CC index						
0	11 868 (65.3)	270 536 (81.4)	−0.370	14588.9 (83.5)	264086.1 (83.5)	0.000
1–2	5248 (28.9)	53 673 (16.1)	0.309	2703.1 (15.5)	48931.9 (15.5)	0.000
3–4	845 (4.7)	6652 (2.0)	0.148	162.2 (0.9)	2935.8 (0.9)	0.000
≥5	209 (1.2)	1528 (0.5)	0.077	11.8 (0.1)	214.2 (0.1)	0.000
Comorbidities						
Atrial fibrillation	661 (3.6)	6300 (1.9)	0.106	160.6 (0.9)	2906.4 (0.9)	0.000
Autoimmune	2270 (12.5)	19 580 (5.9)	0.230	943.2 (5.4)	17073.8 (5.4)	0.000
Cancer	978 (5.4)	10 142 (3.1)	0.116	376.0 (2.2)	6806.0 (2.2)	0.000
Congestive heart failure	462 (2.5)	3380 (1.0)	0.116	59.1 (0.3)	1069.9 (0.3)	0.000
COPD	1979 (10.9)	21 520 (6.5)	0.157	1025.0 (5.9)	18554.0 (5.9)	0.000
IHD or CVD	1518 (8.4)	12 849 (3.9)	0.188	476.8 (2.7)	8631.2 (2.7)	0.000
Renal disease	230 (1.3)	1710 (0.5)	0.080	19.2 (0.1)	347.8 (0.1)	0.000
Immunocompromised	132 (0.7)	1463 (0.4)	0.038	19.3 (0.1)	349.7 (0.1)	0.000
RAAS inhibitors	4841 (26.6)	43 193 (13.0)	0.348	2144.4 (12.3)	38818.6 (12.3)	0.000
Death (composite)	803 (4.4)	5599 (1.7)	0.160	295.1 (1.7)	4304.0 (1.4)	0.019
Death 1	585 (3.2)	4366 (1.3)	0.128	225.7 (1.3)	3443.7 (1.1)	0.014
Death 2	519 (2.9)	3698 (1.1)	0.125	194.6 (1.1)	2825.5 (0.9)	0.016
Death 3	666 (3.7)	4519 (1.4)	0.148	239.4 (1.4)	3442.9 (1.1)	0.018
Hospitalization 1	1160 (6.4)	10 905 (3.3)	0.145	630.3 (3.6)	9051.2 (2.9)	0.035
Hospitalization 2	2680 (14.7)	26 965 (8.1)	0.210	1537.4 (8.8)	23314.6 (7.4)	0.045

TABLE B2 Primary analysis: users (all) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	55 098	332 389		48 453	325 005	
Age (5-y bins)						
16–21	401 (0.7)	22 054 (6.6)	−0.318	2873.1 (5.9)	19271.9 (5.9)	0.000
21–26	782 (1.4)	27 711 (8.3)	−0.325	3655.7 (7.5)	24521.3 (7.5)	0.000
26–31	1137 (2.1)	31 607 (9.5)	−0.323	4193.2 (8.7)	28126.8 (8.7)	0.000
31–36	1703 (3.1)	34 524 (10.4)	−0.294	4647.1 (9.6)	31170.9 (9.6)	0.000
36–41	2571 (4.7)	37 047 (11.1)	−0.242	5085.9 (10.5)	34114.1 (10.5)	0.000
41–46	3335 (6.1)	35 359 (10.6)	−0.166	4952.6 (10.2)	33220.4 (10.2)	0.000
46–51	4243 (7.7)	30 711 (9.2)	−0.055	4453.1 (9.2)	29869.9 (9.2)	0.000
51–56	5301 (9.6)	28 177 (8.5)	0.040	4244.9 (8.8)	28473.1 (8.8)	0.000
56–61	6107 (11.1)	25 009 (7.5)	0.123	3909.8 (8.1)	26225.2 (8.1)	0.000
61–66	6560 (11.9)	19 809 (6.0)	0.210	3256.6 (6.7)	21844.4 (6.7)	0.000
66–71	6134 (11.1)	14 082 (4.2)	0.261	2429.8 (5.0)	16298.2 (5.0)	0.000
71–76	5050 (9.2)	9476 (2.9)	0.268	1677.2 (3.5)	11249.8 (3.5)	0.000
76–81	4480 (8.1)	6813 (2.0)	0.279	1261.9 (2.6)	8464.1 (2.6)	0.000
81–86	4104 (7.4)	5529 (1.7)	0.280	1046.6 (2.2)	7020.4 (2.2)	0.000
86–91	2400 (4.4)	3158 (1.0)	0.213	579.9 (1.2)	3890.1 (1.2)	0.000
91–96	693 (1.3)	1101 (0.3)	0.105	163.1 (0.3)	1093.9 (0.3)	0.000
96–101	95 (0.2)	214 (0.1)	0.031	22.4 (0.0)	150.6 (0.0)	0.000
101–106	2 (0.0)	7 (0.0)	0.003	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	22 645 (41.1)	162 983 (49.0)	−0.160	23137.4 (47.8)	155197.6 (47.8)	0.000
F	32 453 (58.9)	169 406 (51.0)	0.160	25315.6 (52.2)	169807.4 (52.2)	0.000
Vaccination status						
1/1, >90 d	2 (0.0)	2 (0.0)	0.007	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	12 (0.0)	47 (0.0)	0.006	0.4 (0.0)	2.6 (0.0)	0.000
1/1, 14–90 d	5 (0.0)	48 (0.0)	−0.005	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	51 111 (92.8)	322 899 (97.1)	−0.201	47362.7 (97.7)	317691.3 (97.7)	0.000
1/2, >90 d	22 (0.0)	35 (0.0)	0.019	0.3 (0.0)	1.7 (0.0)	0.000
1/2, <14 d	1121 (2.0)	3549 (1.1)	0.078	446.7 (0.9)	2996.3 (0.9)	0.000
1/2, 14–90 d	1791 (3.3)	3880 (1.2)	0.142	527.3 (1.1)	3536.7 (1.1)	0.000
2/2, >90 d	239 (0.4)	363 (0.1)	0.062	14.4 (0.0)	96.6 (0.0)	0.000
2/2, <14 d	242 (0.4)	420 (0.1)	0.059	25.9 (0.1)	174.1 (0.1)	0.000
2/2, 14–90 d	553 (1.0)	1146 (0.3)	0.081	75.4 (0.2)	505.6 (0.2)	0.000
Period						
Before 10.01.2021	32 317 (58.7)	192 599 (57.9)	0.014	28551.6 (58.9)	191513.4 (58.9)	0.000
10.01.2021 to 15.07.2021.	22 102 (40.1)	132 866 (40.0)	0.003	19136.9 (39.5)	128363.1 (39.5)	0.000
After 15.07.2021	679 (1.2)	6924 (2.1)	−0.067	764.6 (1.6)	5128.4 (1.6)	0.000
CC index						
0	23 477 (42.6)	270 536 (81.4)	−0.872	37855.7 (78.1)	253922.3 (78.1)	0.000
1–2	21 575 (39.2)	53 673 (16.1)	0.532	9159.4 (18.9)	61437.6 (18.9)	0.000
3–4	7228 (13.1)	6652 (2.0)	0.430	1237.2 (2.6)	8298.8 (2.6)	0.000
≥5	2818 (5.1)	1528 (0.5)	0.286	200.7 (0.4)	1346.3 (0.4)	0.000

(Continues)

TABLE B2 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Comorbidities						
Atrial fibrillation	5687 (10.3)	6300 (1.9)	0.357	1056.1 (2.2)	7083.9 (2.2)	0.000
Autoimmune	10 034 (18.2)	19 580 (5.9)	0.385	3301.9 (6.8)	22148.1 (6.8)	0.000
Cancer	6253 (11.3)	10 142 (3.1)	0.325	1648.1 (3.4)	11054.9 (3.4)	0.000
Congestive heart failure	4234 (7.7)	3380 (1.0)	0.331	559.1 (1.2)	3749.9 (1.2)	0.000
COPD	9700 (17.6)	21 520 (6.5)	0.347	3502.0 (7.2)	23490.0 (7.2)	0.000
IHD or CVD	11 683 (21.2)	12 849 (3.9)	0.543	2520.1 (5.2)	16903.9 (5.2)	0.000
Renal disease	2580 (4.7)	1710 (0.5)	0.264	209.3 (0.4)	1403.7 (0.4)	0.000
Immunocompromised	1873 (3.4)	1463 (0.4)	0.217	194.1 (0.4)	1301.9 (0.4)	0.000
RAAS inhibitors	23 376 (42.4)	43 193 (13.0)	0.696	7816.4 (16.1)	52429.6 (16.1)	0.000
Death (composite)	4356 (7.9)	5599 (1.7)	0.294	1187.6 (2.5)	6488.4 (2.0)	0.022
Death 1	3195 (5.8)	4366 (1.3)	0.244	908.4 (1.9)	5080.8 (1.6)	0.017
Death 2	2839 (5.2)	3698 (1.1)	0.234	779.3 (1.6)	4250.8 (1.3)	0.017
Death 3	3670 (6.7)	4519 (1.4)	0.273	976.1 (2.0)	5285.9 (1.6)	0.020
Hospitalization 1	5824 (10.6)	10 905 (3.3)	0.290	2456.6 (5.1)	11301.8 (3.5)	0.063
Hospitalization 2	12 735 (23.1)	26 965 (8.1)	0.422	5657.7 (11.7)	28764.4 (8.9)	0.080

TABLE B3 Primary analysis: users (1–3 prescriptions) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 996	332 389		17 734	318 312	
Age (5-y bins)						
16–21	305 (1.6)	22 054 (6.6)	−0.255	1162.6 (6.6)	20868.4 (6.6)	0.000
21–26	515 (2.7)	27 711 (8.3)	−0.248	1469.2 (8.3)	26371.8 (8.3)	0.000
26–31	726 (3.8)	31 607 (9.5)	−0.230	1678.0 (9.5)	30119.0 (9.5)	0.000
31–36	1002 (5.3)	34 524 (10.4)	−0.191	1849.8 (10.4)	33202.2 (10.4)	0.000
36–41	1378 (7.3)	37 047 (11.1)	−0.135	2000.5 (11.3)	35907.5 (11.3)	0.000
41–46	1596 (8.4)	35 359 (10.6)	−0.076	1915.7 (10.8)	34385.3 (10.8)	0.000
46–51	1825 (9.6)	30 711 (9.2)	0.013	1677.6 (9.5)	30111.4 (9.5)	0.000
51–56	2101 (11.1)	28 177 (8.5)	0.087	1548.4 (8.7)	27792.6 (8.7)	0.000
56–61	2099 (11.0)	25 009 (7.5)	0.122	1370.9 (7.7)	24606.1 (7.7)	0.000
61–66	2054 (10.8)	19 809 (6.0)	0.176	1082.7 (6.1)	19434.3 (6.1)	0.000
66–71	1680 (8.8)	14 082 (4.2)	0.187	754.0 (4.3)	13534.0 (4.3)	0.000
71–76	1310 (6.9)	9476 (2.9)	0.189	481.3 (2.7)	8639.7 (2.7)	0.000
76–81	1012 (5.3)	6813 (2.0)	0.175	327.7 (1.8)	5881.3 (1.8)	0.000
81–86	826 (4.3)	5529 (1.7)	0.158	253.8 (1.4)	4555.2 (1.4)	0.000
86–91	433 (2.3)	3158 (1.0)	0.106	126.4 (0.7)	2269.6 (0.7)	0.000
91–96	118 (0.6)	1101 (0.3)	0.042	33.1 (0.2)	593.9 (0.2)	0.000
96–101	16 (0.1)	214 (0.1)	0.007	2.2 (0.0)	39.8 (0.0)	0.000
101–106	0 (0.0)	7 (0.0)	−0.006	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000

TABLE B3 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Sex						
M	7707 (40.6)	162 983 (49.0)	-0.171	8565.6 (48.3)	153746.4 (48.3)	0.000
F	11 289 (59.4)	169 406 (51.0)	0.171	9168.4 (51.7)	164565.6 (51.7)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	2 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	47 (0.0)	-0.003	0.2 (0.0)	2.8 (0.0)	0.000
1/1, 14-90 d	2 (0.0)	48 (0.0)	-0.004	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	18 000 (94.8)	322 899 (97.1)	-0.121	17438.7 (98.3)	313011.3 (98.3)	0.000
1/2, >90 d	7 (0.0)	35 (0.0)	0.017	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	332 (1.7)	3549 (1.1)	0.058	136.8 (0.8)	2456.2 (0.8)	0.000
1/2, 14-90 d	431 (2.3)	3880 (1.2)	0.085	134.2 (0.8)	2408.8 (0.8)	0.000
2/2, >90 d	36 (0.2)	363 (0.1)	0.021	2.0 (0.0)	36.0 (0.0)	0.000
2/2, <14 d	56 (0.3)	420 (0.1)	0.037	4.9 (0.0)	88.1 (0.0)	0.000
2/2, 14-90 d	129 (0.7)	1146 (0.3)	0.047	17.2 (0.1)	308.8 (0.1)	0.000
Period						
Before 10.01.2021	10 627 (55.9)	192 599 (57.9)	-0.040	10424.6 (58.8)	187114.4 (58.8)	0.000
10.01.2021 to 15.07.2021	8105 (42.7)	132 866 (40.0)	0.055	7019.8 (39.6)	126000.2 (39.6)	0.000
After 15.07.2021	264 (1.4)	6924 (2.1)	-0.053	289.6 (1.6)	5197.4 (1.6)	0.000
CC index						
0	10 660 (56.1)	270 536 (81.4)	-0.567	14658.9 (82.7)	263117.1 (82.7)	0.000
1-2	6259 (32.9)	53 673 (16.1)	0.398	2820.1 (15.9)	50617.9 (15.9)	0.000
3-4	1527 (8.0)	6652 (2.0)	0.279	226.9 (1.3)	4072.1 (1.3)	0.000
≥5	550 (2.9)	1528 (0.5)	0.191	28.1 (0.2)	504.9 (0.2)	0.000
Comorbidities						
Atrial fibrillation	1163 (6.1)	6300 (1.9)	0.217	205.3 (1.2)	3685.7 (1.2)	0.000
Autoimmune	2987 (15.7)	19 580 (5.9)	0.321	997.8 (5.6)	17910.2 (5.6)	0.000
Cancer	1873 (9.9)	10 142 (3.1)	0.280	456.9 (2.6)	8201.1 (2.6)	0.000
Congestive heart failure	783 (4.1)	3380 (1.0)	0.197	84.2 (0.5)	1510.8 (0.5)	0.000
COPD	2626 (13.8)	21 520 (6.5)	0.245	1077.1 (6.1)	19333.9 (6.1)	0.000
IHD or CVD	2437 (12.8)	12 849 (3.9)	0.328	565.8 (3.2)	10155.2 (3.2)	0.000
Renal disease	409 (2.2)	1710 (0.5)	0.143	21.2 (0.1)	380.8 (0.1)	0.000
Immunocompromised	266 (1.4)	1463 (0.4)	0.101	27.2 (0.2)	487.8 (0.2)	0.000
RAAS inhibitors	5450 (28.7)	43 193 (13.0)	0.394	2228.0 (12.6)	39991.0 (12.6)	0.000
Death (composite)	1070 (5.6)	5599 (1.7)	0.211	324.1 (1.8)	4448.5 (1.4)	0.023
Death 1	761 (4.0)	4366 (1.3)	0.168	249.8 (1.4)	3526.4 (1.1)	0.019
Death 2	704 (3.7)	3698 (1.1)	0.170	211.6 (1.2)	2912.6 (0.9)	0.018
Death 3	900 (4.7)	4519 (1.4)	0.197	267.6 (1.5)	3558.5 (1.1)	0.023
Hospitalization 1	1646 (8.7)	10 905 (3.3)	0.229	844.4 (4.8)	9305.2 (2.9)	0.078
Hospitalization 2	3624 (19.1)	26 965 (8.1)	0.324	1931.2 (10.9)	23947.3 (7.5)	0.100

TABLE B4 Primary analysis: users (4–7 prescriptions) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	d	Treated	Control	d
<i>n</i>	17 730	332 389		15 569	316 577	
Age (5-y bins)						
16–21	74 (0.4)	22 054 (6.6)	−0.342	973.2 (6.3)	19787.8 (6.3)	0.000
21–26	168 (0.9)	27 711 (8.3)	−0.357	1252.1 (8.0)	25460.9 (8.0)	0.000
26–31	251 (1.4)	31 607 (9.5)	−0.362	1454.5 (9.3)	29576.5 (9.3)	0.000
31–36	442 (2.5)	34 524 (10.4)	−0.326	1608.6 (10.3)	32709.4 (10.3)	0.000
36–41	707 (4.0)	37 047 (11.1)	−0.273	1724.7 (11.1)	35069.3 (11.1)	0.000
41–46	1006 (5.7)	35 359 (10.6)	−0.182	1663.1 (10.7)	33817.9 (10.7)	0.000
46–51	1352 (7.6)	30 711 (9.2)	−0.058	1460.9 (9.4)	29705.1 (9.4)	0.000
51–56	1727 (9.7)	28 177 (8.5)	0.044	1353.2 (8.7)	27514.8 (8.7)	0.000
56–61	2096 (11.8)	25 009 (7.5)	0.146	1214.2 (7.8)	24688.8 (7.8)	0.000
61–66	2205 (12.4)	19 809 (6.0)	0.226	969.6 (6.2)	19716.4 (6.2)	0.000
66–71	2108 (11.9)	14 082 (4.2)	0.284	692.0 (4.4)	14072.0 (4.4)	0.000
71–76	1709 (9.6)	9476 (2.9)	0.283	454.6 (2.9)	9244.4 (2.9)	0.000
76–81	1469 (8.3)	6813 (2.0)	0.285	316.0 (2.0)	6426.0 (2.0)	0.000
81–86	1359 (7.7)	5529 (1.7)	0.288	255.8 (1.6)	5201.2 (1.6)	0.000
86–91	770 (4.3)	3158 (1.0)	0.213	133.7 (0.9)	2719.3 (0.9)	0.000
91–96	247 (1.4)	1101 (0.3)	0.115	37.3 (0.2)	757.7 (0.2)	0.000
96–101	40 (0.2)	214 (0.1)	0.042	5.4 (0.0)	109.6 (0.0)	0.000
101–106	0 (0.0)	7 (0.0)	−0.006	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7472 (42.1)	162 983 (49.0)	−0.139	7536.1 (48.4)	153236.9 (48.4)	0.000
F	10 258 (57.9)	169 406 (51.0)	0.139	8032.9 (51.6)	163340.1 (51.6)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	2 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	47 (0.0)	−0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	2 (0.0)	48 (0.0)	−0.003	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 370 (92.3)	322 899 (97.1)	−0.217	15319.1 (98.4)	311494.9 (98.4)	0.000
1/2, >90 d	8 (0.0)	35 (0.0)	0.021	0.1 (0.0)	1.9 (0.0)	0.000
1/2, <14 d	367 (2.1)	3549 (1.1)	0.081	107.8 (0.7)	2191.2 (0.7)	0.000
1/2, 14–90 d	621 (3.5)	3880 (1.2)	0.155	126.6 (0.8)	2573.4 (0.8)	0.000
2/2, >90 d	76 (0.4)	363 (0.1)	0.062	2.2 (0.0)	44.8 (0.0)	0.000
2/2, <14 d	89 (0.5)	420 (0.1)	0.067	3.0 (0.0)	62.0 (0.0)	0.000
2/2, 14–90 d	194 (1.1)	1146 (0.3)	0.089	10.3 (0.1)	208.7 (0.1)	0.000
Period						
Before 10.01.2021	10 501 (59.2)	192 599 (57.9)	0.026	9278.7 (59.6)	188671.3 (59.6)	0.000
10.01.2021 to 15.07.2021	7015 (39.6)	132 866 (40.0)	−0.008	6113.8 (39.3)	124317.2 (39.3)	0.000
After 15.07.2021	214 (1.2)	6924 (2.1)	−0.069	176.5 (1.1)	3588.5 (1.1)	0.000
CC index						
0	7204 (40.6)	270 536 (81.4)	−0.920	12760.7 (82.0)	259474.3 (82.0)	0.000
1–2	7253 (40.9)	53 673 (16.1)	0.570	2531.9 (16.3)	51483.1 (16.3)	0.000
3–4	2393 (13.5)	6652 (2.0)	0.440	243.9 (1.6)	4960.1 (1.6)	0.000
≥5	880 (5.0)	1528 (0.5)	0.280	32.4 (0.2)	659.6 (0.2)	0.000

TABLE B4 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	d	Treated	Control	d
Comorbidities						
Atrial fibrillation	1854 (10.5)	6300 (1.9)	0.361	216.0 (1.4)	4393.0 (1.4)	0.000
Autoimmune	3420 (19.3)	19 580 (5.9)	0.412	895.2 (5.7)	18202.8 (5.7)	0.000
Cancer	2040 (11.5)	10 142 (3.1)	0.330	403.5 (2.6)	8205.5 (2.6)	0.000
Congestive heart failure	1353 (7.6)	3380 (1.0)	0.330	99.1 (0.6)	2015.9 (0.6)	0.000
COPD	3152 (17.8)	21 520 (6.5)	0.352	959.0 (6.2)	19501.0 (6.2)	0.000
IHD or CVD	3861 (21.8)	12 849 (3.9)	0.556	570.6 (3.7)	11602.4 (3.7)	0.000
Renal disease	864 (4.9)	1710 (0.5)	0.272	34.7 (0.2)	706.3 (0.2)	0.000
Immunocompromised	620 (3.5)	1463 (0.4)	0.221	31.9 (0.2)	649.1 (0.2)	0.000
RAAS inhibitors	7861 (44.3)	43 193 (13.0)	0.739	2108.7 (13.5)	42877.3 (13.5)	0.000
Death (composite)	1397 (7.9)	5599 (1.7)	0.293	284.3 (1.8)	4930.8 (1.6)	0.013
Death 1	1022 (5.8)	4366 (1.3)	0.243	213.3 (1.4)	3908.5 (1.2)	0.007
Death 2	920 (5.2)	3698 (1.1)	0.235	193.2 (1.2)	3241.1 (1.0)	0.013
Death 3	1170 (6.6)	4519 (1.4)	0.270	230.0 (1.5)	3973.6 (1.3)	0.011
Hospitalization 1	1830 (10.3)	10 905 (3.3)	0.282	615.7 (4.0)	9654.8 (3.0)	0.036
Hospitalization 2	4096 (23.1)	26 965 (8.1)	0.422	1539.5 (9.9)	24851.9 (7.9)	0.057

TABLE B5 Primary analysis: users (≥ 8 prescriptions) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	d	Treated	Control	d
n	18 372	332 389		15 150	313 399	
Age (5-y bins)						
16–21	22 (0.1)	22 054 (6.6)	−0.367	922.9 (6.1)	19092.1 (6.1)	0.000
21–26	99 (0.5)	27 711 (8.3)	−0.386	1190.7 (7.9)	24632.3 (7.9)	0.000
26–31	160 (0.9)	31 607 (9.5)	−0.397	1392.7 (9.2)	28809.3 (9.2)	0.000
31–36	259 (1.4)	34 524 (10.4)	−0.388	1539.3 (10.2)	31842.7 (10.2)	0.000
36–41	486 (2.6)	37 047 (11.1)	−0.340	1692.1 (11.2)	35002.9 (11.2)	0.000
41–46	733 (4.0)	35 359 (10.6)	−0.257	1615.9 (10.7)	33426.1 (10.7)	0.000
46–51	1066 (5.8)	30 711 (9.2)	−0.131	1422.2 (9.4)	29419.8 (9.4)	0.000
51–56	1473 (8.0)	28 177 (8.5)	−0.017	1304.6 (8.6)	26987.4 (8.6)	0.000
56–61	1912 (10.4)	25 009 (7.5)	0.101	1171.1 (7.7)	24226.9 (7.7)	0.000
61–66	2301 (12.5)	19 809 (6.0)	0.228	955.0 (6.3)	19756.0 (6.3)	0.000
66–71	2346 (12.8)	14 082 (4.2)	0.310	679.8 (4.5)	14063.2 (4.5)	0.000
71–76	2031 (11.1)	9476 (2.9)	0.327	450.4 (3.0)	9316.6 (3.0)	0.000
76–81	1999 (10.9)	6813 (2.0)	0.365	340.0 (2.2)	7034.0 (2.2)	0.000
81–86	1919 (10.4)	5529 (1.7)	0.375	272.9 (1.8)	5645.1 (1.8)	0.000
86–91	1197 (6.5)	3158 (1.0)	0.297	152.8 (1.0)	3161.2 (1.0)	0.000
91–96	328 (1.8)	1101 (0.3)	0.142	42.6 (0.3)	880.4 (0.3)	0.000
96–101	39 (0.2)	214 (0.1)	0.040	5.0 (0.0)	103.0 (0.0)	0.000
101–106	2 (0.0)	7 (0.0)	0.011	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000

(Continues)

TABLE B5 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Sex						
M	7466 (40.6)	162 983 (49.0)	-0.169	7301.8 (48.2)	151048.2 (48.2)	0.000
F	10 906 (59.4)	169 406 (51.0)	0.169	7848.2 (51.8)	162350.8 (51.8)	0.000
Vaccination status						
1/1, >90 d	0 (0.0)	2 (0.0)	-0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	8 (0.0)	47 (0.0)	0.017	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14-90 d	1 (0.0)	48 (0.0)	-0.009	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 741 (91.1)	322 899 (97.1)	-0.258	14931.3 (98.6)	308875.7 (98.6)	0.000
1/2, >90 d	7 (0.0)	35 (0.0)	0.018	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	422 (2.3)	3549 (1.1)	0.096	93.7 (0.6)	1939.3 (0.6)	0.000
1/2, 14-90 d	739 (4.0)	3880 (1.2)	0.180	112.4 (0.7)	2325.6 (0.7)	0.000
2/2, >90d	127 (0.7)	363 (0.1)	0.092	1.7 (0.0)	34.3 (0.0)	0.000
2/2, <14 d	97 (0.5)	420 (0.1)	0.070	3.5 (0.0)	72.5 (0.0)	0.000
2/2, 14-90 d	230 (1.3)	1146 (0.3)	0.102	7.3 (0.0)	151.7 (0.0)	0.000
Period						
Before 10.01.2021	11 189 (60.9)	192 599 (57.9)	0.060	9110.5 (60.1)	188463.5 (60.1)	0.000
10.01.2021 to 15.07.2021	6982 (38.0)	132 866 (40.0)	-0.040	5955.5 (39.3)	123197.5 (39.3)	0.000
After 15.07.2021	201 (1.1)	6924 (2.1)	-0.079	84.0 (0.6)	1738.0 (0.6)	0.000
CC index						
0	5613 (30.6)	270 536 (81.4)	-1.192	12354.2 (81.5)	255564.8 (81.5)	0.000
1-2	8063 (43.9)	53 673 (16.1)	0.635	2480.7 (16.4)	51317.3 (16.4)	0.000
3-4	3308 (18.0)	6652 (2.0)	0.553	276.3 (1.8)	5715.7 (1.8)	0.000
≥5	1388 (7.6)	1528 (0.5)	0.368	38.7 (0.3)	801.3 (0.3)	0.000
Comorbidities						
Atrial fibrillation	2670 (14.5)	6300 (1.9)	0.473	240.2 (1.6)	4969.8 (1.6)	0.000
Autoimmune	3627 (19.7)	19 580 (5.9)	0.424	853.0 (5.6)	17645.0 (5.6)	0.000
Cancer	2340 (12.7)	10 142 (3.1)	0.365	382.2 (2.5)	7905.8 (2.5)	0.000
Congestive heart failure	2098 (11.4)	3380 (1.0)	0.441	120.5 (0.8)	2492.5 (0.8)	0.000
COPD	3922 (21.3)	21 520 (6.5)	0.440	943.4 (6.2)	19516.6 (6.2)	0.000
IHD or CVD	5385 (29.3)	12 849 (3.9)	0.728	617.3 (4.1)	12769.7 (4.1)	0.000
Renal disease	1307 (7.1)	1710 (0.5)	0.350	42.8 (0.3)	886.2 (0.3)	0.000
Immunocompromised	987 (5.4)	1463 (0.4)	0.297	42.9 (0.3)	888.1 (0.3)	0.000
RAAS inhibitors	10 065 (54.8)	43 193 (13.0)	0.984	2173.2 (14.3)	44955.8 (14.3)	0.000
Death (composite)	1889 (10.3)	5599 (1.7)	0.369	318.9 (2.1)	5380.0 (1.7)	0.017
Death 1	1412 (7.7)	4366 (1.3)	0.311	244.9 (1.6)	4232.1 (1.4)	0.013
Death 2	1215 (6.6)	3698 (1.1)	0.288	206.5 (1.4)	3529.6 (1.1)	0.012
Death 3	1600 (8.7)	4519 (1.4)	0.341	265.8 (1.8)	4348.9 (1.4)	0.017
Hospitalization 1	2348 (12.8)	10 905 (3.3)	0.355	781.9 (5.2)	9815.0 (3.1)	0.076
Hospitalization 2	5015 (27.3)	26 965 (8.1)	0.519	1646.2 (10.9)	25255.3 (8.1)	0.076

TABLE B6 Primary analysis: users (all) vs. possible users (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	55 098	18 170		41 195	17 344	
Age (5-y bins)						
16–21	401 (0.7)	540 (3.0)	−0.167	639.7 (1.6)	269.3 (1.6)	0.000
21–26	782 (1.4)	759 (4.2)	−0.168	1037.3 (2.5)	436.7 (2.5)	0.000
26–31	1137 (2.1)	981 (5.4)	−0.177	1400.4 (3.4)	589.6 (3.4)	0.000
31–36	1703 (3.1)	1142 (6.3)	−0.152	1896.5 (4.6)	798.5 (4.6)	0.000
36–41	2571 (4.7)	1425 (7.8)	−0.131	2622.8 (6.4)	1104.2 (6.4)	0.000
41–46	3335 (6.1)	1644 (9.0)	−0.114	3264.6 (7.9)	1374.4 (7.9)	0.000
46–51	4243 (7.7)	1775 (9.8)	−0.073	3836.0 (9.3)	1615.0 (9.3)	0.000
51–56	5301 (9.6)	1833 (10.1)	−0.016	4481.3 (10.9)	1886.7 (10.9)	0.000
56–61	6107 (11.1)	1886 (10.4)	0.023	4904.2 (11.9)	2064.8 (11.9)	0.000
61–66	6560 (11.9)	1664 (9.2)	0.090	4726.2 (11.5)	1989.8 (11.5)	0.000
66–71	6134 (11.1)	1332 (7.3)	0.132	3810.6 (9.3)	1604.4 (9.3)	0.000
71–76	5050 (9.2)	1010 (5.6)	0.138	2819.8 (6.8)	1187.2 (6.8)	0.000
76–81	4480 (8.1)	831 (4.6)	0.146	2290.6 (5.6)	964.4 (5.6)	0.000
81–86	4104 (7.4)	755 (4.2)	0.141	2054.2 (5.0)	864.8 (5.0)	0.000
86–91	2400 (4.4)	430 (2.4)	0.111	1134.4 (2.8)	477.6 (2.8)	0.000
91–96	693 (1.3)	135 (0.7)	0.052	247.7 (0.6)	104.3 (0.6)	0.000
96–101	95 (0.2)	28 (0.2)	0.005	28.9 (0.1)	12.1 (0.1)	0.000
101–106	2 (0.0)	0 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	22 645 (41.1)	7582 (41.7)	−0.013	16425.5 (39.9)	6915.5 (39.9)	0.000
F	32 453 (58.9)	10 588 (58.3)	0.013	24769.5 (60.1)	10428.5 (60.1)	0.000
Vaccination status						
1/1, >90 d	2 (0.0)	0 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	12 (0.0)	1 (0.0)	0.014	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	5 (0.0)	0 (0.0)	0.013	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	51 111 (92.8)	17 347 (95.5)	−0.115	40128.9 (97.4)	16895.1 (97.4)	0.000
1/2, >90 d	22 (0.0)	7 (0.0)	0.001	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	1121 (2.0)	295 (1.6)	0.031	429.3 (1.0)	180.7 (1.0)	0.000
1/2, 14–90 d	1791 (3.3)	355 (2.0)	0.082	570.7 (1.4)	240.3 (1.4)	0.000
2/2, >90 d	239 (0.4)	30 (0.2)	0.049	4.2 (0.0)	1.8 (0.0)	0.000
2/2, <14 d	242 (0.4)	44 (0.2)	0.034	18.3 (0.0)	7.7 (0.0)	0.000
2/2, 14–90 d	553 (1.0)	91 (0.5)	0.058	43.6 (0.1)	18.4 (0.1)	0.000
Period						
Before 10.01.2021	32 317 (58.7)	10 566 (58.2)	0.010	25364.8 (61.6)	10679.2 (61.6)	0.000
10.01.2021 to 15.07.2021	22 102 (40.1)	7257 (39.9)	0.004	15540.9 (37.7)	6543.1 (37.7)	0.000
After 15.07.2021	679 (1.2)	347 (1.9)	−0.054	289.2 (0.7)	121.8 (0.7)	0.000
CC index						
0	23 477 (42.6)	11 868 (65.3)	−0.468	23950.4 (58.1)	10083.6 (58.1)	0.000
1–2	21 575 (39.2)	5248 (28.9)	0.218	15047.6 (36.5)	6335.4 (36.5)	0.000
3–4	7228 (13.1)	845 (4.7)	0.301	1962.0 (4.8)	826.0 (4.8)	0.000
≥5	2818 (5.1)	209 (1.2)	0.229	235.0 (0.6)	99.0 (0.6)	0.000

(Continues)

TABLE B6 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Comorbidities						
Atrial fibrillation	5687 (10.3)	661 (3.6)	0.265	1465.1 (3.6)	616.9 (3.6)	0.000
Autoimmune	10 034 (18.2)	2270 (12.5)	0.159	5704.3 (13.8)	2401.7 (13.8)	0.000
Cancer	6253 (11.3)	978 (5.4)	0.217	2348.3 (5.7)	988.7 (5.7)	0.000
Congestive heart failure	4234 (7.7)	462 (2.5)	0.235	764.9 (1.9)	322.1 (1.9)	0.000
COPD	9700 (17.6)	1979 (10.9)	0.193	4953.5 (12.0)	2085.5 (12.0)	0.000
IHD or CVD	11 683 (21.2)	1518 (8.4)	0.368	4733.2 (11.5)	1992.8 (11.5)	0.000
Renal disease	2580 (4.7)	230 (1.3)	0.202	225.9 (0.5)	95.1 (0.5)	0.000
Immunocompromised	1873 (3.4)	132 (0.7)	0.189	194.9 (0.5)	82.1 (0.5)	0.000
RAAS inhibitors	23 376 (42.4)	4841 (26.6)	0.337	14109.6 (34.3)	5940.4 (34.3)	0.000
Death (composite)	4356 (7.9)	803 (4.4)	0.145	1904.4 (4.6)	860.4 (5.0)	-0.014
Death 1	3195 (5.8)	585 (3.2)	0.125	1446.9 (3.5)	633.7 (3.7)	-0.007
Death 2	2839 (5.2)	519 (2.9)	0.117	1233.5 (3.0)	552.2 (3.2)	-0.010
Death 3	3670 (6.7)	666 (3.7)	0.136	1566.0 (3.8)	705.8 (4.1)	-0.012
Hospitalization 1	5824 (10.6)	1160 (6.4)	0.151	2900.0 (7.0)	1169.8 (6.7)	0.011
Hospitalization 2	12 735 (23.1)	2680 (14.7)	0.215	6913.2 (16.8)	2799.2 (16.1)	0.016

TABLE B7 Primary analysis: users (1–3 prescriptions) vs. possible users (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 996	18 170		15 998	16 517	
Age (5-y bins)						
16–21	305 (1.6)	540 (3.0)	-0.091	404.4 (2.5)	417.6 (2.5)	0.000
21–26	515 (2.7)	759 (4.2)	-0.080	604.2 (3.8)	623.8 (3.8)	0.000
26–31	726 (3.8)	981 (5.4)	-0.075	802.0 (5.0)	828.0 (5.0)	0.000
31–36	1002 (5.3)	1142 (6.3)	-0.043	1020.4 (6.4)	1053.6 (6.4)	0.000
36–41	1378 (7.3)	1425 (7.8)	-0.022	1316.6 (8.2)	1359.4 (8.2)	0.000
41–46	1596 (8.4)	1644 (9.0)	-0.023	1523.3 (9.5)	1572.7 (9.5)	0.000
46–51	1825 (9.6)	1775 (9.8)	-0.005	1672.4 (10.5)	1726.6 (10.5)	0.000
51–56	2101 (11.1)	1833 (10.1)	0.032	1791.9 (11.2)	1850.1 (11.2)	0.000
56–61	2099 (11.0)	1886 (10.4)	0.022	1795.4 (11.2)	1853.6 (11.2)	0.000
61–66	2054 (10.8)	1664 (9.2)	0.055	1599.1 (10.0)	1650.9 (10.0)	0.000
66–71	1680 (8.8)	1332 (7.3)	0.056	1201.0 (7.5)	1240.0 (7.5)	0.000
71–76	1310 (6.9)	1010 (5.6)	0.055	836.4 (5.2)	863.6 (5.2)	0.000
76–81	1012 (5.3)	831 (4.6)	0.035	599.8 (3.7)	619.2 (3.7)	0.000
81–86	826 (4.3)	755 (4.2)	0.010	514.2 (3.2)	530.8 (3.2)	0.000
86–91	433 (2.3)	430 (2.4)	-0.006	258.8 (1.6)	267.2 (1.6)	0.000
91–96	118 (0.6)	135 (0.7)	-0.015	54.6 (0.3)	56.4 (0.3)	0.000
96–101	16 (0.1)	28 (0.2)	-0.020	3.4 (0.0)	3.6 (0.0)	0.000
101–106	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000

TABLE B7 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Sex						
M	7707 (40.6)	7582 (41.7)	-0.024	6375.6 (39.9)	6582.4 (39.9)	0.000
F	11 289 (59.4)	10 588 (58.3)	0.024	9622.4 (60.1)	9934.6 (60.1)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	0 (0.0)	0.010	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	1 (0.0)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14-90 d	2 (0.0)	0 (0.0)	0.015	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	18 000 (94.8)	17 347 (95.5)	-0.033	15649.7 (97.8)	16157.3 (97.8)	0.000
1/2, >90 d	7 (0.0)	7 (0.0)	-0.001	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	332 (1.7)	295 (1.6)	0.010	155.5 (1.0)	160.5 (1.0)	0.000
1/2, 14-90 d	431 (2.3)	355 (2.0)	0.022	171.2 (1.1)	176.8 (1.1)	0.000
2/2, >90 d	36 (0.2)	30 (0.2)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
2/2, <14 d	56 (0.3)	44 (0.2)	0.010	4.9 (0.0)	5.1 (0.0)	0.000
2/2, 14-90 d	129 (0.7)	91 (0.5)	0.023	16.7 (0.1)	17.3 (0.1)	0.000
Period						
Before 10.01.2021	10 627 (55.9)	10 566 (58.2)	-0.045	9477.8 (59.2)	9785.2 (59.2)	0.000
10.01.2021 to 15.07.2021	8105 (42.7)	7257 (39.9)	0.055	6362.8 (39.8)	6569.2 (39.8)	0.000
After 15.07.2021	264 (1.4)	347 (1.9)	-0.041	157.4 (1.0)	162.6 (1.0)	0.000
CC index						
0	10 660 (56.1)	11 868 (65.3)	-0.189	10760.5 (67.3)	11109.5 (67.3)	0.000
1-2	6259 (32.9)	5248 (28.9)	0.088	4724.9 (29.5)	4878.1 (29.5)	0.000
3-4	1527 (8.0)	845 (4.7)	0.139	454.6 (2.8)	469.4 (2.8)	0.000
≥5	550 (2.9)	209 (1.2)	0.124	58.1 (0.4)	59.9 (0.4)	0.000
Comorbidities						
Atrial fibrillation	1163 (6.1)	661 (3.6)	0.116	313.4 (2.0)	323.6 (2.0)	0.000
Autoimmune	2987 (15.7)	2270 (12.5)	0.093	1935.6 (12.1)	1998.4 (12.1)	0.000
Cancer	1873 (9.9)	978 (5.4)	0.169	768.0 (4.8)	793.0 (4.8)	0.000
Congestive heart failure	783 (4.1)	462 (2.5)	0.088	158.4 (1.0)	163.6 (1.0)	0.000
COPD	2626 (13.8)	1979 (10.9)	0.089	1603.0 (10.0)	1655.0 (10.0)	0.000
IHD or CVD	2437 (12.8)	1518 (8.4)	0.146	1112.5 (7.0)	1148.5 (7.0)	0.000
Renal disease	409 (2.2)	230 (1.3)	0.068	36.4 (0.2)	37.6 (0.2)	0.000
Immunocompromised	266 (1.4)	132 (0.7)	0.066	33.5 (0.2)	34.5 (0.2)	0.000
RAAS inhibitors	5450 (28.7)	4841 (26.6)	0.046	3998.1 (25.0)	4127.9 (25.0)	0.000
Death (composite)	1070 (5.6)	803 (4.4)	0.056	566.1 (3.5)	561.3 (3.4)	0.006
Death 1	761 (4.0)	585 (3.2)	0.042	430.1 (2.7)	423.1 (2.6)	0.007
Death 2	704 (3.7)	519 (2.9)	0.048	370.4 (2.3)	375.6 (2.3)	0.002
Death 3	900 (4.7)	666 (3.7)	0.053	466.1 (2.9)	456.5 (2.8)	0.007
Hospitalization 1	1646 (8.7)	1160 (6.4)	0.087	1027.7 (6.4)	884.3 (5.4)	0.041
Hospitalization 2	3624 (19.1)	2680 (14.7)	0.116	2383.4 (14.9)	2167.9 (13.1)	0.047

TABLE B8 Primary analysis: users (4–7 prescriptions) vs. possible users (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	17 730	18 170		13 115	16 594	
Age (5-y bins)						
16–21	74 (0.4)	540 (3.0)	–0.199	248.5 (1.9)	314.5 (1.9)	0.000
21–26	168 (0.9)	759 (4.2)	–0.205	385.4 (2.9)	487.6 (2.9)	0.000
26–31	251 (1.4)	981 (5.4)	–0.221	514.3 (3.9)	650.7 (3.9)	0.000
31–36	442 (2.5)	1142 (6.3)	–0.186	661.3 (5.0)	836.7 (5.0)	0.000
36–41	707 (4.0)	1425 (7.8)	–0.164	885.5 (6.8)	1120.5 (6.8)	0.000
41–46	1006 (5.7)	1644 (9.0)	–0.129	1092.6 (8.3)	1382.4 (8.3)	0.000
46–51	1352 (7.6)	1775 (9.8)	–0.076	1257.7 (9.6)	1591.3 (9.6)	0.000
51–56	1727 (9.7)	1833 (10.1)	–0.012	1419.7 (10.8)	1796.3 (10.8)	0.000
56–61	2096 (11.8)	1886 (10.4)	0.046	1548.6 (11.8)	1959.4 (11.8)	0.000
61–66	2205 (12.4)	1664 (9.2)	0.106	1435.6 (10.9)	1816.4 (10.9)	0.000
66–71	2108 (11.9)	1332 (7.3)	0.155	1165.0 (8.9)	1474.0 (8.9)	0.000
71–76	1709 (9.6)	1010 (5.6)	0.154	848.5 (6.5)	1073.5 (6.5)	0.000
76–81	1469 (8.3)	831 (4.6)	0.152	665.3 (5.1)	841.7 (5.1)	0.000
81–86	1359 (7.7)	755 (4.2)	0.149	595.5 (4.5)	753.5 (4.5)	0.000
86–91	770 (4.3)	430 (2.4)	0.110	311.2 (2.4)	393.8 (2.4)	0.000
91–96	247 (1.4)	135 (0.7)	0.063	68.0 (0.5)	86.0 (0.5)	0.000
96–101	40 (0.2)	28 (0.2)	0.016	12.4 (0.1)	15.6 (0.1)	0.000
101–106	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7472 (42.1)	7582 (41.7)	0.008	5331.8 (40.7)	6746.2 (40.7)	0.000
F	10 258 (57.9)	10 588 (58.3)	–0.008	7783.2 (59.3)	9847.8 (59.3)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	0 (0.0)	0.011	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	1 (0.0)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	2 (0.0)	0 (0.0)	0.015	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 370 (92.3)	17 347 (95.5)	–0.132	12798.5 (97.6)	16193.5 (97.6)	0.000
1/2, >90 d	8 (0.0)	7 (0.0)	0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	367 (2.1)	295 (1.6)	0.033	124.5 (0.9)	157.5 (0.9)	0.000
1/2, 14–90 d	621 (3.5)	355 (2.0)	0.095	173.5 (1.3)	219.5 (1.3)	0.000
2/2, >90 d	76 (0.4)	30 (0.2)	0.048	2.2 (0.0)	2.8 (0.0)	0.000
2/2, <14 d	89 (0.5)	44 (0.2)	0.043	5.7 (0.0)	7.3 (0.0)	0.000
2/2, 14–90 d	194 (1.1)	91 (0.5)	0.067	10.6 (0.1)	13.4 (0.1)	0.000
Period						
Before 10.01.2021	10 501 (59.2)	10 566 (58.2)	0.022	8111.2 (61.8)	10262.8 (61.8)	0.000
10.01.2021 to 15.07.2021	7015 (39.6)	7257 (39.9)	–0.008	4915.1 (37.5)	6218.9 (37.5)	0.000
After 15.07.2021	214 (1.2)	347 (1.9)	–0.057	88.7 (0.7)	112.3 (0.7)	0.000
CC index						
0	7204 (40.6)	11 868 (65.3)	–0.510	8116.9 (61.9)	10270.1 (61.9)	0.000
1–2	7253 (40.9)	5248 (28.9)	0.254	4430.8 (33.8)	5606.2 (33.8)	0.000
3–4	2393 (13.5)	845 (4.7)	0.312	508.1 (3.9)	642.9 (3.9)	0.000
≥5	880 (5.0)	209 (1.2)	0.223	59.2 (0.5)	74.8 (0.5)	0.000

TABLE B8 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Comorbidities						
Atrial fibrillation	1854 (10.5)	661 (3.6)	0.269	386.7 (2.9)	489.3 (2.9)	0.000
Autoimmune	3420 (19.3)	2270 (12.5)	0.187	1715.5 (13.1)	2170.5 (13.1)	0.000
Cancer	2040 (11.5)	978 (5.4)	0.222	637.5 (4.9)	806.5 (4.9)	0.000
Congestive heart failure	1353 (7.6)	462 (2.5)	0.233	194.2 (1.5)	245.8 (1.5)	0.000
COPD	3152 (17.8)	1979 (10.9)	0.197	1447.5 (11.0)	1831.5 (11.0)	0.000
IHD or CVD	3861 (21.8)	1518 (8.4)	0.382	1265.6 (9.7)	1601.4 (9.7)	0.000
Renal disease	864 (4.9)	230 (1.3)	0.210	60.9 (0.5)	77.1 (0.5)	0.000
Immunocompromised	620 (3.5)	132 (0.7)	0.194	48.1 (0.4)	60.9 (0.4)	0.000
RAAS inhibitors	7861 (44.3)	4841 (26.6)	0.376	4181.8 (31.9)	5291.2 (31.9)	0.000
Death (composite)	1397 (7.9)	803 (4.4)	0.144	516.4 (3.9)	744.4 (4.5)	-0.023
Death 1	1022 (5.8)	585 (3.2)	0.123	387.8 (3.0)	552.0 (3.3)	-0.018
Death 2	920 (5.2)	519 (2.9)	0.119	331.8 (2.5)	477.8 (2.9)	-0.018
Death 3	1170 (6.6)	666 (3.7)	0.133	423.4 (3.2)	609.1 (3.7)	-0.020
Hospitalization 1	1830 (10.3)	1160 (6.4)	0.143	801.4 (6.1)	1047.5 (6.3)	-0.007
Hospitalization 2	4096 (23.1)	2680 (14.7)	0.214	1987.0 (15.2)	2536.9 (15.3)	-0.004

TABLE B9 Primary analysis: users (≥ 8 prescriptions) vs. possible users (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 372	18 170		12 082	16 564	
Age (5-y bins)						
16-21	22 (0.1)	540 (3.0)	-0.233	205.8 (1.7)	282.2 (1.7)	0.000
21-26	99 (0.5)	759 (4.2)	-0.242	326.0 (2.7)	447.0 (2.7)	0.000
26-31	160 (0.9)	981 (5.4)	-0.262	442.4 (3.7)	606.6 (3.7)	0.000
31-36	259 (1.4)	1142 (6.3)	-0.256	539.0 (4.5)	739.0 (4.5)	0.000
36-41	486 (2.6)	1425 (7.8)	-0.235	757.9 (6.3)	1039.1 (6.3)	0.000
41-46	733 (4.0)	1644 (9.0)	-0.206	924.5 (7.7)	1267.5 (7.7)	0.000
46-51	1066 (5.8)	1775 (9.8)	-0.148	1079.3 (8.9)	1479.7 (8.9)	0.000
51-56	1473 (8.0)	1833 (10.1)	-0.072	1219.3 (10.1)	1671.7 (10.1)	0.000
56-61	1912 (10.4)	1886 (10.4)	0.001	1377.5 (11.4)	1888.5 (11.4)	0.000
61-66	2301 (12.5)	1664 (9.2)	0.108	1337.4 (11.1)	1833.6 (11.1)	0.000
66-71	2346 (12.8)	1332 (7.3)	0.182	1108.8 (9.2)	1520.2 (9.2)	0.000
71-76	2031 (11.1)	1010 (5.6)	0.200	851.6 (7.0)	1167.4 (7.0)	0.000
76-81	1999 (10.9)	831 (4.6)	0.238	748.2 (6.2)	1025.8 (6.2)	0.000
81-86	1919 (10.4)	755 (4.2)	0.244	672.7 (5.6)	922.3 (5.6)	0.000
86-91	1197 (6.5)	430 (2.4)	0.202	395.2 (3.3)	541.8 (3.3)	0.000
91-96	328 (1.8)	135 (0.7)	0.093	88.6 (0.7)	121.4 (0.7)	0.000
96-101	39 (0.2)	28 (0.2)	0.014	7.6 (0.1)	10.4 (0.1)	0.000
101-106	2 (0.0)	0 (0.0)	0.015	0.0 (0.0)	0.0 (0.0)	0.000
106-111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000

(Continues)

TABLE B9 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Sex						
M	7466 (40.6)	7582 (41.7)	-0.022	4793.0 (39.7)	6571.0 (39.7)	0.000
F	10 906 (59.4)	10 588 (58.3)	0.022	7289.0 (60.3)	9993.0 (60.3)	0.000
Vaccination status						
1/1, >90 d	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	8 (0.0)	1 (0.0)	0.024	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14-90 d	1 (0.0)	0 (0.0)	0.010	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 741 (91.1)	17 347 (95.5)	-0.175	11810.0 (97.7)	16191.0 (97.7)	0.000
1/2, >90 d	7 (0.0)	7 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	422 (2.3)	295 (1.6)	0.049	105.4 (0.9)	144.6 (0.9)	0.000
1/2, 14-90 d	739 (4.0)	355 (2.0)	0.122	157.7 (1.3)	216.3 (1.3)	0.000
2/2, >90 d	127 (0.7)	30 (0.2)	0.081	0.8 (0.0)	1.2 (0.0)	0.000
2/2, <14 d	97 (0.5)	44 (0.2)	0.046	2.5 (0.0)	3.5 (0.0)	0.000
2/2, 14-90 d	230 (1.3)	91 (0.5)	0.081	5.5 (0.0)	7.5 (0.0)	0.000
Period						
Before 10.01.2021	11 189 (60.9)	10 566 (58.2)	0.056	7623.5 (63.1)	10451.5 (63.1)	0.000
10.01.2021 to 15.07.2021	6982 (38.0)	7257 (39.9)	-0.040	4415.1 (36.5)	6052.9 (36.5)	0.000
After 15.07.2021	201 (1.1)	347 (1.9)	-0.067	43.4 (0.4)	59.6 (0.4)	0.000
CC index						
0	5613 (30.6)	11 868 (65.3)	-0.742	6993.8 (57.9)	9588.2 (57.9)	0.000
1 -2	8063 (43.9)	5248 (28.9)	0.316	4411.3 (36.5)	6047.7 (36.5)	0.000
3-4	3308 (18.0)	845 (4.7)	0.431	612.8 (5.1)	840.2 (5.1)	0.000
≥5	1388 (7.6)	209 (1.2)	0.318	64.1 (0.5)	87.9 (0.5)	0.000
Comorbidities						
Atrial fibrillation	2670 (14.5)	661 (3.6)	0.386	463.5 (3.8)	635.5 (3.8)	0.000
Autoimmune	3627 (19.7)	2270 (12.5)	0.198	1552.1 (12.8)	2127.9 (12.8)	0.000
Cancer	2340 (12.7)	978 (5.4)	0.258	609.0 (5.0)	835.0 (5.0)	0.000
Congestive heart failure	2098 (11.4)	462 (2.5)	0.354	249.7 (2.1)	342.3 (2.1)	0.000
COPD	3922 (21.3)	1979 (10.9)	0.287	1446.2 (12.0)	1982.8 (12.0)	0.000
IHD or CVD	5385 (29.3)	1518 (8.4)	0.556	1469.9 (12.2)	2015.1 (12.2)	0.000
Renal disease	1307 (7.1)	230 (1.3)	0.295	80.1 (0.7)	109.9 (0.7)	0.000
Immunocompromised	987 (5.4)	132 (0.7)	0.273	65.4 (0.5)	89.6 (0.5)	0.000
RAAS inhibitors	10 065 (54.8)	4841 (26.6)	0.598	4462.7 (36.9)	6118.3 (36.9)	0.000
Death (composite)	1889 (10.3)	803 (4.4)	0.226	591.2 (4.9)	897.6 (5.4)	-0.020
Death 1	1412 (7.7)	585 (3.2)	0.198	453.1 (3.8)	662.4 (4.0)	-0.011
Death 2	1215 (6.6)	519 (2.9)	0.178	380.0 (3.1)	560.3 (3.4)	-0.011
Death 3	1600 (8.7)	666 (3.7)	0.210	485.6 (4.0)	736.1 (4.4)	-0.018
Hospitalization 1	2348 (12.8)	1160 (6.4)	0.219	872.1 (7.2)	1141.0 (6.9)	0.011
Hospitalization 2	5015 (27.3)	2680 (14.7)	0.312	2035.9 (16.9)	2725.3 (16.5)	0.010

B.1.2 | Sensitivity analysis

TABLE B10 Sensitivity analysis: possible users vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 170	332 389		16 795	307 785	
Age (5-y bins)						
16–21	540 (3.0)	22 054 (6.6)	−0.172	1147.6 (6.8)	21031.4 (6.8)	0.000
21–26	759 (4.2)	27 711 (8.3)	−0.172	1447.7 (8.6)	26530.3 (8.6)	0.000
26–31	981 (5.4)	31 607 (9.5)	−0.157	1645.6 (9.8)	30156.4 (9.8)	0.000
31–36	1142 (6.3)	34 524 (10.4)	−0.149	1804.1 (10.7)	33061.9 (10.7)	0.000
36–41	1425 (7.8)	37 047 (11.1)	−0.113	1941.8 (11.6)	35586.2 (11.6)	0.000
41–46	1644 (9.0)	35 359 (10.6)	−0.053	1858.2 (11.1)	34052.8 (11.1)	0.000
46–51	1775 (9.8)	30 711 (9.2)	0.018	1615.1 (9.6)	29597.9 (9.6)	0.000
51–56	1833 (10.1)	28 177 (8.5)	0.056	1469.3 (8.7)	26925.7 (8.7)	0.000
56–61	1886 (10.4)	25 009 (7.5)	0.100	1275.4 (7.6)	23372.6 (7.6)	0.000
61–66	1664 (9.2)	19 809 (6.0)	0.121	981.2 (5.8)	17981.8 (5.8)	0.000
66–71	1332 (7.3)	14 082 (4.2)	0.133	641.4 (3.8)	11754.6 (3.8)	0.000
71–76	1010 (5.6)	9476 (2.9)	0.135	396.7 (2.4)	7269.3 (2.4)	0.000
76–81	831 (4.6)	6813 (2.0)	0.141	249.7 (1.5)	4576.3 (1.5)	0.000
81–86	755 (4.2)	5529 (1.7)	0.149	194.9 (1.2)	3571.1 (1.2)	0.000
86–91	430 (2.4)	3158 (1.0)	0.111	94.8 (0.6)	1738.2 (0.6)	0.000
91–96	135 (0.7)	1101 (0.3)	0.056	28.2 (0.2)	516.8 (0.2)	0.000
96–101	28 (0.2)	214 (0.1)	0.027	3.4 (0.0)	61.6 (0.0)	0.000
101–106	0 (0.0)	7 (0.0)	−0.006	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7582 (41.7)	162 983 (49.0)	−0.147	8099.7 (48.2)	148434.3 (48.2)	0.000
F	10 588 (58.3)	169 406 (51.0)	0.147	8695.3 (51.8)	159350.7 (51.8)	0.000
Vaccination status						
1/1, >90 d	0 (0.0)	2 (0.0)	−0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	1 (0.0)	47 (0.0)	−0.009	0.1 (0.0)	1.9 (0.0)	0.000
1/1, 14–90 d	0 (0.0)	48 (0.0)	−0.017	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated						
1/2, >90 d	7 (0.0)	35 (0.0)	0.018	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	295 (1.6)	3549 (1.1)	0.048	117.4 (0.7)	2150.6 (0.7)	0.000
1/2, 14–90 d	355 (2.0)	3880 (1.2)	0.063	114.1 (0.7)	2091.9 (0.7)	0.000
2/2, >90 d	30 (0.2)	363 (0.1)	0.015	1.4 (0.0)	25.6 (0.0)	0.000
2/2, <14 d	44 (0.2)	420 (0.1)	0.027	4.3 (0.0)	78.7 (0.0)	0.000
2/2, 14–90 d	91 (0.5)	1146 (0.3)	0.024	16.1 (0.1)	295.9 (0.1)	0.000
Period						
Before 10.01.2021	10 566 (58.2)	192 599 (57.9)	0.004	9891.2 (58.9)	181 265.8 (58.9)	0.000
10.01.2021 to 15.07.2021	7257 (39.9)	132 866 (40.0)	−0.001	6607.6 (39.3)	121 090.4 (39.3)	0.000
After 15.07.2021	347 (1.9)	6924 (2.1)	−0.012	296.2 (1.8)	5428.8 (1.8)	0.000
Comorbidities						
Acute myocardial infarction	198 (1.1)	2103 (0.6)	0.049	24.9 (0.1)	457.1 (0.1)	0.000
Congestive heart failure	462 (2.5)	3380 (1.0)	0.116	31.8 (0.2)	582.2 (0.2)	0.000
Peripheral vascular disease	301 (1.7)	2579 (0.8)	0.080	30.6 (0.2)	560.4 (0.2)	0.000

(Continues)

TABLE B10 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Cerebrovascular disease	604 (3.3)	5189 (1.6)	0.114	104.7 (0.6)	1918.3 (0.6)	0.000
Alzheimer dementia	249 (1.4)	2294 (0.7)	0.067	41.8 (0.2)	766.2 (0.2)	0.000
Other dementia	1979 (10.9)	21 520 (6.5)	0.157	916.1 (5.5)	16787.9 (5.5)	0.000
Mild liver disease	340 (1.9)	3363 (1.0)	0.072	109.4 (0.7)	2004.6 (0.7)	0.000
Diabetes without complications	2449 (13.5)	21 896 (6.6)	0.231	829.0 (4.9)	15193.0 (4.9)	0.000
Diabetes with complications	202 (1.1)	1735 (0.5)	0.066	20.3 (0.1)	371.7 (0.1)	0.000
Renal disease	252 (1.4)	1904 (0.6)	0.083	14.9 (0.1)	272.1 (0.1)	0.000
Cancer	971 (5.3)	10 088 (3.0)	0.115	322.7 (1.9)	5913.3 (1.9)	0.000
Moderate to severe liver disease	7 (0.0)	66 (0.0)	0.011	0.0 (0.0)	0.0 (0.0)	0.000
Metastatic cancer	52 (0.3)	375 (0.1)	0.039	2.0 (0.0)	36.0 (0.0)	0.000
HIV/AIDS	1 (0.0)	21 (0.0)	-0.001	0.1 (0.0)	1.9 (0.0)	0.000
RAAS inhibitors	4841 (26.6)	43 193 (13.0)	0.348	1875.0 (11.2)	34362.0 (11.2)	0.000
Beta blockers	2450 (13.5)	22 235 (6.7)	0.227	796.3 (4.7)	14592.7 (4.7)	0.000
Diuretics	1872 (10.3)	14 387 (4.3)	0.231	451.7 (2.7)	8277.3 (2.7)	0.000
Immunosuppressant drugs	75 (0.4)	800 (0.2)	0.030	6.9 (0.0)	126.1 (0.0)	0.000
Systemic corticosteroids	72 (0.4)	617 (0.2)	0.039	4.6 (0.0)	83.4 (0.0)	0.000
Antineoplastic drugs	118 (0.6)	1241 (0.4)	0.039	20.9 (0.1)	382.1 (0.1)	0.000
Antiviral agents	16 (0.1)	215 (0.1)	0.008	0.8 (0.0)	14.2 (0.0)	0.000
Death (composite)	803 (4.4)	5599 (1.7)	0.160	228.1 (1.4)	3429.1 (1.1)	0.014
Death 1	585 (3.2)	4366 (1.3)	0.128	176.7 (1.1)	2762.8 (0.9)	0.010
Death 2	519 (2.9)	3698 (1.1)	0.125	153.4 (0.9)	2237.9 (0.7)	0.013
Death 3	666 (3.7)	4519 (1.4)	0.148	183.0 (1.1)	2681.0 (0.9)	0.014
Hospitalization 1	1160 (6.4)	10 905 (3.3)	0.145	557.7 (3.3)	8146.0 (2.6)	0.032
Hospitalization 2	2680 (14.7)	26 965 (8.1)	0.210	1396.5 (8.3)	21199.4 (6.9)	0.045

TABLE B11 Sensitivity analysis: users (all) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	55 098	332 389		40 653	317 678	
Age (5-y bins)						
16-21	401 (0.7)	22 054 (6.6)	-0.318	2493.1 (6.1)	19481.9 (6.1)	0.000
21-26	782 (1.4)	27 711 (8.3)	-0.325	3172.5 (7.8)	24791.5 (7.8)	0.000
26-31	1137 (2.1)	31 607 (9.5)	-0.323	3648.6 (9.0)	28511.4 (9.0)	0.000
31-36	1703 (3.1)	34 524 (10.4)	-0.294	4047.0 (10.0)	31625.0 (10.0)	0.000
36-41	2571 (4.7)	37 047 (11.1)	-0.242	4416.0 (10.9)	34508.0 (10.9)	0.000
41-46	3335 (6.1)	35 359 (10.6)	-0.166	4279.5 (10.5)	33441.5 (10.5)	0.000
46-51	4243 (7.7)	30 711 (9.2)	-0.055	3831.9 (9.4)	29944.1 (9.4)	0.000
51-56	5301 (9.6)	28 177 (8.5)	0.040	3612.5 (8.9)	28229.5 (8.9)	0.000
56-61	6107 (11.1)	25 009 (7.5)	0.123	3267.2 (8.0)	25530.8 (8.0)	0.000
61-66	6560 (11.9)	19 809 (6.0)	0.210	2649.6 (6.5)	20705.4 (6.5)	0.000
66-71	6134 (11.1)	14 082 (4.2)	0.261	1895.1 (4.7)	14808.9 (4.7)	0.000
71-76	5050 (9.2)	9476 (2.9)	0.268	1243.8 (3.1)	9719.2 (3.1)	0.000
76-81	4480 (8.1)	6813 (2.0)	0.279	883.0 (2.2)	6900.0 (2.2)	0.000
81-86	4104 (7.4)	5529 (1.7)	0.280	712.4 (1.8)	5566.6 (1.8)	0.000

TABLE B11 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
86–91	2400 (4.4)	3158 (1.0)	0.213	382.0 (0.9)	2985.0 (0.9)	0.000
91–96	693 (1.3)	1101 (0.3)	0.105	106.3 (0.3)	830.7 (0.3)	0.000
96–101	95 (0.2)	214 (0.1)	0.031	12.6 (0.0)	98.4 (0.0)	0.000
101–106	2 (0.0)	7 (0.0)	0.003	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	22 645 (41.1)	162 983 (49.0)	−0.160	19383.8 (47.7)	151472.2 (47.7)	0.000
F	32 453 (58.9)	169 406 (51.0)	0.160	21269.2 (52.3)	166205.8 (52.3)	0.000
Vaccination status						
1/1, >90 d	2 (0.0)	2 (0.0)	0.007	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	12 (0.0)	47 (0.0)	0.006	0.3 (0.0)	2.7 (0.0)	0.000
1/1, 14–90d	5 (0.0)	48 (0.0)	−0.005	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	51 111 (92.8)	322 899 (97.1)	−0.201	39861.2 (98.1)	311490.8 (98.1)	0.000
1/2, >90 d	22 (0.0)	35 (0.0)	0.019	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	1121 (2.0)	3549 (1.1)	0.078	339.2 (0.8)	2650.8 (0.8)	0.000
1/2, 14–90 d	1791 (3.3)	3880 (1.2)	0.142	372.5 (0.9)	2910.5 (0.9)	0.000
2/2, >90 d	239 (0.4)	363 (0.1)	0.062	10.3 (0.0)	80.7 (0.0)	0.000
2/2, <14 d	242 (0.4)	420 (0.1)	0.059	13.7 (0.0)	107.3 (0.0)	0.000
2/2, 14–90 d	553 (1.0)	1146 (0.3)	0.081	55.7 (0.1)	435.3 (0.1)	0.000
Period						
Before 10.01.2021	32 317 (58.7)	192 599 (57.9)	0.014	24002.4 (59.0)	187563.6 (59.0)	0.000
10.01.2021 to 15.07.2021	22 102 (40.1)	132 866 (40.0)	0.003	15979.3 (39.3)	124868.7 (39.3)	0.000
After 15.07.2021	679 (1.2)	6924 (2.1)	−0.067	671.3 (1.7)	5245.7 (1.7)	0.000
Comorbidities						
Acute myocardial infarction	2830 (5.1)	2103 (0.6)	0.272	231.4 (0.6)	1808.6 (0.6)	0.000
Congestive heart failure	4234 (7.7)	3380 (1.0)	0.331	265.6 (0.7)	2075.4 (0.7)	0.000
Peripheral vascular disease	2238 (4.1)	2579 (0.8)	0.215	166.8 (0.4)	1303.2 (0.4)	0.000
Cerebrovascular disease	4552 (8.3)	5189 (1.6)	0.314	533.1 (1.3)	4165.9 (1.3)	0.000
Alzheimer dementia	1540 (2.8)	2294 (0.7)	0.161	187.6 (0.5)	1466.4 (0.5)	0.000
Other dementia	9700 (17.6)	21 520 (6.5)	0.347	2676.2 (6.6)	20912.8 (6.6)	0.000
Mild liver disease	1724 (3.1)	3363 (1.0)	0.149	338.3 (0.8)	2643.7 (0.8)	0.000
Diabetes without complications	11 803 (21.4)	21 896 (6.6)	0.438	2611.1 (6.4)	20403.9 (6.4)	0.000
Diabetes with complications	1499 (2.7)	1735 (0.5)	0.175	99.5 (0.2)	777.5 (0.2)	0.000
Renal disease	2805 (5.1)	1904 (0.6)	0.275	112.0 (0.3)	875.0 (0.3)	0.000
Cancer	6173 (11.2)	10 088 (3.0)	0.322	1116.0 (2.7)	8721.0 (2.7)	0.000
Moderate to severe liver disease	127 (0.2)	66 (0.0)	0.060	0.5 (0.0)	3.5 (0.0)	0.000
Metastatic cancer	611 (1.1)	375 (0.1)	0.128	25.3 (0.1)	197.7 (0.1)	0.000
HIV/AIDS	8 (0.0)	21 (0.0)	0.008	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	23 376 (42.4)	43 193 (13.0)	0.696	5933.6 (14.6)	46367.4 (14.6)	0.000
Beta blockers	16 969 (30.8)	22 235 (6.7)	0.650	3053.4 (7.5)	23860.6 (7.5)	0.000
Diuretics	13 757 (25.0)	14 387 (4.3)	0.610	1912.2 (4.7)	14942.8 (4.7)	0.000
Immunosuppressant drugs	1454 (2.6)	800 (0.2)	0.202	73.6 (0.2)	575.4 (0.2)	0.000
Systemic corticosteroids	2535 (4.6)	617 (0.2)	0.292	76.7 (0.2)	599.3 (0.2)	0.000
Antineoplastic drugs	975 (1.8)	1241 (0.4)	0.136	95.6 (0.2)	747.4 (0.2)	0.000
Antiviral agents	417 (0.8)	215 (0.1)	0.108	5.6 (0.0)	43.4 (0.0)	0.000

(Continues)

TABLE B11 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Death (composite)	4356 (7.9)	5599 (1.7)	0.294	747.4 (1.8)	5063.8 (1.6)	0.012
Death 1	3195 (5.8)	4366 (1.3)	0.244	588.8 (1.4)	4008.6 (1.3)	0.010
Death 2	2839 (5.2)	3698 (1.1)	0.234	487.1 (1.2)	3296.7 (1.0)	0.009
Death 3	3670 (6.7)	4519 (1.4)	0.273	613.6 (1.5)	4063.6 (1.3)	0.012
Hospitalization 1	5824 (10.6)	10 905 (3.3)	0.290	1842.0 (4.5)	9831.0 (3.1)	0.057
Hospitalization 2	12 735 (23.1)	26 965 (8.1)	0.422	4343.4 (10.7)	25487.1 (8.0)	0.075

TABLE B12 Sensitivity analysis: users (1–3 prescriptions) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 996	332 389		16 157	308 555	
Age (5-y bins)						
16–21	305 (1.6)	22 054 (6.6)	–0.255	1084.9 (6.7)	20719.1 (6.7)	0.000
21–26	515 (2.7)	27 711 (8.3)	–0.248	1374.2 (8.5)	26243.8 (8.5)	0.000
26–31	726 (3.8)	31 607 (9.5)	–0.230	1570.9 (9.7)	29999.1 (9.7)	0.000
31–36	1002 (5.3)	34 524 (10.4)	–0.191	1734.6 (10.7)	33125.4 (10.7)	0.000
36–41	1378 (7.3)	37 047 (11.1)	–0.135	1873.1 (11.6)	35770.9 (11.6)	0.000
41–46	1596 (8.4)	35 359 (10.6)	–0.076	1783.4 (11.0)	34058.6 (11.0)	0.000
46–51	1825 (9.6)	30 711 (9.2)	0.013	1557.6 (9.6)	29745.4 (9.6)	0.000
51–56	2101 (11.1)	28 177 (8.5)	0.087	1428.9 (8.8)	27288.1 (8.8)	0.000
56–61	2099 (11.0)	25 009 (7.5)	0.122	1238.1 (7.7)	23644.9 (7.7)	0.000
61–66	2054 (10.8)	19 809 (6.0)	0.176	955.9 (5.9)	18256.1 (5.9)	0.000
66–71	1680 (8.8)	14 082 (4.2)	0.187	637.2 (3.9)	12167.8 (3.9)	0.000
71–76	1310 (6.9)	9476 (2.9)	0.189	388.9 (2.4)	7427.1 (2.4)	0.000
76–81	1012 (5.3)	6813 (2.0)	0.175	239.9 (1.5)	4582.1 (1.5)	0.000
81–86	826 (4.3)	5529 (1.7)	0.158	178.1 (1.1)	3400.9 (1.1)	0.000
86–91	433 (2.3)	3158 (1.0)	0.106	90.0 (0.6)	1718.0 (0.6)	0.000
91–96	118 (0.6)	1101 (0.3)	0.042	20.6 (0.1)	392.4 (0.1)	0.000
96–101	16 (0.1)	214 (0.1)	0.007	0.8 (0.0)	15.2 (0.0)	0.000
101–106	0 (0.0)	7 (0.0)	–0.006	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	–0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7707 (40.6)	162 983 (49.0)	–0.171	7778.4 (48.1)	148545.6 (48.1)	0.000
F	11 289 (59.4)	169 406 (51.0)	0.171	8378.6 (51.9)	160009.4 (51.9)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	2 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	47 (0.0)	–0.003	0.1 (0.0)	2.9 (0.0)	0.000
1/1, 14–90 d	2 (0.0)	48 (0.0)	–0.004	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	18 000 (94.8)	322 899 (97.1)	–0.121	15906.8 (98.5)	303776.2 (98.5)	0.000
1/2, >90 d	7 (0.0)	35 (0.0)	0.017	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	332 (1.7)	3549 (1.1)	0.058	119.9 (0.7)	2289.1 (0.7)	0.000
1/2, 14–90 d	431 (2.3)	3880 (1.2)	0.085	108.5 (0.7)	2071.5 (0.7)	0.000

TABLE B12 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
2/2, >90 d	36 (0.2)	363 (0.1)	0.021	2.3 (0.0)	44.7 (0.0)	0.000
2/2, <14 d	56 (0.3)	420 (0.1)	0.037	3.8 (0.0)	73.2 (0.0)	0.000
2/2, 14–90 d	129 (0.7)	1146 (0.3)	0.047	15.6 (0.1)	297.4 (0.1)	0.000
Period						
Before 10.01.2021	10 627 (55.9)	192 599 (57.9)	−0.040	9501.1 (58.8)	181444.9 (58.8)	0.000
10.01.2021 to 15.07.2021	8105 (42.7)	132 866 (40.0)	0.055	6377.9 (39.5)	121800.1 (39.5)	0.000
After 15.07.2021	264 (1.4)	6924 (2.1)	−0.053	278.0 (1.7)	5310.0 (1.7)	0.000
Comorbidities						
Acute myocardial infarction	515 (2.7)	2103 (0.6)	0.163	41.2 (0.3)	786.8 (0.3)	0.000
Congestive heart failure	783 (4.1)	3380 (1.0)	0.197	36.9 (0.2)	704.1 (0.2)	0.000
Peripheral vascular disease	476 (2.5)	2579 (0.8)	0.136	33.0 (0.2)	630.0 (0.2)	0.000
Cerebrovascular disease	980 (5.2)	5189 (1.6)	0.201	117.2 (0.7)	2238.8 (0.7)	0.000
Alzheimer dementia	266 (1.4)	2294 (0.7)	0.070	34.0 (0.2)	649.0 (0.2)	0.000
Other dementia	2626 (13.8)	21 520 (6.5)	0.245	906.4 (5.6)	17310.6 (5.6)	0.000
Mild liver disease	502 (2.6)	3363 (1.0)	0.122	106.8 (0.7)	2039.2 (0.7)	0.000
Diabetes without complications	2729 (14.4)	21 896 (6.6)	0.256	769.6 (4.8)	14697.4 (4.8)	0.000
Diabetes with complications	304 (1.6)	1735 (0.5)	0.105	18.1 (0.1)	345.9 (0.1)	0.000
Renal disease	442 (2.3)	1904 (0.6)	0.147	12.3 (0.1)	234.7 (0.1)	0.000
Cancer	1848 (9.7)	10 088 (3.0)	0.276	348.3 (2.2)	6651.7 (2.2)	0.000
Moderate to severe liver disease	33 (0.2)	66 (0.0)	0.049	0.1 (0.0)	1.9 (0.0)	0.000
Metastatic cancer	183 (1.0)	375 (0.1)	0.116	6.0 (0.0)	115.0 (0.0)	0.000
HIV/AIDS	2 (0.0)	21 (0.0)	0.005	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	5450 (28.7)	43 193 (13.0)	0.394	1807.7 (11.2)	34522.3 (11.2)	0.000
Beta blockers	3309 (17.4)	22 235 (6.7)	0.334	797.6 (4.9)	15232.4 (4.9)	0.000
Diuretics	2567 (13.5)	14 387 (4.3)	0.326	436.3 (2.7)	8332.7 (2.7)	0.000
Immunosuppressant drugs	203 (1.1)	800 (0.2)	0.103	13.3 (0.1)	253.7 (0.1)	0.000
Systemic corticosteroids	539 (2.8)	617 (0.2)	0.219	15.4 (0.1)	294.6 (0.1)	0.000
Antineoplastic drugs	233 (1.2)	1241 (0.4)	0.096	24.6 (0.2)	470.4 (0.2)	0.000
Antiviral agents	80 (0.4)	215 (0.1)	0.072	1.1 (0.0)	20.9 (0.0)	0.000
Death (composite)	1070 (5.6)	5599 (1.7)	0.211	225.7 (1.4)	3369.8 (1.1)	0.016
Death 1	761 (4.0)	4366 (1.3)	0.168	183.2 (1.1)	2703.0 (0.9)	0.016
Death 2	704 (3.7)	3698 (1.1)	0.170	151.8 (0.9)	2222.7 (0.7)	0.014
Death 3	900 (4.7)	4519 (1.4)	0.197	183.2 (1.1)	2626.1 (0.9)	0.017
Hospitalization 1	1646 (8.7)	10 905 (3.3)	0.229	706.8 (4.4)	8214.2 (2.7)	0.073
Hospitalization 2	3624 (19.1)	26 965 (8.1)	0.324	1639.3 (10.1)	21297.6 (6.9)	0.096

TABLE B13 Sensitivity analysis: users (4–7 prescriptions) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	17 730	332 389		12 812	306 627	
Age (5-y bins)						
16–21	74 (0.4)	22 054 (6.6)	–0.342	841.4 (6.6)	20136.6 (6.6)	0.000
21–26	168 (0.9)	27 711 (8.3)	–0.357	1060.5 (8.3)	25381.5 (8.3)	0.000
26–31	251 (1.4)	31 607 (9.5)	–0.362	1234.0 (9.6)	29534.0 (9.6)	0.000
31–36	442 (2.5)	34 524 (10.4)	–0.326	1367.6 (10.7)	32729.4 (10.7)	0.000
36–41	707 (4.0)	37 047 (11.1)	–0.273	1462.9 (11.4)	35010.1 (11.4)	0.000
41–46	1006 (5.7)	35 359 (10.6)	–0.182	1393.0 (10.9)	33339.0 (10.9)	0.000
46–51	1352 (7.6)	30 711 (9.2)	–0.058	1230.7 (9.6)	29454.3 (9.6)	0.000
51–56	1727 (9.7)	28 177 (8.5)	0.044	1124.5 (8.8)	26911.5 (8.8)	0.000
56–61	2096 (11.8)	25 009 (7.5)	0.146	996.0 (7.8)	23836.0 (7.8)	0.000
61–66	2205 (12.4)	19 809 (6.0)	0.226	770.8 (6.0)	18447.2 (6.0)	0.000
66–71	2108 (11.9)	14 082 (4.2)	0.284	526.5 (4.1)	12600.5 (4.1)	0.000
71–76	1709 (9.6)	9476 (2.9)	0.283	323.1 (2.5)	7733.9 (2.5)	0.000
76–81	1469 (8.3)	6813 (2.0)	0.285	209.0 (1.6)	5002.0 (1.6)	0.000
81–86	1359 (7.7)	5529 (1.7)	0.288	164.4 (1.3)	3934.6 (1.3)	0.000
86–91	770 (4.3)	3158 (1.0)	0.213	83.1 (0.6)	1987.9 (0.6)	0.000
91–96	247 (1.4)	1101 (0.3)	0.115	21.8 (0.2)	521.2 (0.2)	0.000
96–101	40 (0.2)	214 (0.1)	0.042	2.8 (0.0)	67.2 (0.0)	0.000
101–106	0 (0.0)	7 (0.0)	–0.006	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	–0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7472 (42.1)	162 983 (49.0)	–0.139	6195.7 (48.4)	148280.3 (48.4)	0.000
F	10 258 (57.9)	169 406 (51.0)	0.139	6616.3 (51.6)	158346.7 (51.6)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	2 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	47 (0.0)	–0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	2 (0.0)	48 (0.0)	–0.003	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 370 (92.3)	322 899 (97.1)	–0.217	12637.4 (98.6)	302447.6 (98.6)	0.000
1/2, >90 d	8 (0.0)	35 (0.0)	0.021	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	367 (2.1)	3549 (1.1)	0.081	75.9 (0.6)	1817.1 (0.6)	0.000
1/2, 14–90 d	621 (3.5)	3880 (1.2)	0.155	88.3 (0.7)	2112.7 (0.7)	0.000
2/2, >90 d	76 (0.4)	363 (0.1)	0.062	1.5 (0.0)	36.5 (0.0)	0.000
2/2, <14 d	89 (0.5)	420 (0.1)	0.067	1.2 (0.0)	29.8 (0.0)	0.000
2/2, 14–90 d	194 (1.1)	1146 (0.3)	0.089	7.7 (0.1)	183.3 (0.1)	0.000
Period						
Before 10.01.2021	10 501 (59.2)	192 599 (57.9)	0.026	7642.2 (59.6)	182899.8 (59.6)	0.000
10.01.2021 to 15.07.2021	7015 (39.6)	132 866 (40.0)	–0.008	5026.0 (39.2)	120285.0 (39.2)	0.000
After 15.07.2021	214 (1.2)	6924 (2.1)	–0.069	143.8 (1.1)	3442.2 (1.1)	0.000
Comorbidities						
Acute myocardial infarction	934 (5.3)	2103 (0.6)	0.277	42.3 (0.3)	1012.7 (0.3)	0.000
Congestive heart failure	1353 (7.6)	3380 (1.0)	0.330	39.8 (0.3)	952.2 (0.3)	0.000
Peripheral vascular disease	748 (4.2)	2579 (0.8)	0.222	28.2 (0.2)	673.8 (0.2)	0.000
Cerebrovascular disease	1451 (8.2)	5189 (1.6)	0.311	105.8 (0.8)	2532.2 (0.8)	0.000
Alzheimer dementia	461 (2.6)	2294 (0.7)	0.151	32.4 (0.3)	775.6 (0.3)	0.000

TABLE B13 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Other dementia	3152 (17.8)	21 520 (6.5)	0.352	727.8 (5.7)	17419.2 (5.7)	0.000
Mild liver disease	578 (3.3)	3363 (1.0)	0.156	77.7 (0.6)	1859.3 (0.6)	0.000
Diabetes without complications	3888 (21.9)	21 896 (6.6)	0.450	646.7 (5.0)	15477.3 (5.0)	0.000
Diabetes with complications	450 (2.5)	1735 (0.5)	0.165	12.8 (0.1)	307.2 (0.1)	0.000
Renal disease	939 (5.3)	1904 (0.6)	0.283	17.3 (0.1)	413.7 (0.1)	0.000
Cancer	2017 (11.4)	10 088 (3.0)	0.327	263.3 (2.1)	6301.7 (2.1)	0.000
Moderate to severe liver disease	43 (0.2)	66 (0.0)	0.062	0.0 (0.0)	0.0 (0.0)	0.000
Metastatic cancer	208 (1.2)	375 (0.1)	0.133	3.6 (0.0)	86.4 (0.0)	0.000
HIV/AIDS	4 (0.0)	21 (0.0)	0.014	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	7861 (44.3)	43 193 (13.0)	0.739	1548.8 (12.1)	37066.2 (12.1)	0.000
Beta blockers	5842 (32.9)	22 235 (6.7)	0.698	742.2 (5.8)	17762.8 (5.8)	0.000
Diuretics	4586 (25.9)	14 387 (4.3)	0.631	411.2 (3.2)	9841.8 (3.2)	0.000
Immunosuppressant drugs	560 (3.2)	800 (0.2)	0.227	15.8 (0.1)	377.2 (0.1)	0.000
Systemic corticosteroids	920 (5.2)	617 (0.2)	0.313	14.0 (0.1)	334.0 (0.1)	0.000
Antineoplastic drugs	337 (1.9)	1241 (0.4)	0.144	16.3 (0.1)	390.7 (0.1)	0.000
Antiviral agents	150 (0.8)	215 (0.1)	0.116	0.8 (0.0)	18.2 (0.0)	0.000
Death (composite)	1397 (7.9)	5599 (1.7)	0.293	169.7 (1.3)	3681.6 (1.2)	0.006
Death 1	1022 (5.8)	4366 (1.3)	0.243	126.6 (1.0)	2948.4 (1.0)	0.001
Death 2	920 (5.2)	3698 (1.1)	0.235	113.4 (0.9)	2409.1 (0.8)	0.006
Death 3	1170 (6.6)	4519 (1.4)	0.270	139.5 (1.1)	2925.9 (1.0)	0.007
Hospitalization 1	1830 (10.3)	10 905 (3.3)	0.282	424.0 (3.3)	8374.5 (2.7)	0.023
Hospitalization 2	4096 (23.1)	26 965 (8.1)	0.422	1150.9 (9.0)	21800.4 (7.1)	0.053

TABLE B14 Sensitivity analysis: users (≥ 8 prescriptions) vs. nonusers (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 372	332 389		11 684	303 530	
Age (5-y bins)						
16–21	22 (0.1)	22 054 (6.6)	−0.367	735.1 (6.3)	19095.9 (6.3)	0.000
21–26	99 (0.5)	27 711 (8.3)	−0.386	957.0 (8.2)	24862.0 (8.2)	0.000
26–31	160 (0.9)	31 607 (9.5)	−0.397	1116.9 (9.6)	29014.1 (9.6)	0.000
31–36	259 (1.4)	34 524 (10.4)	−0.388	1235.7 (10.6)	32101.3 (10.6)	0.000
36–41	486 (2.6)	37 047 (11.1)	−0.340	1337.4 (11.4)	34743.6 (11.4)	0.000
41–46	733 (4.0)	35 359 (10.6)	−0.257	1277.9 (10.9)	33197.1 (10.9)	0.000
46–51	1066 (5.8)	30 711 (9.2)	−0.131	1121.7 (9.6)	29139.3 (9.6)	0.000
51–56	1473 (8.0)	28 177 (8.5)	−0.017	1024.8 (8.8)	26623.2 (8.8)	0.000
56–61	1912 (10.4)	25 009 (7.5)	0.101	898.8 (7.7)	23349.2 (7.7)	0.000
61–66	2301 (12.5)	19 809 (6.0)	0.228	708.9 (6.1)	18417.1 (6.1)	0.000
66–71	2346 (12.8)	14 082 (4.2)	0.310	483.6 (4.1)	12564.4 (4.1)	0.000
71–76	2031 (11.1)	9476 (2.9)	0.327	302.8 (2.6)	7866.2 (2.6)	0.000
76–81	1999 (10.9)	6813 (2.0)	0.365	208.2 (1.8)	5409.8 (1.8)	0.000
81–86	1919 (10.4)	5529 (1.7)	0.375	162.9 (1.4)	4232.1 (1.4)	0.000
86–91	1197 (6.5)	3158 (1.0)	0.297	86.6 (0.7)	2248.4 (0.7)	0.000

(Continues)

TABLE B14 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
91–96	328 (1.8)	1101 (0.3)	0.142	23.6 (0.2)	612.4 (0.2)	0.000
96–101	39 (0.2)	214 (0.1)	0.040	2.1 (0.0)	53.9 (0.0)	0.000
101–106	2 (0.0)	7 (0.0)	0.011	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	1 (0.0)	−0.002	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7466 (40.6)	162 983 (49.0)	−0.169	5643.5 (48.3)	146607.5 (48.3)	0.000
F	10 906 (59.4)	169 406 (51.0)	0.169	6040.5 (51.7)	156922.5 (51.7)	0.000
Vaccination status						
1/1, >90 d	0 (0.0)	2 (0.0)	−0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	8 (0.0)	47 (0.0)	0.017	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	1 (0.0)	48 (0.0)	−0.009	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 741 (91.1)	322 899 (97.1)	−0.258	11547.8 (98.8)	299992.2 (98.8)	0.000
1/2, >90 d	7 (0.0)	35 (0.0)	0.018	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	422 (2.3)	3549 (1.1)	0.096	66.0 (0.6)	1714.0 (0.6)	0.000
1/2, 14–90 d	739 (4.0)	3880 (1.2)	0.180	63.8 (0.5)	1656.2 (0.5)	0.000
2/2, >90 d	127 (0.7)	363 (0.1)	0.092	0.6 (0.0)	14.4 (0.0)	0.000
2/2, <14 d	97 (0.5)	420 (0.1)	0.070	1.0 (0.0)	27.0 (0.0)	0.000
2/2, 14–90 d	230 (1.3)	1146 (0.3)	0.102	4.9 (0.0)	126.1 (0.0)	0.000
Period						
Before 10.01.2021	11 189 (60.9)	192 599 (57.9)	0.060	7050.3 (60.3)	183155.7 (60.3)	0.000
10.01.2021 to 15.07.2021	6982 (38.0)	132 866 (40.0)	−0.040	4566.1 (39.1)	118618.9 (39.1)	0.000
After 15.07.2021	201 (1.1)	6924 (2.1)	−0.079	67.6 (0.6)	1755.4 (0.6)	0.000
Comorbidities						
Acute myocardial infarction	1381 (7.5)	2103 (0.6)	0.354	44.6 (0.4)	1159.4 (0.4)	0.000
Congestive heart failure	2098 (11.4)	3380 (1.0)	0.441	46.6 (0.4)	1209.4 (0.4)	0.000
Peripheral vascular disease	1014 (5.5)	2579 (0.8)	0.274	25.1 (0.2)	651.9 (0.2)	0.000
Cerebrovascular disease	2121 (11.5)	5189 (1.6)	0.412	104.0 (0.9)	2701.0 (0.9)	0.000
Alzheimer dementia	813 (4.4)	2294 (0.7)	0.238	42.6 (0.4)	1105.4 (0.4)	0.000
Other dementia	3922 (21.3)	21 520 (6.5)	0.440	653.6 (5.6)	16979.4 (5.6)	0.000
Mild liver disease	644 (3.5)	3363 (1.0)	0.168	65.6 (0.6)	1703.4 (0.6)	0.000
Diabetes without complications	5186 (28.2)	21 896 (6.6)	0.595	622.5 (5.3)	16171.5 (5.3)	0.000
Diabetes with complications	745 (4.1)	1735 (0.5)	0.238	17.1 (0.1)	443.9 (0.1)	0.000
Renal disease	1424 (7.8)	1904 (0.6)	0.365	18.0 (0.2)	468.0 (0.2)	0.000
Cancer	2308 (12.6)	10 088 (3.0)	0.361	233.0 (2.0)	6052.0 (2.0)	0.000
Moderate to severe liver disease	51 (0.3)	66 (0.0)	0.067	0.1 (0.0)	1.9 (0.0)	0.000
Metastatic cancer	220 (1.2)	375 (0.1)	0.135	2.7 (0.0)	71.3 (0.0)	0.000
HIV/AIDS	2 (0.0)	21 (0.0)	0.005	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	10 065 (54.8)	43 193 (13.0)	0.984	1491.2 (12.8)	38739.8 (12.8)	0.000
Beta blockers	7818 (42.6)	22 235 (6.7)	0.916	724.2 (6.2)	18812.8 (6.2)	0.000
Diuretics	6604 (35.9)	14 387 (4.3)	0.858	434.1 (3.7)	11275.9 (3.7)	0.000
Immunosuppressant drugs	691 (3.8)	800 (0.2)	0.253	11.4 (0.1)	296.6 (0.1)	0.000
Systemic corticosteroids	1076 (5.9)	617 (0.2)	0.336	12.1 (0.1)	313.9 (0.1)	0.000
Antineoplastic drugs	405 (2.2)	1241 (0.4)	0.163	15.8 (0.1)	411.2 (0.1)	0.000
Antiviral agents	187 (1.0)	215 (0.1)	0.130	0.7 (0.0)	17.3 (0.0)	0.000
Death (composite)	1889 (10.3)	5599 (1.7)	0.369	164.5 (1.4)	3929.9 (1.3)	0.005

TABLE B14 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Death 1	1412 (7.7)	4366 (1.3)	0.311	130.7 (1.1)	3134.8 (1.0)	0.004
Death 2	1215 (6.6)	3698 (1.1)	0.288	100.7 (0.9)	2549.6 (0.8)	0.001
Death 3	1600 (8.7)	4519 (1.4)	0.341	134.8 (1.2)	3129.3 (1.0)	0.006
Hospitalization 1	2348 (12.8)	10 905 (3.3)	0.355	539.3 (4.6)	8339.3 (2.7)	0.070
Hospitalization 2	5015 (27.3)	26 965 (8.1)	0.519	1143.0 (9.8)	21977.6 (7.2)	0.069

TABLE B15 Sensitivity analysis: users (all) vs. possible (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	55 098	18 170		33 272	16 434	
Age (5-y bins)						
16–21	401 (0.7)	540 (3.0)	−0.167	591.7 (1.8)	292.3 (1.8)	0.000
21–26	782 (1.4)	759 (4.2)	−0.168	954.5 (2.9)	471.5 (2.9)	0.000
26–31	1137 (2.1)	981 (5.4)	−0.177	1291.2 (3.9)	637.8 (3.9)	0.000
31–36	1703 (3.1)	1142 (6.3)	−0.152	1737.0 (5.2)	858.0 (5.2)	0.000
36–41	2571 (4.7)	1425 (7.8)	−0.131	2405.1 (7.2)	1187.9 (7.2)	0.000
41–46	3335 (6.1)	1644 (9.0)	−0.114	2923.2 (8.8)	1443.8 (8.8)	0.000
46–51	4243 (7.7)	1775 (9.8)	−0.073	3412.5 (10.3)	1685.5 (10.3)	0.000
51–56	5301 (9.6)	1833 (10.1)	−0.016	3823.5 (11.5)	1888.5 (11.5)	0.000
56–61	6107 (11.1)	1886 (10.4)	0.023	3982.1 (12.0)	1966.9 (12.0)	0.000
61–66	6560 (11.9)	1664 (9.2)	0.090	3707.0 (11.1)	1831.0 (11.1)	0.000
66–71	6134 (11.1)	1332 (7.3)	0.132	2824.1 (8.5)	1394.9 (8.5)	0.000
71–76	5050 (9.2)	1010 (5.6)	0.138	2016.8 (6.1)	996.2 (6.1)	0.000
76–81	4480 (8.1)	831 (4.6)	0.146	1446.5 (4.3)	714.5 (4.3)	0.000
81–86	4104 (7.4)	755 (4.2)	0.141	1300.6 (3.9)	642.4 (3.9)	0.000
86–91	2400 (4.4)	430 (2.4)	0.111	684.1 (2.1)	337.9 (2.1)	0.000
91–96	693 (1.3)	135 (0.7)	0.052	158.0 (0.5)	78.0 (0.5)	0.000
96–101	95 (0.2)	28 (0.2)	0.005	14.1 (0.0)	6.9 (0.0)	0.000
101–106	2 (0.0)	0 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	22 645 (41.1)	7582 (41.7)	−0.013	12892.8 (38.7)	6368.2 (38.7)	0.000
F	32 453 (58.9)	10 588 (58.3)	0.013	20379.2 (61.3)	10065.8 (61.3)	0.000
Vaccination status						
1/1, >90 d	2 (0.0)	0 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	12 (0.0)	1 (0.0)	0.014	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	5 (0.0)	0 (0.0)	0.013	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	51 111 (92.8)	17 347 (95.5)	−0.115	32515.6 (97.7)	16060.4 (97.7)	0.000
1/2, >90 d	22 (0.0)	7 (0.0)	0.001	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	1121 (2.0)	295 (1.6)	0.031	315.9 (0.9)	156.1 (0.9)	0.000
1/2, 14–90 d	1791 (3.3)	355 (2.0)	0.082	399.6 (1.2)	197.4 (1.2)	0.000
2/2, >90 d	239 (0.4)	30 (0.2)	0.049	4.0 (0.0)	2.0 (0.0)	0.000

(Continues)

TABLE B15 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
2/2, <14 d	242 (0.4)	44 (0.2)	0.034	9.4 (0.0)	4.6 (0.0)	0.000
2/2, 14–90 d	553 (1.0)	91 (0.5)	0.058	27.4 (0.1)	13.6 (0.1)	0.000
Period						
Before 10.01.2021	32 317 (58.7)	10 566 (58.2)	0.010	20363.1 (61.2)	10057.9 (61.2)	0.000
10.01.2021 to 15.07.2021	22 102 (40.1)	7257 (39.9)	0.004	12637.8 (38.0)	6242.2 (38.0)	0.000
After 15.07.2021	679 (1.2)	347 (1.9)	−0.054	271.1 (0.8)	133.9 (0.8)	0.000
Comorbidities						
Acute myocardial infarction	2830 (5.1)	198 (1.1)	0.235	254.4 (0.8)	125.6 (0.8)	0.000
Congestive heart failure	4234 (7.7)	462 (2.5)	0.235	309.9 (0.9)	153.1 (0.9)	0.000
Peripheral vascular disease	2238 (4.1)	301 (1.7)	0.145	184.7 (0.6)	91.3 (0.6)	0.000
Cerebrovascular disease	4552 (8.3)	604 (3.3)	0.213	742.3 (2.2)	366.7 (2.2)	0.000
Alzheimer dementia	1540 (2.8)	249 (1.4)	0.100	209.5 (0.6)	103.5 (0.6)	0.000
Other dementia	9700 (17.6)	1979 (10.9)	0.193	3488.1 (10.5)	1722.9 (10.5)	0.000
Mild liver disease	2849 (5.2)	337 (1.9)	0.181	634.6 (1.9)	313.4 (1.9)	0.000
Diabetes without complications	1724 (3.1)	340 (1.9)	0.081	403.0 (1.2)	199.0 (1.2)	0.000
Diabetes with complications	11 803 (21.4)	2449 (13.5)	0.210	3901.8 (11.7)	1927.2 (11.7)	0.000
Renal disease	1499 (2.7)	202 (1.1)	0.118	91.0 (0.3)	45.0 (0.3)	0.000
Cancer	2805 (5.1)	252 (1.4)	0.210	119.8 (0.4)	59.2 (0.4)	0.000
Moderate to severe liver disease	6173 (11.2)	971 (5.3)	0.214	1419.7 (4.3)	701.3 (4.3)	0.000
Metastatic cancer	127 (0.2)	7 (0.0)	0.052	0.0 (0.0)	0.0 (0.0)	0.000
HIV/AIDS	611 (1.1)	52 (0.3)	0.099	23.4 (0.1)	11.6 (0.1)	0.000
RAAS inhibitors	8 (0.0)	1 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
Beta blockers	23 376 (42.4)	4841 (26.6)	0.337	10210.0 (30.7)	5043.0 (30.7)	0.000
Diuretics	16 969 (30.8)	2450 (13.5)	0.426	5316.2 (16.0)	2625.8 (16.0)	0.000
Immunosuppressant drugs	13 757 (25.0)	1872 (10.3)	0.392	3547.0 (10.7)	1752.0 (10.7)	0.000
Systemic corticosteroids	1454 (2.6)	75 (0.4)	0.182	77.6 (0.2)	38.4 (0.2)	0.000
Antineoplastic drugs	2535 (4.6)	72 (0.4)	0.272	81.0 (0.2)	40.0 (0.2)	0.000
Antiviral agents	975 (1.8)	118 (0.6)	0.103	100.4 (0.3)	49.6 (0.3)	0.000
Comorbidities	417 (0.8)	16 (0.1)	0.103	0.0 (0.0)	0.0 (0.0)	0.000
Death (composite)	4356 (7.9)	803 (4.4)	0.145	1082.8 (3.3)	609.8 (3.7)	−0.019
Death 1	3195 (5.8)	585 (3.2)	0.125	854.1 (2.6)	458.4 (2.8)	−0.011
Death 2	2839 (5.2)	519 (2.9)	0.117	708.2 (2.1)	395.1 (2.4)	−0.014
Death 3	3670 (6.7)	666 (3.7)	0.136	885.2 (2.7)	498.2 (3.0)	−0.017
Hospitalization 1	5824 (10.6)	1160 (6.4)	0.151	1943.7 (5.8)	910.2 (5.5)	0.011
Hospitalization 2	12 735 (23.1)	2680 (14.7)	0.215	4821.5 (14.5)	2280.9 (13.9)	0.016

TABLE B16 Sensitivity analysis: users (1–3 prescriptions) vs. possible (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 996	18 170		14 205	15 405	
Age (5-y bins)						
16–21	305 (1.6)	540 (3.0)	–0.091	383.3 (2.7)	415.7 (2.7)	0.000
21–26	515 (2.7)	759 (4.2)	–0.080	580.5 (4.1)	629.5 (4.1)	0.000
26–31	726 (3.8)	981 (5.4)	–0.075	767.1 (5.4)	831.9 (5.4)	0.000
31–36	1002 (5.3)	1142 (6.3)	–0.043	969.1 (6.8)	1050.9 (6.8)	0.000
36–41	1378 (7.3)	1425 (7.8)	–0.022	1261.7 (8.9)	1368.3 (8.9)	0.000
41–46	1596 (8.4)	1644 (9.0)	–0.023	1427.7 (10.1)	1548.3 (10.1)	0.000
46–51	1825 (9.6)	1775 (9.8)	–0.005	1559.1 (11.0)	1690.9 (11.0)	0.000
51–56	2101 (11.1)	1833 (10.1)	0.032	1646.0 (11.6)	1785.0 (11.6)	0.000
56–61	2099 (11.0)	1886 (10.4)	0.022	1586.5 (11.2)	1720.5 (11.2)	0.000
61–66	2054 (10.8)	1664 (9.2)	0.055	1383.1 (9.7)	1499.9 (9.7)	0.000
66–71	1680 (8.8)	1332 (7.3)	0.056	975.8 (6.9)	1058.2 (6.9)	0.000
71–76	1310 (6.9)	1010 (5.6)	0.055	655.8 (4.6)	711.2 (4.6)	0.000
76–81	1012 (5.3)	831 (4.6)	0.035	433.7 (3.1)	470.3 (3.1)	0.000
81–86	826 (4.3)	755 (4.2)	0.010	360.8 (2.5)	391.2 (2.5)	0.000
86–91	433 (2.3)	430 (2.4)	–0.006	179.4 (1.3)	194.6 (1.3)	0.000
91–96	118 (0.6)	135 (0.7)	–0.015	34.5 (0.2)	37.5 (0.2)	0.000
96–101	16 (0.1)	28 (0.2)	–0.020	1.0 (0.0)	1.0 (0.0)	0.000
101–106	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7707 (40.6)	7582 (41.7)	–0.024	5553.9 (39.1)	6023.1 (39.1)	0.000
F	11 289 (59.4)	10 588 (58.3)	0.024	8651.1 (60.9)	9381.9 (60.9)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	0 (0.0)	0.010	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	1 (0.0)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	2 (0.0)	0 (0.0)	0.015	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	18 000 (94.8)	17 347 (95.5)	–0.033	13918.6 (98.0)	15094.4 (98.0)	0.000
1/2, >90 d	7 (0.0)	7 (0.0)	–0.001	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	332 (1.7)	295 (1.6)	0.010	131.4 (0.9)	142.6 (0.9)	0.000
1/2, 14–90 d	431 (2.3)	355 (2.0)	0.022	139.6 (1.0)	151.4 (1.0)	0.000
2/2, >90 d	36 (0.2)	30 (0.2)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
2/2, <14 d	56 (0.3)	44 (0.2)	0.010	3.4 (0.0)	3.6 (0.0)	0.000
2/2, 14–90 d	129 (0.7)	91 (0.5)	0.023	12.0 (0.1)	13.0 (0.1)	0.000
Period						
Before 10.01.2021	10 627 (55.9)	10 566 (58.2)	–0.045	8404.5 (59.2)	9114.5 (59.2)	0.000
10.01.2021 to 15.07.2021	8105 (42.7)	7257 (39.9)	0.055	5644.1 (39.7)	6120.9 (39.7)	0.000
After 15.07.2021	264 (1.4)	347 (1.9)	–0.041	156.4 (1.1)	169.6 (1.1)	0.000
Comorbidities						
Acute myocardial infarction	515 (2.7)	198 (1.1)	0.119	54.2 (0.4)	58.8 (0.4)	0.000
Congestive heart failure	783 (4.1)	462 (2.5)	0.088	70.5 (0.5)	76.5 (0.5)	0.000
Peripheral vascular disease	476 (2.5)	301 (1.7)	0.060	56.1 (0.4)	60.9 (0.4)	0.000
Cerebrovascular disease	980 (5.2)	604 (3.3)	0.091	196.7 (1.4)	213.3 (1.4)	0.000
Alzheimer dementia	266 (1.4)	249 (1.4)	0.003	48.9 (0.3)	53.1 (0.3)	0.000

(Continues)

TABLE B16 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Other dementia	2626 (13.8)	1979 (10.9)	0.089	1282.8 (9.0)	1391.2 (9.0)	0.000
Mild liver disease	502 (2.6)	340 (1.9)	0.052	160.7 (1.1)	174.3 (1.1)	0.000
Diabetes without complications	2729 (14.4)	2449 (13.5)	0.026	1266.5 (8.9)	1373.5 (8.9)	0.000
Diabetes with complications	304 (1.6)	202 (1.1)	0.042	21.6 (0.2)	23.4 (0.2)	0.000
Renal disease	442 (2.3)	252 (1.4)	0.070	22.5 (0.2)	24.5 (0.2)	0.000
Cancer	1848 (9.7)	971 (5.3)	0.167	542.1 (3.8)	587.9 (3.8)	0.000
Moderate to severe liver disease	33 (0.2)	7 (0.0)	0.042	0.0 (0.0)	0.0 (0.0)	0.000
Metastatic cancer	183 (1.0)	52 (0.3)	0.086	9.6 (0.1)	10.4 (0.1)	0.000
HIV/AIDS	2 (0.0)	1 (0.0)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	5450 (28.7)	4841 (26.6)	0.046	3196.5 (22.5)	3466.5 (22.5)	0.000
Beta blockers	3309 (17.4)	2450 (13.5)	0.109	1435.9 (10.1)	1557.1 (10.1)	0.000
Diuretics	2567 (13.5)	1872 (10.3)	0.099	893.7 (6.3)	969.3 (6.3)	0.000
Immunosuppressant drugs	203 (1.1)	75 (0.4)	0.077	21.6 (0.2)	23.4 (0.2)	0.000
Systemic corticosteroids	539 (2.8)	72 (0.4)	0.194	26.9 (0.2)	29.1 (0.2)	0.000
Antineoplastic drugs	233 (1.2)	118 (0.6)	0.060	33.1 (0.2)	35.9 (0.2)	0.000
Antiviral agents	80 (0.4)	16 (0.1)	0.066	0.0 (0.0)	0.0 (0.0)	0.000
Death (composite)	1070 (5.6)	803 (4.4)	0.056	363.2 (2.6)	386.9 (2.5)	0.002
Death 1	761 (4.0)	585 (3.2)	0.042	288.2 (2.0)	297.0 (1.9)	0.005
Death 2	704 (3.7)	519 (2.9)	0.048	244.2 (1.7)	256.4 (1.7)	0.003
Death 3	900 (4.7)	666 (3.7)	0.053	292.9 (2.1)	317.5 (2.1)	0.000
Hospitalization 1	1646 (8.7)	1160 (6.4)	0.087	803.4 (5.7)	701.2 (4.6)	0.042
Hospitalization 2	3624 (19.1)	2680 (14.7)	0.116	1912.6 (13.5)	1801.1 (11.7)	0.047

TABLE B17 Sensitivity analysis: users (4–7 prescriptions) vs. possible (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	17 730	18 170		10 315	15 414	
Age (5-y bins)						
16–21	74 (0.4)	540 (3.0)	−0.199	224.5 (2.2)	335.5 (2.2)	0.000
21–26	168 (0.9)	759 (4.2)	−0.205	334.0 (3.2)	499.0 (3.2)	0.000
26–31	251 (1.4)	981 (5.4)	−0.221	453.4 (4.4)	677.6 (4.4)	0.000
31–36	442 (2.5)	1142 (6.3)	−0.186	585.7 (5.7)	875.3 (5.7)	0.000
36–41	707 (4.0)	1425 (7.8)	−0.164	771.3 (7.5)	1152.7 (7.5)	0.000
41–46	1006 (5.7)	1644 (9.0)	−0.129	937.3 (9.1)	1400.7 (9.1)	0.000
46–51	1352 (7.6)	1775 (9.8)	−0.076	1086.5 (10.5)	1623.5 (10.5)	0.000
51–56	1727 (9.7)	1833 (10.1)	−0.012	1172.7 (11.4)	1752.3 (11.4)	0.000
56–61	2096 (11.8)	1886 (10.4)	0.046	1228.8 (11.9)	1836.2 (11.9)	0.000
61–66	2205 (12.4)	1664 (9.2)	0.106	1083.7 (10.5)	1619.3 (10.5)	0.000
66–71	2108 (11.9)	1332 (7.3)	0.155	840.7 (8.2)	1256.3 (8.2)	0.000
71–76	1709 (9.6)	1010 (5.6)	0.154	578.9 (5.6)	865.1 (5.6)	0.000
76–81	1469 (8.3)	831 (4.6)	0.152	410.5 (4.0)	613.5 (4.0)	0.000
81–86	1359 (7.7)	755 (4.2)	0.149	367.2 (3.6)	548.8 (3.6)	0.000

TABLE B17 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
86–91	770 (4.3)	430 (2.4)	0.110	191.6 (1.9)	286.4 (1.9)	0.000
91–96	247 (1.4)	135 (0.7)	0.063	42.5 (0.4)	63.5 (0.4)	0.000
96–101	40 (0.2)	28 (0.2)	0.016	5.6 (0.1)	8.4 (0.1)	0.000
101–106	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7472 (42.1)	7582 (41.7)	0.008	4092.1 (39.7)	6114.9 (39.7)	0.000
F	10 258 (57.9)	10 588 (58.3)	−0.008	6222.9 (60.3)	9299.1 (60.3)	0.000
Vaccination status						
1/1, >90 d	1 (0.0)	0 (0.0)	0.011	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	2 (0.0)	1 (0.0)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90 d	2 (0.0)	0 (0.0)	0.015	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 370 (92.3)	17 347 (95.5)	−0.132	10105.3 (98.0)	15100.7 (98.0)	0.000
1/2, >90 d	8 (0.0)	7 (0.0)	0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	367 (2.1)	295 (1.6)	0.033	87.4 (0.8)	130.6 (0.8)	0.000
1/2, 14–90 d	621 (3.5)	355 (2.0)	0.095	112.3 (1.1)	167.7 (1.1)	0.000
2/2, >90 d	76 (0.4)	30 (0.2)	0.048	2.0 (0.0)	3.0 (0.0)	0.000
2/2, <14 d	89 (0.5)	44 (0.2)	0.043	2.8 (0.0)	4.2 (0.0)	0.000
2/2, 14–90 d	194 (1.1)	91 (0.5)	0.067	5.2 (0.1)	7.8 (0.1)	0.000
Period						
Before 10.01.2021	10 501 (59.2)	10 566 (58.2)	0.022	6370.9 (61.8)	9520.1 (61.8)	0.000
10.01.2021 to 15.07.2021	7015 (39.6)	7257 (39.9)	−0.008	3868.4 (37.5)	5780.6 (37.5)	0.000
After 15.07.2021	214 (1.2)	347 (1.9)	−0.057	75.8 (0.7)	113.2 (0.7)	0.000
Comorbidities						
Acute myocardial infarction	934 (5.3)	198 (1.1)	0.240	60.5 (0.6)	90.5 (0.6)	0.000
Congestive heart failure	1353 (7.6)	462 (2.5)	0.233	71.4 (0.7)	106.6 (0.7)	0.000
Peripheral vascular disease	748 (4.2)	301 (1.7)	0.152	38.1 (0.4)	56.9 (0.4)	0.000
Cerebrovascular disease	1451 (8.2)	604 (3.3)	0.210	192.4 (1.9)	287.6 (1.9)	0.000
Alzheimer dementia	461 (2.6)	249 (1.4)	0.088	47.3 (0.5)	70.7 (0.5)	0.000
Other dementia	3152 (17.8)	1979 (10.9)	0.197	991.4 (9.6)	1481.6 (9.6)	0.000
Mild liver disease	578 (3.3)	340 (1.9)	0.088	106.2 (1.0)	158.8 (1.0)	0.000
Diabetes without complications	3888 (21.9)	2449 (13.5)	0.223	1096.5 (10.6)	1638.5 (10.6)	0.000
Diabetes with complications	450 (2.5)	202 (1.1)	0.107	17.2 (0.2)	25.8 (0.2)	0.000
Renal disease	939 (5.3)	252 (1.4)	0.219	24.5 (0.2)	36.5 (0.2)	0.000
Cancer	2017 (11.4)	971 (5.3)	0.219	362.4 (3.5)	541.6 (3.5)	0.000
Moderate to severe liver disease	43 (0.2)	7 (0.0)	0.054	0.0 (0.0)	0.0 (0.0)	0.000
Metastatic cancer	208 (1.2)	52 (0.3)	0.104	2.8 (0.0)	4.2 (0.0)	0.000
HIV/AIDS	4 (0.0)	1 (0.0)	0.014	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	7861 (44.3)	4841 (26.6)	0.376	2970.7 (28.8)	4439.3 (28.8)	0.000
Beta blockers	5842 (32.9)	2450 (13.5)	0.474	1503.0 (14.6)	2246.0 (14.6)	0.000
Diuretics	4586 (25.9)	1872 (10.3)	0.413	975.0 (9.5)	1457.0 (9.5)	0.000
Immunosuppressant drugs	560 (3.2)	75 (0.4)	0.208	21.2 (0.2)	31.8 (0.2)	0.000
Systemic corticosteroids	920 (5.2)	72 (0.4)	0.294	22.5 (0.2)	33.5 (0.2)	0.000
Antineoplastic drugs	337 (1.9)	118 (0.6)	0.112	21.2 (0.2)	31.8 (0.2)	0.000
Antiviral agents	150 (0.8)	16 (0.1)	0.111	0.0 (0.0)	0.0 (0.0)	0.000

(Continues)

TABLE B17 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Death (composite)	1397 (7.9)	803 (4.4)	0.144	282.6 (2.7)	519.7 (3.4)	-0.026
Death 1	1022 (5.8)	585 (3.2)	0.123	216.0 (2.1)	395.9 (2.6)	-0.023
Death 2	920 (5.2)	519 (2.9)	0.119	179.8 (1.7)	340.6 (2.2)	-0.024
Death 3	1170 (6.6)	666 (3.7)	0.133	234.7 (2.3)	421.2 (2.7)	-0.021
Hospitalization 1	1830 (10.3)	1160 (6.4)	0.143	501.9 (4.9)	812.1 (5.3)	-0.015
Hospitalization 2	4096 (23.1)	2680 (14.7)	0.214	1322.5 (12.8)	2031.5 (13.2)	-0.009

TABLE B18 Sensitivity analysis: users (≥ 8 prescriptions) vs. possible (counts/weighted counts, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	18 372	18 170		8752	15 337	
Age (5-y bins)						
16-21	22 (0.1)	540 (3.0)	-0.233	176.9 (2.0)	310.1 (2.0)	0.000
21-26	99 (0.5)	759 (4.2)	-0.242	273.2 (3.1)	478.8 (3.1)	0.000
26-31	160 (0.9)	981 (5.4)	-0.262	374.9 (4.3)	657.1 (4.3)	0.000
31-36	259 (1.4)	1142 (6.3)	-0.256	451.2 (5.2)	790.8 (5.2)	0.000
36-41	486 (2.6)	1425 (7.8)	-0.235	616.6 (7.0)	1080.4 (7.0)	0.000
41-46	733 (4.0)	1644 (9.0)	-0.206	743.0 (8.5)	1302.0 (8.5)	0.000
46-51	1066 (5.8)	1775 (9.8)	-0.148	860.7 (9.8)	1508.3 (9.8)	0.000
51-56	1473 (8.0)	1833 (10.1)	-0.072	942.8 (10.8)	1652.2 (10.8)	0.000
56-61	1912 (10.4)	1886 (10.4)	0.001	1007.5 (11.5)	1765.5 (11.5)	0.000
61-66	2301 (12.5)	1664 (9.2)	0.108	948.6 (10.8)	1662.4 (10.8)	0.000
66-71	2346 (12.8)	1332 (7.3)	0.182	757.5 (8.7)	1327.5 (8.7)	0.000
71-76	2031 (11.1)	1010 (5.6)	0.200	542.1 (6.2)	949.9 (6.2)	0.000
76-81	1999 (10.9)	831 (4.6)	0.238	417.8 (4.8)	732.2 (4.8)	0.000
81-86	1919 (10.4)	755 (4.2)	0.244	380.0 (4.3)	666.0 (4.3)	0.000
86-91	1197 (6.5)	430 (2.4)	0.202	205.3 (2.3)	359.7 (2.3)	0.000
91-96	328 (1.8)	135 (0.7)	0.093	50.9 (0.6)	89.1 (0.6)	0.000
96-101	39 (0.2)	28 (0.2)	0.014	2.9 (0.0)	5.1 (0.0)	0.000
101-106	2 (0.0)	0 (0.0)	0.015	0.0 (0.0)	0.0 (0.0)	0.000
106-111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	7466 (40.6)	7582 (41.7)	-0.022	3395.9 (38.8)	5951.1 (38.8)	0.000
F	10 906 (59.4)	10 588 (58.3)	0.022	5356.1 (61.2)	9385.9 (61.2)	0.000
Vaccination status						
1/1, >90 d	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	8 (0.0)	1 (0.0)	0.024	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14-90 d	1 (0.0)	0 (0.0)	0.010	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	16 741 (91.1)	17 347 (95.5)	-0.175	8590.3 (98.2)	15053.7 (98.2)	0.000
1/2, >90 d	7 (0.0)	7 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14 d	422 (2.3)	295 (1.6)	0.049	69.4 (0.8)	121.6 (0.8)	0.000
1/2, 14-90 d	739 (4.0)	355 (2.0)	0.122	87.2 (1.0)	152.8 (1.0)	0.000

TABLE B18 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
2/2, >90 d	127 (0.7)	30 (0.2)	0.081	0.7 (0.0)	1.3 (0.0)	0.000
2/2, <14 d	97 (0.5)	44 (0.2)	0.046	0.7 (0.0)	1.3 (0.0)	0.000
2/2, 14–90 d	230 (1.3)	91 (0.5)	0.081	3.6 (0.0)	6.4 (0.0)	0.000
Period						
Before 10.01.2021	11 189 (60.9)	10 566 (58.2)	0.056	5507.2 (62.9)	9650.8 (62.9)	0.000
10.01.2021 to 15.07.2021	6982 (38.0)	7257 (39.9)	−0.040	3205.6 (36.6)	5617.4 (36.6)	0.000
After 15.07.2021	201 (1.1)	347 (1.9)	−0.067	39.2 (0.4)	68.8 (0.4)	0.000
Comorbidities						
Acute myocardial infarction	1381 (7.5)	198 (1.1)	0.321	67.9 (0.8)	119.1 (0.8)	0.000
Congestive heart failure	2098 (11.4)	462 (2.5)	0.354	78.8 (0.9)	138.2 (0.9)	0.000
Peripheral vascular disease	1014 (5.5)	301 (1.7)	0.209	44.0 (0.5)	77.0 (0.5)	0.000
Cerebrovascular disease	2121 (11.5)	604 (3.3)	0.317	198.0 (2.3)	347.0 (2.3)	0.000
Alzheimer dementia	813 (4.4)	249 (1.4)	0.183	68.7 (0.8)	120.3 (0.8)	0.000
Other dementia	3922 (21.3)	1979 (10.9)	0.287	891.2 (10.2)	1561.8 (10.2)	0.000
Mild liver disease	644 (3.5)	340 (1.9)	0.101	85.7 (1.0)	150.3 (1.0)	0.000
Diabetes without complications	5186 (28.2)	2449 (13.5)	0.369	1118.7 (12.8)	1960.3 (12.8)	0.000
Diabetes with complications	745 (4.1)	202 (1.1)	0.186	24.3 (0.3)	42.7 (0.3)	0.000
Renal disease	1424 (7.8)	252 (1.4)	0.308	32.3 (0.4)	56.7 (0.4)	0.000
Cancer	2308 (12.6)	971 (5.3)	0.255	315.7 (3.6)	553.3 (3.6)	0.000
Moderate to severe liver disease	51 (0.3)	7 (0.0)	0.060	0.0 (0.0)	0.0 (0.0)	0.000
Metastatic cancer	220 (1.2)	52 (0.3)	0.106	4.0 (0.0)	7.0 (0.0)	0.000
HIV/AIDS	2 (0.0)	1 (0.0)	0.006	0.0 (0.0)	0.0 (0.0)	0.000
RAAS inhibitors	10 065 (54.8)	4841 (26.6)	0.598	2894.6 (33.1)	5072.4 (33.1)	0.000
Beta blockers	7818 (42.6)	2450 (13.5)	0.684	1511.8 (17.3)	2649.2 (17.3)	0.000
Diuretics	6604 (35.9)	1872 (10.3)	0.638	1022.0 (11.7)	1791.0 (11.7)	0.000
Immunosuppressant drugs	691 (3.8)	75 (0.4)	0.236	17.1 (0.2)	29.9 (0.2)	0.000
Systemic corticosteroids	1076 (5.9)	72 (0.4)	0.318	15.3 (0.2)	26.7 (0.2)	0.000
Antineoplastic drugs	405 (2.2)	118 (0.6)	0.131	24.0 (0.3)	42.0 (0.3)	0.000
Antiviral agents	187 (1.0)	16 (0.1)	0.126	0.0 (0.0)	0.0 (0.0)	0.000
Death (composite)	1889 (10.3)	803 (4.4)	0.226	294.1 (3.4)	626.1 (4.1)	−0.028
Death 1	1412 (7.7)	585 (3.2)	0.198	235.3 (2.7)	467.1 (3.0)	−0.016
Death 2	1215 (6.6)	519 (2.9)	0.178	188.1 (2.1)	401.7 (2.6)	−0.022
Death 3	1600 (8.7)	666 (3.7)	0.210	238.5 (2.7)	509.0 (3.3)	−0.025
Hospitalization 1	2348 (12.8)	1160 (6.4)	0.219	516.4 (5.9)	866.4 (5.6)	0.009
Hospitalization 2	5015 (27.3)	2680 (14.7)	0.312	1265.1 (14.5)	2153.2 (14.0)	0.010

B.2 | Sensitivity analysis to account for potential misclassification of possible users

TABLE B19 Sensitivity analysis to account for potential misclassification of possible users: users (all; treated) vs. unclassified patients (control; count/weighted count, %)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
<i>n</i>	55 098	27 952		43 637	26 320	
Age (5-y bins)						
16–21	401 (0.7)	560 (2.0)	−0.110	567.6 (1.3)	342.4 (1.3)	0.000
21–26	782 (1.4)	1082 (3.9)	−0.153	1123.4 (2.6)	677.6 (2.6)	0.000
26–31	1137 (2.1)	1333 (4.8)	−0.149	1475.8 (3.4)	890.2 (3.4)	0.000
31–36	1703 (3.1)	1770 (6.3)	−0.153	2064.7 (4.7)	1245.3 (4.7)	0.000
36–41	2571 (4.7)	2319 (8.3)	−0.148	2898.7 (6.6)	1748.3 (6.6)	0.000
41–46	3335 (6.1)	2683 (9.6)	−0.132	3551.7 (8.1)	2142.3 (8.1)	0.000
46–51	4243 (7.7)	2792 (10.0)	−0.081	4110.0 (9.4)	2479.0 (9.4)	0.000
51–56	5301 (9.6)	3113 (11.1)	−0.050	4823.6 (11.1)	2909.4 (11.1)	0.000
56–61	6107 (11.1)	3105 (11.1)	−0.001	5182.9 (11.9)	3126.1 (11.9)	0.000
61–66	6560 (11.9)	2812 (10.1)	0.059	5001.4 (11.5)	3016.6 (11.5)	0.000
66–71	6134 (11.1)	2136 (7.6)	0.120	4155.5 (9.5)	2506.5 (9.5)	0.000
71–76	5050 (9.2)	1524 (5.5)	0.143	2995.3 (6.9)	1806.7 (6.9)	0.000
76–81	4480 (8.1)	1122 (4.0)	0.173	2337.9 (5.4)	1410.1 (5.4)	0.000
81–86	4104 (7.4)	924 (3.3)	0.184	2039.1 (4.7)	1229.9 (4.7)	0.000
86–91	2400 (4.4)	510 (1.8)	0.147	1054.2 (2.4)	635.8 (2.4)	0.000
91–96	693 (1.3)	137 (0.5)	0.083	233.9 (0.5)	141.1 (0.5)	0.000
96–101	95 (0.2)	29 (0.1)	0.018	21.2 (0.0)	12.8 (0.0)	0.000
101–106	2 (0.0)	1 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
106–111	0 (0.0)	0 (0.0)	0.000	0.0 (0.0)	0.0 (0.0)	0.000
Sex						
M	22 645 (41.1)	11 132 (39.8)	0.026	17146.8 (39.3)	10342.2 (39.3)	0.000
F	32 453 (58.9)	16 820 (60.2)	−0.026	26490.2 (60.7)	15977.8 (60.7)	0.000
Vaccination status						
1/1, >90 d	2 (0.0)	0 (0.0)	0.009	0.0 (0.0)	0.0 (0.0)	0.000
1/1, <14 d	12 (0.0)	5 (0.0)	0.003	0.0 (0.0)	0.0 (0.0)	0.000
1/1, 14–90d	5 (0.0)	13 (0.0)	−0.022	0.0 (0.0)	0.0 (0.0)	0.000
Not vaccinated	51 111 (92.8)	26 612 (95.2)	−0.103	42388.8 (97.1)	25567.2 (97.1)	0.000
1/2, >90d	22 (0.0)	6 (0.0)	0.011	0.0 (0.0)	0.0 (0.0)	0.000
1/2, <14d	1121 (2.0)	419 (1.5)	0.041	441.6 (1.0)	266.4 (1.0)	0.000
1/2, 14–90d	1791 (3.3)	595 (2.1)	0.069	688.0 (1.6)	415.0 (1.6)	0.000
2/2, >90d	239 (0.4)	61 (0.2)	0.038	15.0 (0.0)	9.0 (0.0)	0.000
2/2, <14d	242 (0.4)	79 (0.3)	0.026	32.4 (0.1)	19.6 (0.1)	0.000
2/2, 14–90d	553 (1.0)	162 (0.6)	0.048	71.1 (0.2)	42.9 (0.2)	0.000
Period						
Before 10.01.2021	32 317 (58.7)	16 822 (60.2)	−0.031	27021.7 (61.9)	16298.3 (61.9)	0.000
10.01.2021 to 15.07.2021	22 102 (40.1)	10 664 (38.2)	0.040	16319.0 (37.4)	9843.0 (37.4)	0.000
After 15.07.2021	679 (1.2)	466 (1.7)	−0.036	296.3 (0.7)	178.7 (0.7)	0.000

TABLE B19 (Continued)

Characteristics	Before matching			After matching		
	Treated	Control	<i>d</i>	Treated	Control	<i>d</i>
Weighted CC index						
0	23 477 (42.6)	16 823 (60.2)	-0.357	24388.1 (55.9)	14709.9 (55.9)	0.000
1-2	21 575 (39.2)	8827 (31.6)	0.159	16179.3 (37.1)	9758.7 (37.1)	0.000
3-4	7228 (13.1)	1741 (6.2)	0.235	2607.4 (6.0)	1572.6 (6.0)	0.000
≥5	2818 (5.1)	561 (2.0)	0.168	462.2 (1.1)	278.8 (1.1)	0.000
Comorbidities						
Atrial fibrillation	5687 (10.3)	1347 (4.8)	0.209	1912.5 (4.4)	1153.5 (4.4)	0.000
Autoimmune	10 034 (18.2)	4398 (15.7)	0.066	6598.2 (15.1)	3979.8 (15.1)	0.000
Cancer	6253 (11.3)	2070 (7.4)	0.136	3008.4 (6.9)	1814.6 (6.9)	0.000
Congestive heart failure	4234 (7.7)	851 (3.0)	0.207	1026.7 (2.4)	619.3 (2.4)	0.000
COPD	9700 (17.6)	3819 (13.7)	0.109	5793.6 (13.3)	3494.4 (13.3)	0.000
IHD or CVD	11 683 (21.2)	2907 (10.4)	0.299	5529.7 (12.7)	3335.3 (12.7)	0.000
Renal disease	2580 (4.7)	468 (1.7)	0.172	324.4 (0.7)	195.6 (0.7)	0.000
Immunocompromised	1873 (3.4)	400 (1.4)	0.128	357.4 (0.8)	215.6 (0.8)	0.000
RAAS inhibitors	23 376 (42.4)	6640 (23.8)	0.405	14261.2 (32.7)	8601.8 (32.7)	0.000
Death (composite)	4356 (7.9)	907 (3.2)	0.204	2063.2 (4.7)	973.5 (3.7)	0.045
Death 1	3195 (5.8)	691 (2.5)	0.168	1573.6 (3.6)	775.1 (2.9)	0.033
Death 2	2839 (5.2)	605 (2.2)	0.160	1341.0 (3.1)	657.8 (2.5)	0.031
Death 3	3670 (6.7)	734 (2.6)	0.193	1695.8 (3.9)	772.1 (2.9)	0.045
Hospitalization 1	5824 (10.6)	1536 (5.5)	0.188	3142.3 (7.2)	1475.2 (5.6)	0.059
Hospitalization 2	12 735 (23.1)	3771 (13.5)	0.251	7415.8 (17.0)	3935.5 (15.0)	0.053