Outpatients prescribed with fluvoxamine around the time of COVID-19 diagnosis are not at a reduced risk of unfavorable COVID-19 course compared to their non-prescribed peers: population-based matched cohort study

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Abstract

Purpose. To assess the effect of exposure to fluvoxamine around the COVID-19 diagnosis on subsequent hospitalizations and mortality in COVID-19 outpatients in a real-life setting. Methods. Using nationwide administrative data, we identified adult COVID-19 outpatients diagnosed up to August 15, 2021 and conducted two cohort studies. Study 1 included subjects prescribed fluvoxamine around the index COVID-19 diagnosis (Cohort A), their peers suffering similar psychiatric difficulties but not prescribed fluvoxamine (Cohort B) and those free of psychiatric difficulties/treatments (Cohort C). Study 2 included subjects prescribed fluvoxamine (Cohort Fluvoxamine) and their peers prescribed paroxetine (Cohort Paroxetine). Cohorts were mutually exactly matched and incidence of COVID-19-related hospitalization, 30-day all-cause hospitalization and of COVID-19-related mortality was estimated. Results. Of the 416030 first-episode outpatients, Study 1 included 1016 Cohort A, 95984 Cohort B and 275804 Cohort C patients. Matched Cohort A (n=749) vs. Cohort B (n=31336) relative risks (95%CI/CrI), frequentist and Bayes with skeptical, otpimistic and pesimistic priors, were: COVID-related hospitalization 1.37 (0.56-3.33), 1.15 (0.55-2.11), 1.03 (0.56.1.96) and 1.43 (0.63-2.94), respectively; 30-day all-cause hospitalization 1.88 (0.76-4.67), 1.76 (1.39-2.25), 1.76 (1.39-2.24) and 1.86 (1.43-2.38), respectively; COVID-19 related mortality 0.73 (0.35-1.55), 0.93 (0.53-1.76), 0.79 (0.40-1.54) and 0.88 (0.37-2.11), respectively. Matched Cohort A vs. C (866 vs. 222792) comparison yielded similar estimates, as did the matched Cohort Fluvoxamine vs. Paroxetine comparison in Study 2 (344 of 994 matched to 535 of 1796 patients). Conslusion. Outpatients prescribed fluvoxamine around the time of COVID-19 diagnosis were not at a reduced risk of hospitalizations and mortality compared to their non-prescribed peers.

Introduction

Fluvoxamine, a selective serotonin re-uptake inhibitor (SSRI) has attracted much attention in efforts on drug repurposing for COVID-19 disease. Two randomized controlled trials (RCTs) [1,2] indicated that it reduced the risk of disease deterioration when started early upon diagnosis, but other RCTs indicated no benefit [3-6]. Fluvoxamine came into focus based on a reasonably sound pharmacodynamic rationale [7], but also owing to early non-randomized observations (reviewed in [8,9]): fluvoxamine was either proactively offerred and patients opted to take it or not, or "standard" pharmacoepidemiological studies (on administrative data) were performed. Regarding the former, it should be noted that besides other potential limitations (like sample size, confouding), studies of this type are burdened by uncorrectable selection bias. Regarding the

latter, it should be appreciated that in the setting of fluvoxamine for COVID-19 outpatients, such studies of interventions face obstacles beyond their standard limitations [10]. Since fluvoxamine has no approved use in infectious/inflammatory conditions, people treated with fluvoxamine during early COVID-19 are treated for some underlying psychiatric disorder, and mental disorders might contribute to poorer COVID-19 outcomes (reviewed in e.g. [11,12]). Hence, when using such data to evaluate benefits/harms of fluvoxamine, one needs to separate the effects of two co-exposures (fluvoxamine, underlying psychiatric condition): fluvoxamine exposed and non-exposed subjects should come from the same population (i.e., people suffering psychiatric difficulties). This limits the exposed vs. non-exposed comparison to only a subset of people with COVID-19 and data are informative about the treatment in broader terms (i.e., are generlizable) only if its effect is not conditional on the presence/absence of psychiatric difficulties. Furthermore, if participants in such studies are identified in databases of hospitalized patients or patients seeking help for COVID-19, estimates about the "fluvoxamine effect" are likely to be biased: by selective inclusion one conditions on a factor (a non-mild disease form) on a path between the cause (COVID-19 infection) and the outcome (hospitalization/death) and this is likely to generate spurious associations between the intervention of interest (fluvoxamine) and the outcome [13]. On the other hand, population-based studies embracing COVID-19 outpatients at the time of the diagnosis are likely to be devoid of such biases, even if including only COVID-19 positive patients, since there is considerable evidence that psychiatric disorders (including mood disorders and their treatments) do not affect one's susceptibility to SarsCov2 infection [14]. An important step is such an effort is definition of "fluvoxamine non-exposed" subjects. People suffering conditions requiring antidepressant/anxiolytic treatment not treated with fluvoxamine are likely exposed to other treatments. Biological (mechanistic) rationale to support their use in COVID-19 has been argued for a range of antidepressants/anxiolytics not only for SSRIs [8,9], with, seemingly, an emphasis on fluvoxamine and fluoxetine [15]. One early observational study based on administrative data on COVID-19 patients identfied based on the fact of emergency department vistis of hospitalizations suggested that those prescribed fluoxetine (n=470) had by 28% lower mortality than propensity score-matched controls not prescribed with any SSRI [16]. However, unlike for fluvoxamine, there are no RCTs pertainting to fluoxetine or any other SSRI or non-SSRI antidepressant/anxiolytic to indicate clinical benefit (reviewed in [8,9]; we also could not identify any data by searching PubMed and OVID Medline, Scopus, Web of Science, ClinicalTrials.gov and the International Clinical Trials Registry Platform; September 25, 2022). Therefore, "no exposure to fluvoxamine" seems to be an adequate definition of a control condition vs. "exposure to fluvoxamine".In an attempt to estimate whether in adults diagnosed with COVID-19 in outpatient settings the fact of being prescribed with (and presumably exposed to) fluvoxamine at the time around the COVID-19 diagnosis affected the probability of subsequent hospitalization or death, we conducted two population-based matched cohort studies comparing fluvoxamine-exposed outpatients to their non-exposed peers. Although the study (primarily) pertains to people who at the time of COVID-19 diagnosis suffered psychiatric conditions for which fluvoxamine was one of the possible treatments, it may still contribute to the overall knowledge on utility of fluvoxamine in early COVID-19 treatment by providing complementary information in the sense of being in agreement or not with the estimates generated in RCTs.

Patients and Methods

Study outline

We conducted two nationwide matched cohort studies (Study 1, Study 2) using administrative data (Fig 1A). In Study 1, we defined three COVID-19 outpatient cohorts (Fig 1A): *Cohort A* – patients suffering conditions that required antidepressants/anxiolytics and were exposed to fluvoxamine around the index COVID-19 diagnosis; *Cohort B* – patients suffering such conditions but were *not exposed* to fluvoxamine; and *Cohort C*- patients free of psychiatric disorders and treatments around the index COVID-19 diagnosis (Table 1 for details). The three cohorts were mutually exactly matched on a range of pre-COVID-19 characteristics: (i) comparison between Cohort A (treatment) and Cohort B (control) was of primary interest; (ii) comparisons of Cohorts A or B with Cohort C were considered supportive, and informed about the "joint" effect of two

co-exposures (antidepressant/anxiolytic + underlying conditions). We expected a limited number of people prescribed fluvoxmine (unlike most of the other antidpressants/anxiolytics, it is only partly reimbursed), hence to improve precision of the Cohort A vs. Cohort B estimates, we conducted network meta-analysis of results in matched sets A vs. B, A vs. C and B vs. C. Although derived from the same pool of original patients, matched contrasts were based on different pseudopopulations (by selection and weighting).

Study 2 also aimed to estimate effect of specifically fluvoxamine exposure (treatment), but through a contrast to a specific "other" antidepressant/anxiolytic – paroxetine (control). Fluvoxamine and Paroxetine Cohort subjects (definitions in Table 1) were exactly matched on the same covariates as in Study 1 (Table 2).

Prescriptions for fluvoxamine and paroxetine are repeatable – one issued prescription can cover a maximum of 12 months of treatment. We reasoned that prescriptions that would pertain to a period shorter than 3 months were not likely, and also that prescriptions for a period much longer than 3 months were not very likely since the treated conditions require medical follow-up and reconsideration of treatment. Therefore (Table 1), we considered that subjects were prescribed and (presumably) exposed to treatment if at least 1 prescription was issued over a period of time between 3 months prior to- and 7 days after the index COVID-19 diagnosis; and were not prescribed (exposed) if no prescriptions were issued within 6 months prior to- and up to 21 days after the index COVID-19 diagnosis.

We used anonymzed data routinely managed by the Croatian Institute for Public Health (CIPH), who prepared the initial raw dataset from databases on: (i) COVID-19 laboratory test results (polymerase chain reaction [PCR]-based or rapid antigen tests [RAT]) and COVID-19 patients diagnosed on clinical/epidemiological criteria; (ii) COVID-19 vaccinations; (iii) all hospitalizations; (iv) deceased individuals; (v) Central Health Information System (CEZIH) - primary healthcare database maintained by the Ministry of Health (Fig 1B). It included all subjects diagnosed with COVID-19 at points of mass outpatient testing (managed by CIPH) or by their general practitioners (i.e., we omitted subjects first diagnosed when seeking hospital assistance for any reason) between February 25, 2020 (first recorded case in Croatia) and October 15, 2021. Each individual was linked to her/his data on: date and mode of COVID-19 diagnosis; demographics and COVID-19 vaccination status at diagnosis; medical histories from January 1 2019 to October 31 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 (Fig 1B). We received a merged database and a) excluded subjects <16 years of age and 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; b) identified subjects with more than one COVID-19 episode: we considered that positive PCR/RAT tests or ICD-10 code U07.1/U07.2 entries or hospitalizations related to COVID-19 that were [?]30 days apart indicated two separate COVID-19 episodes. Only the first documented COVID-19 episode for each subject was included in the analysis; c) we set the cut-off date for COVID-19 diagnosis at August 15 2021, to allow for a follow-up period long-enough for outcomes to occur (until October 31) (Fig 1A). Finally, we identified patient subsets of interest (Table 1), their outcomes and their matching covariates (Table 2).

This study used anonymized administrative data standardly collected through routine procedures, hence ethical approval was waived by the Ethics Committee of the Zagreb University School of Medicine and Croatian Institute for Public Healthy.

Outcomes

We defined three outcomes informing about unfavorable develompents in COVID-19 outpatients. *COVID-19-related hospitalization* – hospitalization follows within 45 days since the index COVID-19 diagnosis, with U07.1/U07.2 as the leading diagnosis; or hospitalization follows within 30 days since the index COVID-19 diagnosis and U07.1/U07.2 is listed among diagnoses. *30-day all-cause hospitalization* – hospitalization follows within 30 days since the index COVID-19 diagnosis. *COVID-19-related death* – we considered that death was "related to" COVID-19 if meeting any of the following (i) death occurred after the index COVID-

19 diagnosis with U07.1/U07.2 as a cause of death, regardless of the time elapsed since the COVID-19 diagnosis (shortest possible period of observation was 77 days - patients diagnosed on August 15, 2021); (ii) death occurred within 14 days since the index COVID-19 diagnosis, regardless of the declared cause; (iii) death occurred in hospital, where hospitalization was COVID-19 related hospitalization (as defined above), regardless of the declared cause of death and time elapsed since the COVID-19 diagnosis.

Identification of exposures, other treatments, comorbidities and vaccination status

Exposure/non-exposure to fluvoxamine or paroxetine was identified based on timing of prescriptions with the respective ATC codes (N06AB08 and N06AB05, respectively) relative to the index COVID-19 diagnosis. Subjects were considered to suffer conditions in which antidepressants/anxiolytics (including fluvoxamine or paroxetine) might have been the main or one of the required treatments if they had at least one entry of any ICD-10 F codes or G30/G31.1 codes between January 1, 2019 up to 7 days after the index COVID-19 diagnosis. Regarding vaccination, patients were classified as "not vaccinated", or as: a) vaccinated with a single-dose vaccine; b) received 1^{st} dose of a two-dose vaccine; c) received 2^{nd} (full) dose of a two-dose vaccine; and were further sub-classified based on time elapsed between the last vaccine administration and the index COVID-19 diagnosis (<14 days, 14-90 days and >90 days). Online Resource 1 – Supplemental Methods – provides details on indentification of all treatments and (co)morbidities used to identify patients subsets and in covariate matching.

Matching and data analysis

We implemented exact matching using package *MatchIt* [17] in R [18] with average treatment effect as the estimand (ATE). Outcomes were analyzed by fitting weighted log-binomial models, frequentist (with cluster robust sandwich estimator of the standard error) and Bayesian with three different priors: (i) *skeptical prior* – moderatly informative neutral prior consistent with an *a priori* hypothesis of no effect, centered at 0 for the Ln(RR) with standard deviation 0.355. It assigns 95% probability between RR=0.50 and RR=2.0; (ii) *optimistic prior* – moderately informative prior centered at -0.199 for the Ln(RR), with standard deviation 0.4, i.e., 18% relative risk reduction as seen in an up-dated Bayesian meta-analysis of randomized trials of fluvoxamine in this setting [19], but with 30% probability of an RR >1.0; (iii) *pesimistic prior* – weakly informative prior centered at 0.199 for Ln(RR) with a standard deviation of 0.77. Although it suggests harm, it leaves 40% probability of an RR <1.0. We used SAS 9.4 for Windows (SAS Inc, Cary, NC) and R package *rstanarm* [20] . In Study 1, we additonally performed frequentist (R package *netmeta* [21]) and Bayesian (R packages *BUGSnet* [22] and *gemtc* [23], with default priors) network meta-analysis using weighted counts and also the effect measures generated in Bayesian analyses with the skeptical prior.

Sensitivity to unmeasured confounding/bias

We assumed a hypothetical unmeasured confounding that "worked" to diminsh the (presumed) beneficial (risk-reducing) effect of fluvoxamine. Specifically, we assumed that among control subjects (Cohort B in Study 1, Cohort Paroxetine in Study 2), 40% were using some treatment (e.g., other antidepressant/anxiolytic, or any other) that was actually effective against COVID-19 with a marked effect of 30% reduction of the risk of disease deterioration (corresponds to the largest effect reported from RCTs of fluvoxamine [2]), and that only 1% of the fluvoxamine-exposed subjects were co-treated with such a treatment, and we corrected the observed estimates for this bias.

Results

Patients

We identified 504912 COVID-19 diagnoses in outpatient settings, eventually resulting in 416030 eligible first COVID-19 episodes in adult outpatients (Fig 1B). Of those: (i) in Study 1, 1016 patients met the criteria for Cohort A, 95984 met the criteria for Cohort B and 275804 met the criteria for Cohort C (Fig 1B); (ii) in Study 2, 944 patients met the criteria for Cohort Fluvoxamine and 1796 met the criteria for Cohort Paroxetine (Fig 1B). Raw data (berfore matching) across the studies/cohorts indicated (Table 3): (i) $< 1\%$ of the patients in each cohort were fully vaccinated and 95% received no vaccination whatsoever; (ii) in Study 1, Cohort C patients (free of psychiatric difficulties/treatments) appeared younger and had clearly lower prevalence of all comorbidities than Cohort A (psychiatric difficulties, prescribed fluvoxamine) and Cohort B (psychiatric difficulties, not prescribed fluvoxamine) patients, who were closely similar in all aspects (Table 3); (ii) in Study 2, patients in the two cohorts were closely similar in respect to all pre-COVID-19 characteristics, and were in this respect also similar to Cohort A and Cohort B in Study 1 (Table 3).

In Study 1, raw incidence of all outcomes was closely similar in Cohort A and Cohort B - 3.35% vs. 3.25%, 12.5% vs. 11.5% and 3.74% vs. 4.44% for COVID-related hospitalizations, 30-day all-cause hospitalizations and COVID-related mortality, respectively (Table 3) - and was clearly higher than in Cohort C patients (0.94%, 5.18%, 1.05%, respectively) (Table 3). In Study 2, raw incidence of all outcomes was closely similar in the two cohorts and also similar to Cohorts A and B in Study 1 (Table 3).

Analysis in matched sets: Study 1

Eventually, 749 Cohort A patients were matched to 31336 Cohort B patients; and 866 of the former and 82323 of the latter were matched to 222792 and to 268778 Cohort C patients, respectively (Online Resource 2 – Supplemental results – provides all pairwise data before and after matching).

Incidence of all outcomes was lower in all matched sets than before matching, and there was no indication that outpatients prescribed fluvoxmine around the time of COVID-19 diagnosis (Cohort A) were at a reduced risk of any outcome as compared to their peers burdened with similar psychiatric difficulties but not prescribed fluvoxamine (Cohort B), or as compared to COVID-19 outpatients free of psychiatric difficulties and related treatments (Cohort C) (Fig 2): all relative risk estimates were around 1.0 or somewhat higher than 1.0. Comparisons between matched cohorts B and C yielded more precise estimates (higher nubmer of subjects) (Fig 2), but in terms of the point-estimates, A vs. C and B vs. C differences were closely similar (Fig 2).

In the network analysis, direct and indirect Cohort A to Cohort B comparisons were consistent (Fig 3): there was no indication that Cohort A patients were at a reduced risk of any of the outcomes compared to their Cohort B peers (Fig 3).

Analysis in matched sets: Study 2

Eventually, 344 Cohort Fluvoxamine patients were exactly matched to 535 Cohort Paroxetine patients (Online resource 2 – Supplemental Results - lists all covariates before and after matching). Incidence of all outcomes was lower than before matching (Fig 4). Incidence of "all-cause 30-day hospitalization" (Fig 4) was resonable (weighted event counts 21.9 vs. 28.8). There was no signal that outpatients prescribed fluvoxmine (but not paroxetine) around the time of COVID-19 diagnosis were at a reduced risk of this outcome as compared to their peers prescribed paroxetine (and not fluvoxamine) (Fig 4): all RR estimates were around 1.0. Incidence of COVID-19-related hospitalization and of COVID-19-related mortality was vary low ($<1.0\%$) (Fig 4), hence estimates were imprecise – however, point-estimates were closely similar to the estimates for Cohort A vs. Cohort B in Study 1 not indicating any benefit of fluvoxamine (Fig 2).

Sensitivity to unmeasured confounding

Estimates corrected for (hypothetical) bias arising from a 1:40 imbalance in co-treatment with an effective (30% risk reduction) non-fluvoxamine therapy between fluvoxamine-exposed and control subjects (Cohort B in Study 1, Cohort Paroxetine in Study 2) did not relevantly differ from the acutally observed estimates (Table 4).

Discussion

We observed no signal to indicate that outpatients prescribed with (and presumably exposed to) fluvoxamine around the time of COVID-19 diagnosis were at a reduced risk of subsequent hospitalization or death compared to their non-prescribed (non-exposed, control) peers. By definition, both subject subsets had to have ICD-10 code entries documenting history of a particular spectrum of psychiatric difficulties, and were then matched exactly on a range of psychiatric and other (co)morbidities, demographic and epidemiological characteristics. In both analyses (Study 1, Study 2), exposure to the treatment of interest (fluvoxamine) was always positively identifed, and in Study 2 it also included explicit exclusion of exposure to paroxetine. Control status was always defined by explicit exclusion of exposure to fluvoxamine, and in Study 2 it also included a positive identification of exposure to paroxetine. Apart from these definitions, both exposed and control subjects in both analyses could have been exposed (prescribed with) other psychiatric treatments including other antidepressants/anxiolytics, e.g., as a part of augmentation strategies and/or to treat residual symptoms [26-28]. Although we did not explicitly match patient subsets regarding these "other treatments", it is reasonable to consider that potential imbalances in this respect were minor, if any, given that patients were exactly matched on a wide range of psychiatric diagnoses. Moreover, and as elaborated in the Introduction section, it is highly unlikely that any of the "other treatments" exerted any clinically relevant anti-COVID-19 effect. Furthermore, even the estimates corrected for a strong hypothetical confounding bias arising from a large imbalance between fluvoxamine-exposed and control subjects in prevalence of a highly effective anti-COVID-19 treatment did not indicate any relevant benefit of exposure to fluvoxamine. In this respect, and having in mind all the (elaborated) limitations for such extrapolations, the present data are more in line with RCTs not supporting a benefit of early fluvoxamine therapy in COVID-19 outpatients [3-6] than with RCTs suggesting a benefit [1,2].

Since based on administrative data, present work has several (inherent) limitations common to studies of this type. First, "(non)exposure" is implied based on prescription (non)issuance within a certain time-frame, however compliance and actual doses taken remained unknown. Next, information about presence and severity of symptoms at COVID-19 diagnosis was missing. To minimize the impact of this drawback, we restricted the analysis to patients diagnosed exclusively in outpatient settings, hence likely (at this point) suffering only milder symptoms (if any). Further, some inaccurracies in identification of exposures, comorbidities and outcomes were probable. We believe, however, that if present, such inaccurracies did not relevantly bias present observations: i) we used data managed by dedicated professional institutions; ii) data on key variables such as age, sex, vaccination status, date of COVID-19 test/test result or diagnosis were missing or erroneously entered in only 0.38% of the identified COVID-19 diagnoses (and these patients were excluded) indicating that if present, chance errors were sporadic; iii) it does not seem resonable to think that occurrence of chance errors is "prejudiced" in respect to (non)-issuance of fluvoxamine (or any other) prescriptions; iv) we left a period of a minimum one year + 2 months (from January 1 2019 to the first COVID-19 case in February 2020) to precede the index COVID-19 diagnosis not to miss entries of relevant comorbidities and issued prescriptions and other health care services into the Central Health Information System; v) raw incidence of all outcomes was within the expectations. Incidence of 30-day all-cause hospitalization was closely similar in all cohorts that included patients suffering psychiatric difficulties (around 12.0%), and these patients were also closely similar regarding age and comorbidities. Incidence was twice lower in patients free of such difficulties (Cohort C in Study 1), who were also younger and less comorbid. In Study 1 (larger), overall incidence of 6.9% (across all three cohorts) at the average age of 46.5

years is in agreement with expected 4.3% to 8.5% hospitalizations among people aged 40-49 years who test positive for COVID-19 [29]. Although one could consider all hospitalizations that occur within a month since the COVID-19 diagnosis as "COVID-19-related", we defined a separate outcome where COVID-19 was the lead or at least one of the discharge diagnoses (the latter part of the definition implying that COVID-19 could have triggerred/worsened some underlying condition). It seems reasonable to assume that these were the "more severe" COVID-19 patients. Again, all cohorts including patients with psychiatric difficulties were similar in this respect (around 3.3%) and incidence was (expectedly) much lower (0.94%) in the younger and considerably less comorbid patients free of psychiatric difficulties (Cohort C in Study 1). The overall crude incidence across all cohorts in Study 1 of 1.5% is within the range of the reported expected incidence of severe/critical disease in 30-50-year olds who tested positive for COVID-19 (1.2-2.5%) [30]. The relationship between cohorts in Study 1 regarding (COVID-19-related) mortality was similar to that regarding other two outcomes, and the overall incidence (across all cohorts) of 2.5% is in line with the ratio of cumulative COVID-19-confirmed deaths and COVID-19 confirmed cases in Croatia up to October 31, 2021 [31]. Finally, due to exact matching on a number of covariates, matches between cohorts were found mainly among less comorbid subjects resulting in relatively low incidence of COVID-19 related death outcomes in matched sets and consequent imprecise estimates. However, all comparisons (A vs. B, or A or B vs. C in Study 1, and Fluvoxamine vs. Paroxetine in Study 2) were numerically closely similar indicating consistency of findings. Overall, it appears safe to conclude that we were able to resonably accurrately capture exposures, comorbidities, cotreatments and outcomes, and to adequatly control confounding. Under such circumstances, we observed no estimate that would go "in favor" of the fact of being prescribed fluvoxamine around the time of COVID-19 diagnosis.

In conclusion, the present population-based matched cohort studies strongly suggest that outpatients prescribed with fluvoxamine around the time of COVID-19 diagnosis are not at a reduced risk of subsequent hospitalizations or death compared to their peers suffering similar psychiatric difficulties but not prescribed with fluvoxamine, or prescribed paroxetine, or as compared to their peers free of psychiatric difficulties and respective treatments. Considering the specifics of the setting, extrapolation of the present data to the general question of efficacy of fluvoxamine in early COVID-19 can only be an approximation under several strong assumptions; in this context, present observations agree with trial data that failed to demonstrate a practically relevant benefit of fluvoxamine in this setting.

Disclosures and Declarations

Disclosures and Declarations Authorship.

Both authors meet the ICMJE criteria for authorship.

Competing interests.

Authors declare no competing interests.

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Ethics approval.

This study used anonymized administrative data standardly collected on routine procedures, hence ethical approval was waived by the Ethics Committee of the Zagreb University School of Medicine and Croatian Institute for Public Healthy.

Author contributions.

Vladimir Trkulja and Ivan Kodvanj designed the study, prepared and analyzed the data, drafted the manuscript and completed the final version.

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Data availability.

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

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Table 1. Subsets of people diagnosed with COVID-19 (up to August 15, 2021) in respect to exposure to fluvoxamine around the time of COVID-19 diagnosis.

Study 1

- **Cohort A**. People suffering difficulties requiring antidepressants/anxyolytics **and prescribed/ exposed to fluvoxamine** – (i) at least one International Classification of Disease (ICD-10) F or G30/31.1 code entry (conditions in which fluvoxamine or other antidepressants/anxiolytics might have been the main or one of the required treatments) at any time between January 1, 2019 up to 7 days after the date of the index COVID-19 diagnosis; (ii) at least one prescription for fluvoxamine issued in the period betrween 90 days prior to- and 7 days after the index COVID-19 diagnosis; (iii) could have been prescribed other psychiatric treatments including other antidepressants/ anxiolytics between January 1, 2019 and the date of the index COVID-19 diagnosis.

- **Cohort B**. People suffering difficulties requiring antidepressants/anxyolytics **not prescribed/ exposed to fluvoxamine** – (i) at least one ICD-10 F or G30/G31.1 code entry (conditions in which antidepressants/anxiolytics might have been the main or one of the required treatments) at any time between January 1 2019 up to 7 days after the date of the index COVID-19 diagnosis; (ii) no prescription for fluvoxamine issued in the period between 6 months prior to- and 21 days after the index COVID-19 diagnosis; (iii) could have been prescribed other psychiatric treatments including other antidepressants/ anxiolytics between January 1, 2019 and the date of the index COVID-19 diagnosis.

- **Cohort C**. People free of psychiatric difficulties and **not prescribed/exposed** to fluvoxamine or to any other pharmacological psychiatric treatment – (i) no ICD-10 F code entries at any time between January 1 2019 and 21 days after the index COVID-19 diagnosis, and (ii) no prescriptions for fluvoxamine or any of the other drugs falling into the Anatomical Therapeutic Chemical codes N05, N06 or N07B in the period between 6 months prior to- and 21 days after the index COVID-19 diagnosis.

Study 2

- **Cohort Fluvoxamine.** The same as Cohort A in Study 1, except that "other treatments" **exclude paroxetine**: no prescriptions issued between 6 months prior to- and 21 days after the index COVID-19 diagnosis.

- **Cohort Paroxetine**. People suffering difficulties requiring antidepressants/anxyolytics **and prescribed/exposed to paroxetine** – (i) at least one ICD-10 F or G30/31.1 code entry (conditions in which paroxetine or other antidepressants/anxiolytics might have been the main or one of the required treatments) at any time between January 1, 2019 up to 7 days after the date of the index COVID-19 diagnosis; (ii) at least one prescription for paroxetine issued in the period betrween 90 days prior to- and 7 days after the index COVID-19 diagnosis; (iii) could have been prescribed other psychiatric treatments including other antidepressants/ anxiolytics between January 1, 2019 and the date of the index COVID-19 diagnosis, **except for fluvoxamine**: no prescription issued between 6 months prior to- and 21 days after the index COVID-19 diagnosis.

Table 2. Covariates used for exact matching between patient subsets (Cohorts based on burden of psychiatric conditions and exposure to fluvoxamine/paroxetine).

Matching variables used for all comparisons

Age

As 5-year bins between 16 and 111 years

Sex

Male or female

Vaccination status

Not vaccinated; received a single-dose vaccine (i) <14 days before COVID-19 diagnosis; ii) 14-90 days before or (iii) >90 days before COVID-19 diagnosis; received the 1st dose of a two-dose vaccine (i) <14 days before; (ii) 14-90 days before or (iii) >90 days before COVID-19 diagnosis; received the 2nd dose of a two-dose vaccine (i) <14 days before; (ii) 14-90 days before or (iii) >90 days before COVID-19 diagnosis

Calendar period

Up to January 9 2020 (including) – still no vaccination, Alpha strain(s) prevailing; January 10 – July 15 2021 – Alpha strain(s) prevailing, mass vaccination in progress; after July 15 2021 – Delta strain starts to prevail, mass vaccination in progress.

Comorbidities

Charlson comorbidity index (CCI) subseted at 4 levels: 0, 1-2, 3-4 and [?]5, and also individual comorbidities: atrial fibrillation/undulation, autoimmune disease, malignant disease (cancer), congestive heart failure, chronic obstructive pulmonary disease, history of ischemic heart disease or a cerebrovascular disease, renal disease (in addition to codes in CCI: chronic kidney disease, N18; and dependence on renal dialysis, Z99.2), diabetes without complications, diabetes with complications and dementia (same ICD-10 codes as for the calculation of CCI).

Pharmacological treatments

Inhibitors of the renin-angiotensine-aldosterone system (RAAS) (includes any of the following: angiotensine converting enzyme inhibitors, angiotensine receptor antagonists and mineralocorticoid receptor antagonists); diuretics (any).

Matching variables additionally used in the comparison between patients burdened with psychiatric difficulties that may require antidepressant/anxyolytic treatment. In Study 1 this refers to Cohorts A and B (Cohort C by definition is free of such conditions). In Study 2, it refers to both cohorts.

Mood disorders

Mood (affective) disorders (F30-F39)

Nonpsychotic mood disorders

Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mood disorders (F40-F48)

Substance use

Mental and behavioral disorders due to psychoactive substance use (F10-F19)

Non-mood psychotic disorders

Schizophrenia, schizotypal, delusional and other non-mood psychotic disorders (F20-F29)

Cumulatively: F50-F59, F60-F69, F70-F79, F80-F89, F90-F98, F04-F09

Behavioral syndromes associated with physiological disturbances and physical factors; Disorders of adult personality and behavior; Intellectual disabilities; Pervasive and specific developmental disorders; Behavioral and emotional disorders with onset in childhood and adolescence; mental disorders due to know physiological condition (F04,05,06, 07, 09)

Table 3 Subject characteristics across subsets based on burden of psychiatric conditions and exposure to fluvoxamine/paroxetine (see Table 1) – before matching [n (%), except age]. Shown are all covariates used for matching (see Table 2). "Vaccination status" refers to number of doses received/number needed for full vaccination and time elapsed since the last vaccine dose.

Study 1

Study 2

Cohort A

Cohort B

Cohort C

Fluvoxamine

Paroxetine

N

1016

95984

275804

994

1796

Age (years)[1] [mean?SD (range)]

55?18 (16-99)

58?17 (16-105)

43?16 (16-96)

55?17(16-98)

58?16(16-95)

Male

441 (43.4)

33604 (35.0)

144548 (52.4)

431 (43.4)

564 (31.4)

Vaccination status

1/1, >90 days

0 (0.0)

1 (<0.1)

1 (<0.1)

0 (0.0)

0 (0.0)

1/1, <14 days

0 (0.0)

13 (<0.1)

38 (0.1)

0 (0.0)

0 (0.0)

1/1, 14-90 days

0 (0.0)

8 (<0.1)

43 (0.2)

0 (0.0)

0 (0.0)

Not vaccinated

958 (94.3)

90719 (94.5)

269392 (97.7)

936 (94.2)

1697 (94.5)

1/2, >90 days

0 (0.0)

28 (0.0)

16 (0.0)

0 (0.0)

0 (0.0)

1/2, <14 days

23 (2.3)

1724 (1.8)

2667 (1.0)

23 (2.3)

27 (1.5)

1/2, 14-90 days

27 (2.7)

2431 (2.5)

2645 (1.0)

27 (2.7)

51 (2.8)

2/2, >90 days

1 (0.1)

237 (0.2)

201 (0.1)

1 (0.1)

5 (0.3)

2/2, <14 days

0 (0.0)

298 (0.3)

205 (0.1)

0 (0.0)

4 (0.2)

2/2, 14-90 days

7 (0.7)

525 (0.5)

596 (0.2)

7 (0.7)

12 (0.7)

Calendar period

Up to January 9, 2021

591 (58.2)

55623 (58.0)

163836 (59.4)

574 (57.7)

1061 (59.1)

January 10 to July 15, 2021

408 (40.2)

39112 (40.7)

106379 (38.6)

403 (40.5)

716 (39.9)

After July 15, 2021

17 (1.7)

1249 (1.3)

5589 (2.0)

17 (1.7)

19 (1.1)

Weighted CCI

0

609 (59.9)

55122 (57.4)

230007 (83.4)

598 (60.2)

981 (54.6)

1-2

293 (28.8)

31229 (32.5)

40370 (14.6)

285 (28.7)

648 (36.1)

3-4

86 (8.5)

7375 (7.7)

4380 (1.6)

85 (8.6)

132 (7.3)

[?] 5

28 (2.8)

2258 (2.4)

1047 (0.4)

26 (2.6)

35 (1.9)

Additional individual conditions

Atrial fibrillation/undulation

61 (6.0)

5850 (6.1)

4017 (1.5)

60 (6.0)

84 (4.7)

Autoimmune disease

112 (11.0)

13295 (13.9)

14281 (5.2)

110 (11.1)

268 (14.9)

Cancer

58 (5.7)

7569 (7.9)

7109 (2.6)

55 (5.5)

128 (7.1)

Congestive heart failure

30 (3.0)

3907 (4.1)

2149 (0.8)

30 (3.0)

66 (3.7)

COPD

112 (11.0)

12808 (13.3)

17171 (6.2)

109 (11.0)

269 (15.0)

IHD or CVD

149 (14.7)

12803 (13.3)

8240 (3.0)

146 (14.7)

241 (13.4)

Renal disease[2]

23 (2.3)

2067 (2.2)

1334 (0.5)

23 (2.3)

31 (1.7)

Diabetes with complications

19 (1.9)

1611 (1.7)

1131 (0.4)

18 (1.8)

34 (1.9)

Diabetes w/o complications

165 (16.2)

15155 (15.8)

15706 (5.7)

159 (16.0)

315 (17.5)

Dementia

37 (3.6)

2356 (2.5)

2482 (0.9)

37 (3.7)

56 (3.1)

Immunocompromised

14 (1.4)

1559 (1.6)

1375 (0.5)

14 (1.4)

23 (1.3)

Using RAAS inhibitors

293 (28.8)

30443 (31.7)

30386 (11.0)

284 (28.6)

644 (35.9)

Using diuretics

125 (12.3)

14193 (14.8)

9719 (3.5)

121 (12.2)

281 (15.6)

F10-F19

28 (2.8)

2650 (2.8)

—

27 (2.7)

44 (2.4)

F20-F29

119 (11.7)

5306 (5.5)

—

117 (11.8)

112 (6.2)

F30-F39

446 (43.9)

20856 (21.7)

—

434 (43.7)

971 (54.1)

F40-F48

692 (68.1)

71242 (74.2)

—

676 (68.0)

1199 (66.8)

Any of F04-F09, F50-F59, F60-F69, F70-F79, F80-F89, F90-F98

229 (22.5)

19431 (20.2)

—

218 (21.9)

307 (17.1)

Outcomes

COVID-related hospitalization

34 (3.35)

3128 (3.25)

2590 (0.94)

32 (3.22)

65 (3.62)

All-cause 30-day hospitalization

127 (12.5)

11266 (11.7)

14297 (5.18)

125 (12.6)

206 (11.5)

COVID-related mortality (composite)

38 (3.74)

4261 (4.44)

2898 (1.05)

37 (3.72)

80 (4.44)

[1] For clarity, age is summarized. In the matching process, it was binned (see Table 2).

CCI – Charlson comorbidity index; COPD – chronic obstructive pulmonary disease; CVD – cerebrovascular disease; IHD – ischemic heart disease; RAAS – renin angiotensin aldosteron system

[2] In addition to codes in CCI: chronic kidney disease, N18; and dependence on renal dialysis, Z99.2

Table 4 Analysis of sensitivity to unmeasured confounding. Estimates of the effect of exposure to fluvoxamine (Cohort A in Study 1, Cohort Fluvoxamine in Study 2) vs. non-exposure (control condition; Cohort B in Study 1, Cohort Paroxetine in Study 2) generated in the Bayesian analysis with a moderately informative skeptical prior were corrected for (hypothetical) unmeasured confounding that diminished the (presumed)

risk-reducing effect of fluvoxamine: a large imbalance (1:40) between fluvoxamine-exposed and control subjects was hypothesized in prevalence of an "other co-treatment" (e.g., other antidepressant/anxiolytic) with a high efficacy (30% risk reduction) against COVID-19 disease progression. Shown are actually observed and bias-corrected estimates of relative risks (RR) for all outcomes in Study 1 and Study 2.

	Observed RR (95%CrI)	Bias-corrected RR (95%CrI)
Study 1		
Cohort A vs. Cohort B		
COVID-19-related hospitalization	1.15 (0.66-2.11)	1.02 (0.58-1.86)
All-cause 30-day hospitalization	1.76 (1.39-2.25)	1.55 (1.23-1.99)
COVID-19-related mortality	0.93 (0.53-1.76)	0.82 (0.47-1.55)
Study 2		
Fluvoxamine vs. Paroxetine		
COVID-19-related hospitalization	1.21 (0.60-2.36)	1.07 (0.52-2.08)
All-cause 30-day hospitalization	1.13 (0.73-1.73)	1.00 (0.64-1.53)
COVID-19-related mortality	0.91 (0.46-1.72)	0.80 (0.41-1.52)

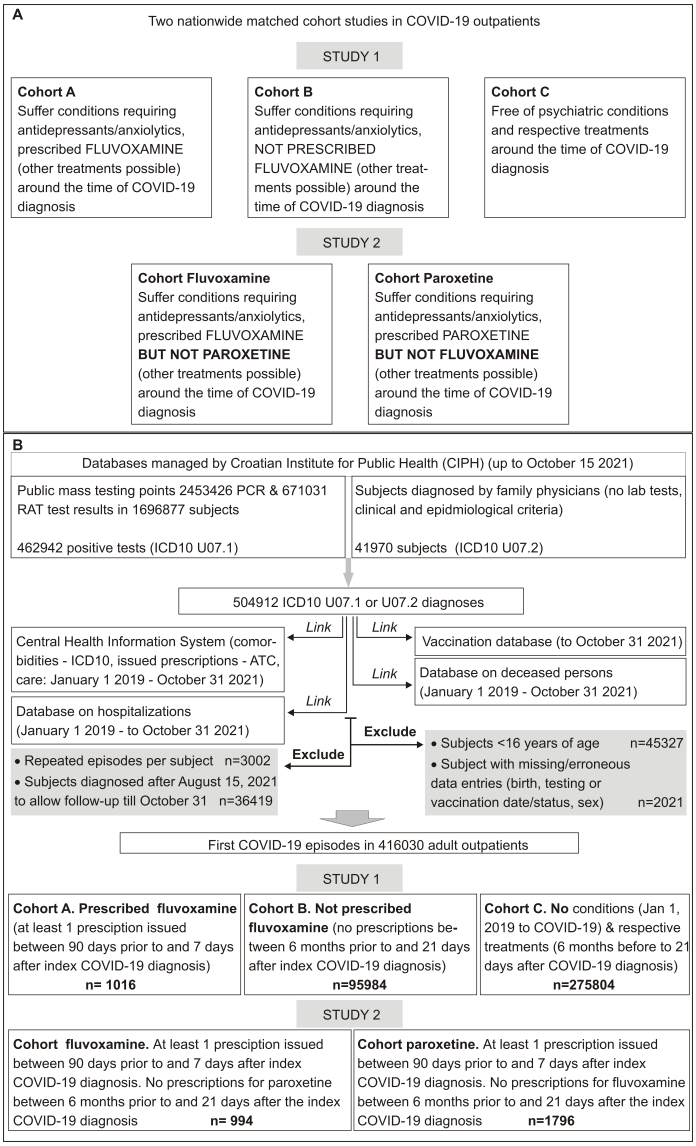

Figure 1: **A** Outline of the present work. We conducted two nationwide matched cohort studies in COVID-19 outpatients using data routinely collected by the Croatian Institute for Public Health (CIPH) (see Study outline for details). **B** Anonymized raw data was prepared by CIPH from several databases 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 (ICD-10 code U07.1), or based on epidemiological/clinical criteria (ICD-10 code U07.2). Patients first diagnosed by PCR/RAT testing when seeking hospital assistance for any reason were excluded at this step (at the time of raw database set-up, there were 23959 such subjects recorded). Individual data were linked to databases on vaccination, deceased persons, hospitalizations and Central Heath Information System (see Study outline for details). Anonymized data were further "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 August 15, 2021, as to allow a sufficiently long (shortest) follow-up for outcomes to occur (until October 31, 2022) (see Study outline for details). Based on International Classification of Disease version 10 (ICD-10) code entries and Anatomical Therapeutic Chemical (ATC) code entries patients were classified into cohorts in respect to issuance of prescriptions and underlying morbidity. Detailed definitions of cohorts in Study 1 and Study 2 are listed in Table 1. See also Study outline.

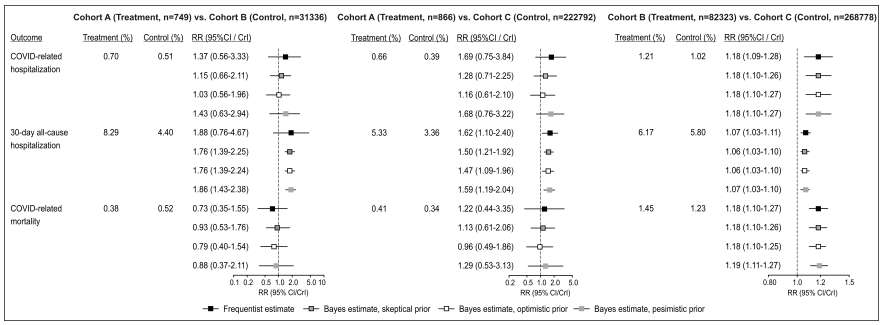

Figure 2: Analysis of outcomes (see subsection *Outcomes* for detailed definitions) in matched sets in Study 1. Shown are pairwise comparisons between patients in Cohort A (burdened with conditions requiring antidepressants/anxyolytics and prescribed fluvoxamine), Cohort B (suffer the same conditions, but not prescribed fluvoxamine) and Cohort C (free of such difficulties and related treatments) (see Table 1 for detailed cohort definitions). Depicted are weighted proportions (percentages) of patients with outcomes in each matched set and respective relative risks (RR). Priors for Bayes estimates: *skeptical* is moderately informative normal prior centered at 0.0 for Ln(RR) with standard deviation 0.355 – gives equal (50%) probability to an RR above and an RR below unity with 95% probability for an RR between 0.5 and 2.0; *optimistic* is a moderately informative normal prior centered at -0.199 for Ln(RR) (i.e., 18% relative risk reduction) with standard deviation 0.40 – suggests a benefit but leaves 30% probability of an RR >1.0; *pesimistic* is a weakly informative normal prior centered at 0.199 for Ln(RR) (i.e., 22% relative risk increase) with standard deviation 0.77 – suggests harm (of the same extent as benefit suggested by the optimistic prior), but leaves 40% probability of an RR <1.0.

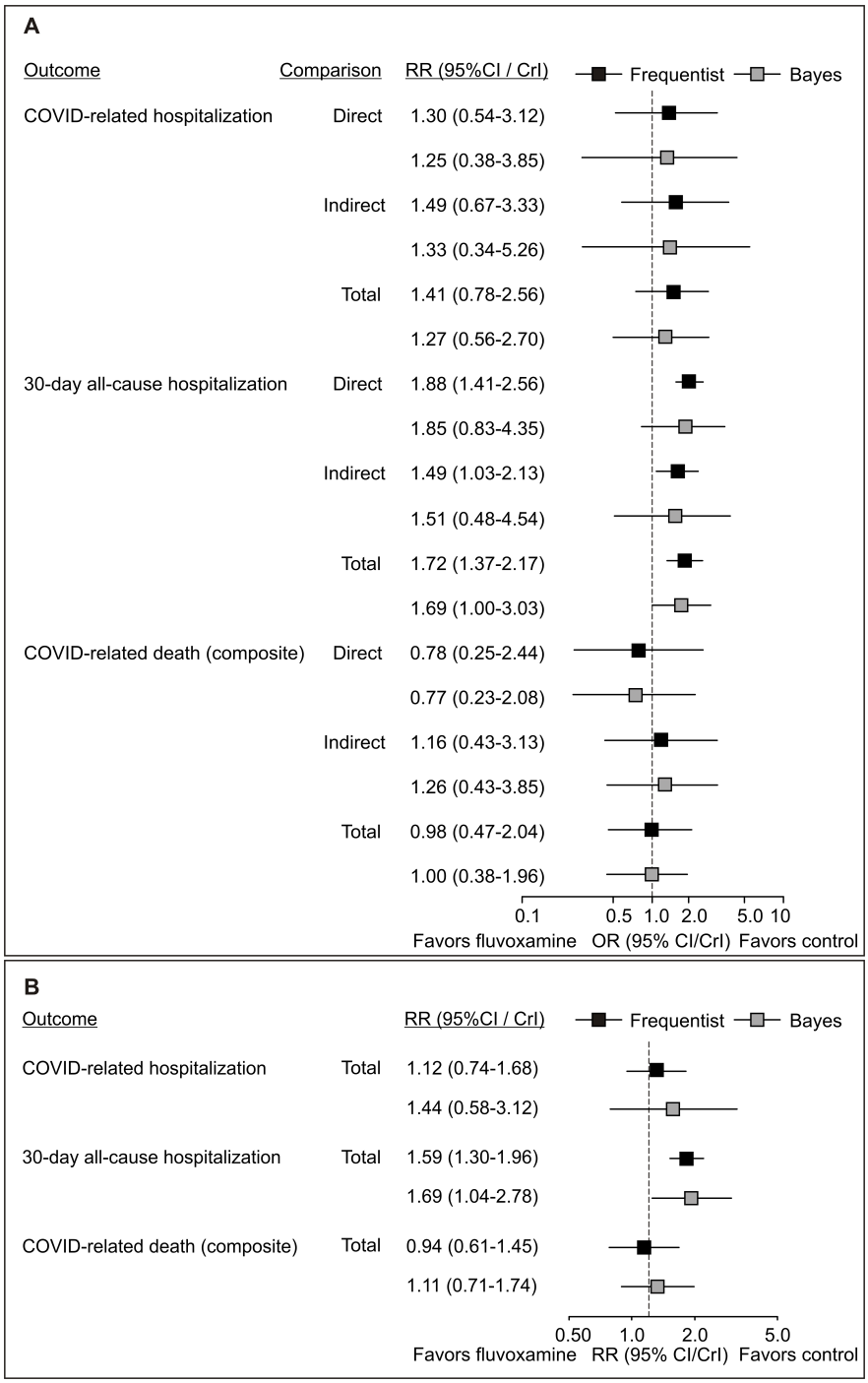

Figure 3: Results of network (frequentist and Bayes) analysis in Study 1: differences between Cohort A patients (burdened with conditions requiring antidepressants/anxyolytics and prescribed fluvoxamine around the time of COVID-19 diagnosis), i.e., treated; and Cohort B patients (suffer similar psychiatric difficulties, but are not prescribed with fluvoxamine), i.e., control patients, regarding the outcomes of interest (see Table 1 for cohort definitions, and *Outcomes* for outcome defiinitions). **A** Meta-analysis based on weighted proportions. Direct, indirect and total (combined, network) differences (relative risks, RR). **B** Meta-analysis based on Ln (RR) generated in primary Bayesian analysis with moderately informative skeptical prior (shown in Figure 2). Only total (combined) effects are shown (as in A, direct and indirect effects were consistent).

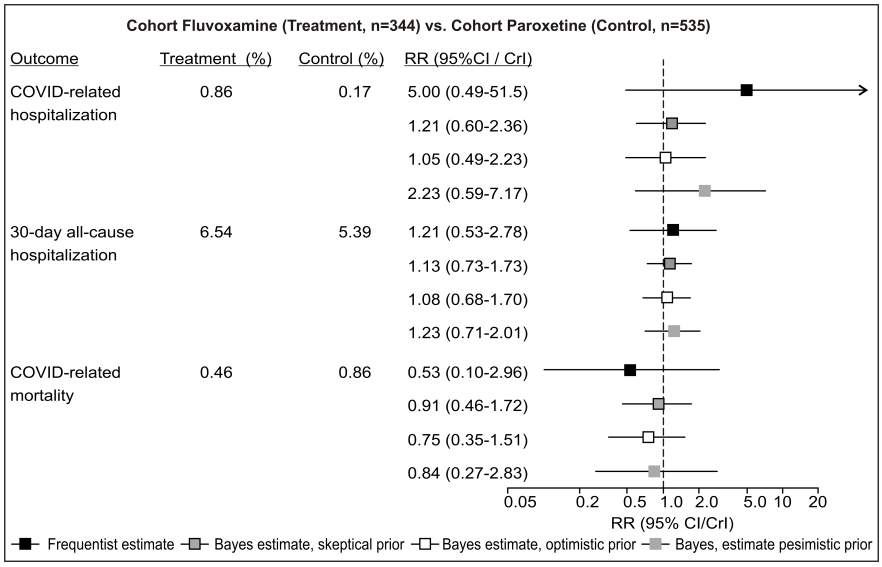

Figure 4: Analysis of outcomes (see *Outcomes* for detailed definitions) in matched sets in Study 2. Shown are pairwise comparisons between patients in Cohort Fluvoxamine (burdened with conditions requiring antidepressants/anxyolytics and prescribed fluvoxamine, but free of paroxetine, around the time of COVID-19 diagnoses) and Cohort Paroxetine (suffer the same conditions and prescribed peroxetine, but free of fluvoxamine, around the time of COVID-19 diagnosis) (see Table 1 for detailed cohort definitions). Depicted are weighted proportions (percentages) of patients with outcomes in matched sets and respective relative risks (RR). Priors for Bayes estimates: *skeptical* is moderately informative normal prior centered at 0.0 for Ln(RR) with standard deviation 0.355 – gives equal (50%) probability to an RR above and an RR below unity with 95% probability for an RR between 0.5 and 2.0; *optimistic* is a moderately informative normal prior centered at -0.199 for Ln(RR) (i.e., 18% relative risk reduction) with standard deviation 0.40 – suggests a benefit but leaves 30% probability of an RR >1.0; *pesimistic* is a weakly informative normal prior centered at 0.199 for Ln(RR) (i.e., 22% relative risk increase) with standard deviation 0.77 – suggests harm (of the same extent as benefit suggested by the optimistic prior), but leaves 40% probability of an RR <1.0.

Supplemental Information

Online Resource 1 – Supplemental Methods

1. Identification of drug prescriptions – Table S1
2. Identification of comorbidities – Table S2-S4
3. Identification of immunocompromised patients
4. Identification of patients suffering from diabetes

Online Resource 2 – Supplemental Results

Table S5. Study 1: Matching covariates in Cohort A and Cohort B before and after matching

Table S6. Study 1: Matching covariates in Cohort A and Cohort C before and after matching

Table S7. Study 1: Matching covariates in Cohort B and Cohort C before and after matching

Table S8. Study 2: Matching covariates in Cohort Fluvoxamine and Cohort Paroxetine before and after matching