

Screening Large Population Health Databases for Potential Coronavirus Disease 2019 Therapeutics: A Pharmacopeia-Wide Association Study of Commonly Prescribed Medications

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Background. For both the current and future pandemics, there is a need for high-throughput drug screening methods to identify existing drugs with potential preventive and/or therapeutic activity. Epidemiologic studies could complement laboratory-focused efforts to identify possible therapeutic agents.

Methods. We performed a pharmacopeia-wide association study (PWAS) to identify commonly prescribed medications and medication classes that are associated with the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older individuals (≥ 65 years) in long-term care homes (LTCHs) and the community, between 15 January 2020 and 31 December 2020, across the province of Ontario, Canada.

Results. A total of 26 121 cases and 2 369 020 controls from LTCHs and the community were included in this analysis. Many of the drugs and drug classes evaluated did not yield significant associations with SARS-CoV-2 detection. However, some drugs and drug classes appeared to be significantly associated with reduced SARS-CoV-2 detection, including cardioprotective drug classes such as statins (weighted odds ratio [OR], 0.91; standard $P < .01$, adjusted $P < .01$) and β -blockers (weighted OR, 0.87; standard $P < .01$, adjusted $P = .01$), along with individual agents ranging from levetiracetam (weighted OR, 0.70; standard $P < .01$, adjusted $P < .01$) to fluoxetine (weighted OR, 0.86; standard $P = .013$, adjusted $P = .198$) to digoxin (weighted OR, 0.89; standard $P < .01$, adjusted $P = .02$).

Conclusions. Using this epidemiologic approach, which can be applied to current and future pandemics, we have identified a variety of target drugs and drug classes that could offer therapeutic benefit in coronavirus disease 2019 (COVID-19) and may warrant further validation. Some of these agents (eg, fluoxetine) have already been identified for their therapeutic potential.

Keywords. case-control; COVID-19; drug screening; epidemiology; SARS-CoV-2.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent of coronavirus disease 2019 (COVID-19), has caused substantial morbidity and mortality since its recognition in China in December 2019 [1]. Hundreds of millions of COVID-19 cases and millions of attributable deaths have been documented worldwide [2]. Mortality has been particularly high in elderly patients and those with comorbid

conditions or residing in long-term care homes (LTCHs) [3]. For those patients who develop infection and recover, they remain at risk for longer-term sequelae that can impact on their physical and mental health as well as their economic productivity [4].

Significant resources have been invested into developing both effective vaccines for the prevention of disease and drugs for the treatment of those infected [5–7]. While vaccines have been shown effective at preventing most severe disease [8], there are still large populations of individuals, including young children, the vaccine-hesitant or ineligible, and those from areas with reduced access to vaccines, that are at particular risk for infection and/or complications of infection [8, 9]. Moreover, even individuals who have been vaccinated can develop severe disease from wild-type strains or emerging variants of concern (VoCs), although to a lesser extent [10–12].

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To date, many of the effective treatments for COVID-19 have been discovered through the “reuse” of existing drugs that serve other indications [6]. These include drugs with antiviral activity (eg, remdesivir, molnupiravir), those with local or systemic immunomodulatory properties (eg, dexamethasone, tocilizumab, baricitinib, budesonide, and sarilumab) [13, 14], and those with still unclear mechanisms (eg, fluvoxamine). Many of these therapies have shown impressive impacts at reducing morbidity and mortality in COVID-19, and the success of these agents supports the value of identifying active therapeutic agents from existing drugs. Moreover, the regulatory pipeline for trialing and then adopting an existing drug for an off-label indication is simpler than developing new agents for treatment [15]. Despite the significant progress that has been made to date with identifying effective agents, there are still major gaps for improving morbidity and mortality in both out-patient and hospitalized patients; mortality can be as high as 29% in patients receiving mechanical ventilation despite receipt of one of the most effective therapies to date (dexamethasone) [13].

A major hurdle in the reuse paradigm is efficiently screening candidate agents for prospective study. In vitro studies are used as a basis for justifying the clinical trials of many agents, but this approach is limited by assays that can assess the direct antiviral effect of agents on target cells or proteins [16] and do not necessarily capture more complicated actions of drugs including immunomodulation [13, 14]. Additionally, developing in vitro or animal models of emerging pathogens in a timely manner may prove challenging.

Rather than using in vitro drug screening, we can use large databases of patients that have exposures to existing drugs and evaluate their relative risk of COVID-19 as a function of these drug exposures. Using techniques from genomic epidemiology, we can perform a corollary of a genome-wide association study (GWAS) but using pharmaceuticals as the exposure. This has been termed a pharmacopeia-wide association study (PWAS) [17]. PWAS and related studies have typically been used for identifying drug harm, such as the evaluation of drug exposure and myocardial infarction risk, but the same approaches could also be used to discover therapeutic agents from existing drugs [17, 18]. PWAS and related studies [18] are not limited to evaluating drugs with direct antiviral activity and can capture immunomodulatory effects along with offering the benefit of assessing population-level impacts of particular exposures. These studies are not meant to achieve perfect adjustment/correction of all confounding or selection bias; rather, they are screening tools to identify targets with potential promise that warrant further evaluation. Evaluating agents that reduce an individual’s risk of infection can provide a window into potential prophylactic and therapeutic agents. Though these approaches represent a fundamentally different approach to drug screening compared

to traditional laboratory-based methods, PWAS could be a promising and complimentary way of identifying candidate drugs for rapid clinical trials in epidemic and pandemic contexts, including the ongoing COVID-19 pandemic. In this study, we applied a PWAS approach to evaluate potential drug targets for COVID-19 infection that would benefit from further study.

METHODS

Study Design

We performed a nested case-control study evaluating the associations between all drug exposures and the detection of SARS-CoV-2 in individuals across the province of Ontario, Canada. We used a PWAS with the aim of identifying potential drug targets for further evaluation and validation, but not to achieve perfect adjustment/correction of all confounding or selection bias. This is commensurate with drug screening approaches that seek to identify targets with promise, but not to definitively confirm effectiveness. We obtained study data from linked population-wide administrative datasets housed at ICES (formerly the Institute for Clinical Evaluative Sciences). These datasets were linked using unique encoded identifiers and analyzed at ICES.

Study Population/Cohort

We considered all Ontario residents aged 66–110 years between 15 January 2020 and 31 December 2020. We excluded residents who had (1) invalid birth or death dates; (2) non-Ontario postal codes; (3) or were not eligible for Ontario universal health insurance program coverage. We classified individuals into community-dwelling residents and residents of LTCHs. The latter group was identified based on recent assessments recorded in the Continuing Care Reporting System Long-Term Care database, or physician billings or prescription drug claims recorded in the Ontario Health Insurance Plan database or the Ontario Drug Benefits (ODB) database, respectively. The ODB database provides near-complete information on all prescription drugs for residents ≥ 65 years of age in Ontario.

Cases

We defined a case as laboratory-confirmed molecular detection of SARS-CoV-2 from nasopharyngeal and/or other respiratory specimens recorded in the Ontario Laboratories Information System. We selected the index date as the specimen collection date of the earliest testing episode positive for SARS-CoV-2.

Controls

We defined a control as any other resident during the study period, this includes individuals that were and were not tested for SARS-CoV-2. We randomly assigned index dates from 15 January 2020 through 31 December 2020.

Exposures

We wished to identify chronic drug exposures, and for each oral prescription drug captured in the ODB database, we determined whether an individual was chronically exposed to the drug by looking for a prescription with sufficient days' supply that overlapped with the index date and also 30 days prior to the index date. For the analyses, we only considered drugs with an exposure prevalence of $\geq 0.1\%$ in each group of residents. We classified drug exposures by the Anatomical Therapeutic Chemical (ATC) classification levels by linking the Drug Identification Number in the ODB database with the Drug Product Database, which is managed by Health Canada. The ATC4 level typically refers to a group of structurally and/or functionally related chemicals whereas the ATC5 level refers to individual drugs [19]. We chose to evaluate both drug classes to look for class effects, and also individual drugs (nested within drug classes) for drug-specific effects.

Covariates

We identified a number of covariates that could act as potential confounders of the association of medication use and SARS-CoV-2 detection. These include demographic (age, sex), geographic (census tract or census subdivision for rural areas for community-dwelling residents), facility (for LTCH residents), comorbidity (Charlson Comorbidity Index, asthma, cancer, chronic kidney disease including dialysis, chronic obstructive lung disease, coronary artery disease, dementia, depression, diabetes, congestive heart failure, hypertension, history of ischemic stroke, immunocompromised [as either diagnosis of human immunodeficiency virus, organ/bone marrow transplant, or immunosuppression condition/therapy], hypothyroidism, advanced liver disease, lupus, hospitalization for pneumonia in the prior year, rheumatoid arthritis), healthcare utilization (number of hospitalizations, number of physician visits, number of emergency department visits, number of prescriptions, receipt of homecare services in the past year) in the past year, quantity of drug exposure (number of unique ATC4 exposures, number of unique ATC5 exposures), and calendar month of index date. Comorbidity data were identified using a previously developed and validated multimorbidity macro [20–25].

Data Analysis

For each drug, we performed conditional logistic regression analyses evaluating the odds ratio (OR) of drug exposure among cases and controls; we applied separate models for the community and LTCH groups of interest. To account for geographic variability in case rates and drug exposures, we conditioned upon either (1) census tracts for community-dwelling individuals, or (2) facility for LTCH residents. We subsequently combined our effect estimates for community and LTCHs using an inverse variance weighted meta-analytic approach (described below). With the exception of the Charlson Comorbidity Index,

which was not available for all individuals, all other covariates were included in the model for each of the 2 populations of interest. We reported adjusted ORs, standard and multiple-testing adjusted *P* values (see below), and in some instances, 95% confidence intervals (CIs).

Meta-analyzed Effect Estimates

To provide a single effect estimate across the 2 studied populations, we combined the adjusted ORs of drug exposure (when a drug had an exposure prevalence of $\geq 0.1\%$ in both LTCH and community populations) for the community and LTCH resident populations using an inverse variance weighting approach to generate a weighted OR (wOR). Variances were pooled to compute the variance, 95% CIs, and standard *P* values of the weighted estimates.

Multiple Testing

We used the conservative Benjamini-Yekutieli procedure to adjust for multiple testing in a fashion assuming an arbitrary *P* value dependence [26]. Recently there has been a concerted effort to present CIs instead of *P* values in scientific reports; however, we have retained our *P* values here as we feel they are an important component of a GWAS-inspired analysis.

Visualization

Rainforest plots [27] were constructed to present drug-specific wORs of exposure and 95% CIs as well as associated standard and adjusted *P* values. Scatterplots were used to compare adjusted ORs of exposure between community and LTCH residents, by drug (ATC5) and drug class (ATC4).

Research Ethics and Patient Consent

ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act and does not require review by a research ethics board.

RESULTS

Our analysis included 2 395 141 individuals from the province of Ontario from 15 January 2020 to 31 December 2020. There were 2 326 441 community-dwelling residents, of which 17 300 (0.7%) had detection of SARS-CoV-2. There were 68 700 LTCH residents, of which 8821 (13%) had detection of SARS-CoV-2 (Supplementary Figure 1). The baseline characteristics of both populations, cases and controls, are shown in Table 1. In LTCH residents, the median age was 86 years in both cases and controls, and the majority of cases and controls were female (67% and 70%, respectively). Cases tended to have a higher mean number of hospitalizations, prescriptions, and some specific comorbidities (Table 1). In the community, the

Table 1. Baseline Characteristics of Cases and Controls From Long-Term Care Homes and Community Populations

Variable	Long-term Care Home Residents			Community Residents		
	Cases (COVID-19 Positive)	Controls	Std Diff	Cases (COVID-19 Positive)	Controls	Std Diff
	(n = 8821)	(n = 59 879)		(n = 17 300)	(n = 2 309 141)	
Age at index date, y						
Mean ± SD	85.05 ± 8.23	85.47 ± 8.18	0.05	76.35 ± 8.44	75.73 ± 7.25	0.08
Median (IQR)	86 (79–91)	86 (80–92)	0.05	74 (69–82)	74 (70–80)	0.01
Sex						
Female	5903 (66.9)	41 756 (69.7)	0.06	8883 (51.3)	1 247 321 (54.0)	0.05
Male	2918 (33.1)	18 123 (30.3)	0.06	8417 (48.7)	1 061 820 (46.0)	0.05
Charlson Comorbidity Index^a						
Mean ± SD	1.83 ± 1.60	1.67 ± 1.58	0.10	1.73 ± 1.78	1.29 ± 1.62	0.26
Median (IQR)	1 (1–3)	1 (1–3)	0.12	1 (0–3)	1 (0–2)	0.29
No. of hospitalizations^a						
Mean ± SD	0.34 ± 0.76	0.31 ± 0.70	0.05	0.24 ± 0.71	0.11 ± 0.43	0.22
Median (IQR)	0 (0–0)	0 (0–0)	0.05	0 (0–0)	0 (0–0)	0.23
No. of physician visits^a						
Mean ± SD	14.36 ± 8.67	13.83 ± 9.69	0.06	7.27 ± 8.22	5.23 ± 6.15	0.28
Median (IQR)	13 (12–15)	12 (11–14)	0.18	5 (2–10)	4 (1–7)	0.34
No. of ED visits^a						
Mean ± SD	0.81 ± 1.53	0.72 ± 1.48	0.06	0.89 ± 1.87	0.45 ± 1.21	0.28
Median (IQR)	0 (0–1)	0 (0–1)	0.09	0 (0–1)	0 (0–0)	0.36
No. of prescriptions^a						
Mean ± SD	12.11 ± 5.76	11.88 ± 5.76	0.04	8.65 ± 5.97	6.12 ± 5.03	0.46
Median (IQR)	11 (8–15)	11 (8–15)	0.04	8 (4–12)	5 (2–9)	0.46
Receipt of home care^a						
	2925 (33.2)	20 387 (34.0)	0.02	4259 (24.6)	265 241 (11.5)	0.35
Comorbidities						
Asthma	1437 (16.3)	8721 (14.6)	0.05	3141 (18.2)	308 143 (13.3)	0.13
Cancer	105 (1.2)	867 (1.4)	0.02	481 (2.8)	61 232 (2.7)	0.01
CKD	1695 (19.2)	9002 (15.0)	0.11	2668 (15.4)	183 944 (8.0)	0.23
COPD	1370 (15.5)	9455 (15.8)	0.01	1754 (10.1)	179 541 (7.8)	0.08
CAD	758 (8.6)	4705 (7.9)	0.03	1353 (7.8)	111 391 (4.8)	0.12
Dementia	7393 (83.8)	47 924 (80.0)	0.1	2224 (12.9)	112 680 (4.9)	0.28
Depression	3358 (38.1)	21 183 (35.4)	0.06	5141 (29.7)	567 629 (24.6)	0.12
Diabetes	3687 (41.8)	22 328 (37.3)	0.09	7397 (42.8)	694 427 (30.1)	0.27
CHF	2137 (24.2)	13 988 (23.4)	0.02	2514 (14.5)	198 384 (8.6)	0.19
Hypertension	7482 (84.8)	49 675 (83.0)	0.05	13 183 (76.2)	1 557 102 (67.4)	0.20
History of ischemic stroke	1069 (12.1)	6821 (11.4)	0.02	653 (3.8)	52 408 (2.3)	0.09
Immunocompromised	592 (6.7)	4360 (7.3)	0.02	1431 (8.3)	160 581 (7.0)	0.05
Hypothyroidism	1032 (11.7)	5966 (10.0)	0.06	2447 (14.1)	261 966 (11.3)	0.08
Advanced liver disease	239 (2.7)	1109 (1.9)	0.06	361 (2.1)	33 743 (1.5)	0.05
Lupus	171 (1.9)	1084 (1.8)	0.01	446 (2.6)	56 451 (2.4)	0.01
Pneumonia hospitalization ^a	327 (3.7)	1929 (3.2)	0.03	328 (1.9)	15 523 (0.7)	0.11
Rheumatoid arthritis	308 (3.5)	2035 (3.4)	0.01	501 (2.9)	61 579 (2.7)	0.01
No. of unique ATC4 exposures						
0 drug exposures	466 (5.3)	3611 (6.0)	0.03	3844 (22.2)	647 912 (28.1)	0.13
1–5 drug exposures	3977 (45.1)	27 184 (45.4)	0.01	9151 (52.9)	1 297 823 (56.2)	0.07
6–10 drug exposures	3764 (42.7)	25 235 (42.1)	0.01	3866 (22.3)	337 366 (14.6)	0.20
>10 drug exposures	614 (7.0)	3849 (6.4)	0.02	439 (2.5)	26 040 (1.1)	0.11
No. of unique ATC5 exposures^a						
0 drug exposures	466 (5.3)	3611 (6.0)	0.03	3844 (22.2)	647 912 (28.1)	0.13
1–5 drug exposures	3897 (44.2)	26 527 (44.3)	0	9123 (52.7)	1 294 145 (56.0)	0.07
6–10 drug exposures	3783 (42.9)	25 398 (42.4)	0.01	3867 (22.4)	339 154 (14.7)	0.20
>10 drug exposures	675 (7.7)	4343 (7.3)	0.02	466 (2.7)	27 930 (1.2)	0.11

If not otherwise specified, values are shown as frequency (%).

Abbreviations: ATC, Anatomical Therapeutic Chemical classification system; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ED, emergency department; IQR, interquartile range; SD, standard deviation; Std Diff, standardized difference.

^aIn the past year.

median age was 74 years for cases and controls, and the majority of cases and controls were female (51% and 54%, respectively). There was a trend toward a higher mean number of hospitalizations, physician visits, and prescriptions in cases vs controls (Table 1).

The wORs of individual drug exposure (ATC5) are shown in Figure 1, along with standard *P* values and multiple testing–adjusted *P* values. Drug exposures are ordered according to effect size, and there are a small subset of individual drugs showing strong associations with either decreased or increased odds of SARS-CoV-2 detection. In total, there are 25 drugs associated with reduced detection of SARS-CoV-2 (wORs, <.9), many of which were found to have multiple-testing *P* values < .05. Adjusted ORs for the specific population (LTCH and community-dwelling residents) are shown in Supplementary Figure 2.

The wORs of drug class exposure (ATC4) are shown in Supplementary Figure 3, along with standard *P* values and multiple testing–adjusted *P* values. Drug class exposures are ordered according to effect size, with some classes showing strong associations with either decreased or increased odds of SARS-CoV-2 detection. In total, there are 17 drug classes associated with reduced detection of SARS-CoV-2 (wORs, <.9), many of which were found to have multiple-testing *P* values < .05. Adjusted ORs for the specific population (LTCH and community-dwelling residents) are shown in Supplementary Figure 4.

We plotted the adjusted ORs of drug exposure by ATC level for LTCH vs community-dwelling residents (Figure 2), where a null association was hypothesized as we expect the majority of effect estimates to be noise with the exception of the strongest associations. Quantile-quantile plots of wORs by drug and drug class are shown in Supplementary Figures 5 and 6.

We performed a sensitivity analysis of the community population, stratifying by age <80 years and age ≥80 years. These adjusted ORs of drug exposure (ATC5) are shown in Supplementary Figure 7. These generally show the strongest association measure as consistent across these age strata. We did not perform this analysis for the LTCH group because the median age was 86 years.

DISCUSSION

In this large, nested case-control study across the entire pharmacopeia of commonly prescribed medications, we demonstrate that PWAS can be used to identify drugs and drug classes that are associated with laboratory-confirmed detection of SARS-CoV-2. We found that the vast majority of commonly used drugs are not associated with either increased or reduced detection of SARS-CoV-2. However, as is the potential power of large drug screens [28], we have identified some existing agents/classes that warrant further investigation as potential COVID-19 therapeutics.

While a number of individual agents showed associations with reduced detection of SARS-CoV-2, we highlight 4 agents that demonstrated particularly pronounced reduced SARS-CoV-2 detection and are also commonly used: ezetimibe, fluoxetine, levetiracetam, and diazepam. Ezetimibe inhibits cholesterol absorption from the small intestine, and this alteration of the cholesterol synthesis pathway (as occurs also with statins and fibrates) may be a mechanism for beneficial effect in COVID-19 [29]. A large case-control study from Israel identified that drugs related to the cholesterol synthesis pathway, including ezetimibe, ubiquinone, and rosuvastatin, were associated with reduced risk of hospitalization with COVID-19 and support our findings [18]. The association between fluoxetine and reduced COVID-19 diagnosis may have a foundation in a unique immunomodulatory effect found with selective serotonin reuptake inhibitors (SSRIs), due to σ -1 receptor (S1R) agonism [30], which may act to reduce proinflammatory cytokine production. The SSRI fluvoxamine has shown promise for treating outpatients with COVID-19 infection [31]; therefore, fluoxetine, which shares similar mechanistic properties including potent S1R agonism, could reduce symptoms of COVID-19 infection and thus yield reduced diagnosis. Levetiracetam (an anti-epileptic agent) and diazepam (an anxiolytic) both have no known antiviral activity against SARS-CoV-2 or clear immunomodulatory effects and may benefit from further evaluation (along with the many other agents demonstrating reduced association with SARS-CoV-2 detection).

We also identified a number of drug classes that showed strong associations with reduced SARS-CoV-2 identification, and the majority of these appeared to be cardioprotective agents, including lipid-modifying agents such as statins, inhibitors/blockers of the renin-angiotensin system (eg, angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]), and β -blockers. There are multiple reasons these agents may have shown reduced associations with SARS-CoV-2 detection. First, they may play a role in protecting individuals from acquiring COVID-19 [32]. In particular, ACE inhibitors and ARBs have been the focus of much speculation in the literature given that SARS-CoV-2 binds to the ACE2 receptor, and there are a number of ongoing and completed prospective clinical trials to evaluate the clinical impact of these drugs [33]. Second, they may reduce the severity of illness, and thus reduce the likelihood of case identification (diagnosis). Other cardioactive classes that showed a reduced association with SARS-CoV-2 identification were the digitalis glycosides, specifically digoxin. This may be due to reduced case finding through a stabilizing effect on cardiac function and thus reduced symptomatology. Interestingly, this could also be due to a direct antiviral effect of digoxin, which has been noted in prior in vitro studies [34].

We also identified classes of drugs associated with increased SARS-CoV-2 detection. Some of these classes include

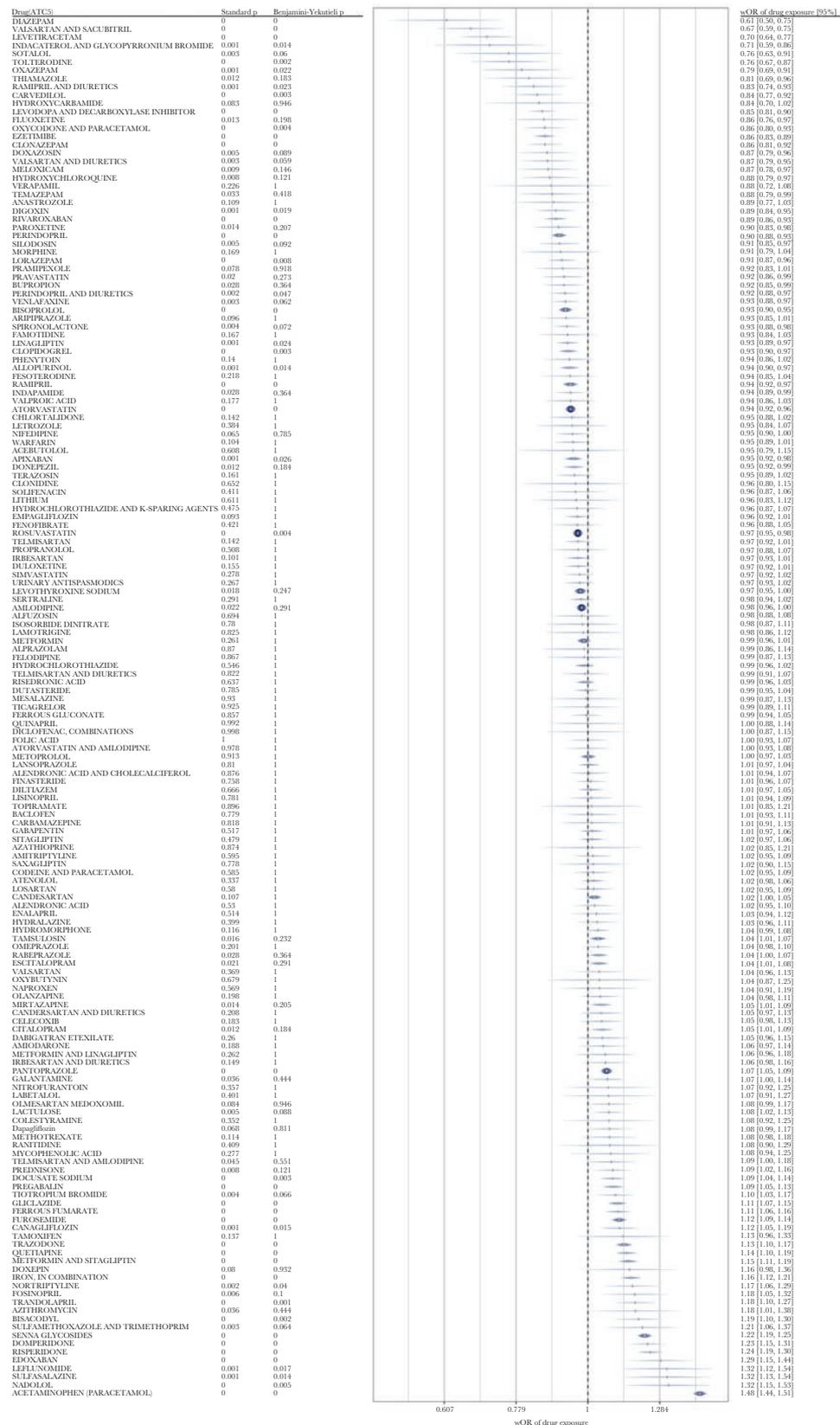


Figure 1. Rainforest plots of the weighted odds ratios (wORs) and 95% confidence intervals (CIs) of drug exposure by ATC5 (Anatomical Therapeutic Chemical classification) drug, along with standard *P* values and Benjamini-Yekutieli-adjusted *P* values.

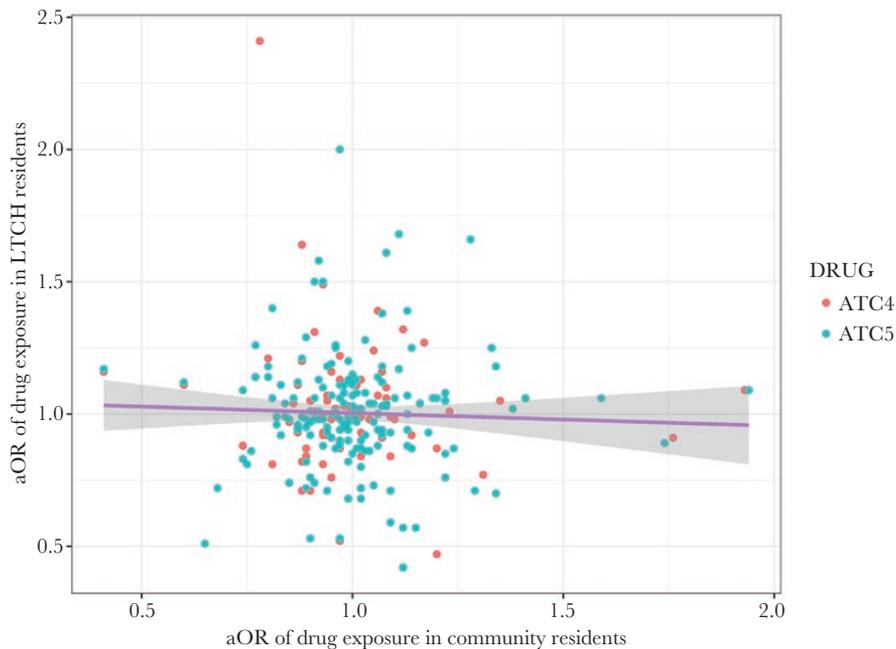


Figure 2. Scatterplot of the adjusted odds ratios (aORs) of drug exposure in long-term care home (LTCH) residents vs community residents, by Anatomical Therapeutic Chemical (ATC) drug classification level, along with trend lines and 95% confidence regions (gray).

immunomodulatory drugs (eg, sulfasalazine and leflunomide) that may alter the predisposition of patients for developing severe disease. Other classes associated with increased SARS-CoV-2 detection include antibiotics (eg, macrolides and sulfa agents), proton pump inhibitors, and iron. The association with antibiotics may be reflective of residual confounding among populations with chronic lung disease or other chronic diseases that require frequent or continuous antibiotic use, and may be at risk of more symptomatic/severe disease. It is unlikely that these findings represent reverse causation, as our exposure definition requires the use of the agent at 1 month prior to the index diagnosis. The harmful association with iron may be due to worse outcomes associated with iron deficiency (with iron use a proxy for iron deficiency) [35, 36], and the harmful association with proton pump inhibitors could relate to suspected detrimental effects of hypochlorhydria [37, 38].

When comparing all drugs or drug classes, we did not find an association between adjusted odds ratios of exposure for LTCH and community-dwelling individuals. This is expected, because only a minority of estimates should be truly concordant between the populations (representing signal) and the rest should be random (representing noise).

As with any epidemiologic study, associations that have been outlined here could be due to residual confounding or selection bias. However, we did adjust for a large array of potential confounders in our analysis. Moreover, we used an approach that offered the least risk of collider stratification bias [39, 40]. Nevertheless, we expect residual confounding or selection bias to be driving many of the protective and harmful

associations in this PWAS analysis, and the goal of PWAS is as a high-throughput screening test to highlight potential targets for further epidemiologic, *in vitro*, or *in vivo* validation. Another potential limitation of our study was the selection of the outcome, namely SARS-CoV-2 detection, which is not a direct measure of symptomatic COVID-19 infection, nor the impacts on outcomes in patients who are diagnosed with COVID-19. However, we chose this outcome to identify drug exposures that might act to prevent acquisition or detection of acquisition, for which there would be an underlying important drug effect that could be repurposed for either prevention or treatment of COVID-19. Last, our study occurred largely in pre-VoC time periods, and findings here may be less generalizable to a viral landscape made up of predominantly VoCs.

Additional steps can be taken to evaluate these candidate drugs, depending upon the agent and other supporting evidence, and may include *in vitro* confirmation of antiviral activity (if suspected), additional observational studies to confirm effects in separate settings/regions, or possibly prospective trial evaluations.

In summary, we present an approach for using large epidemiologic cohorts, in a manner akin to genome-wide association studies, to screen for possible drug candidates for the prevention and treatment of COVID-19 that would benefit from further evaluation. These approaches can be used now to search for possible active agents for the ongoing COVID-19 pandemic, as well as in the future as we experience the emergence of new pathogens of global concern with epidemic/pandemic spread.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. D. R. M. and N. D. conceived the idea for the study. D. R. M., N. D., K. B., S. A. B., H. C., and J. C. K. were involved in the analysis development. H. C. and D. R. M. performed the analyses and visualizations. All authors were involved in critical review of the manuscript and writing/editing of the manuscript.

Disclaimer. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES, the Ontario Ministry of Health (MOH), or the Ontario Ministry of Long-Term Care (MLTC) is intended or should be inferred.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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