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Factors associated with SARS-CoV-2 testing, diagnosis and COVID-19 disease among individuals prescribed opioid-agonist treatment: a nationwide retrospective cohort study

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ABSTRACT

Objectives: Among people receiving opioid-agonist treatment (OAT), the risk of COVID-19 infection and disease may be higher owing to underlying health problems and vulnerable social circumstances. We aimed to determine whether recent OAT, when compared with past exposure, affected the risk of (i) testing for SARS-CoV-2, (ii) testing positive for SARS-CoV-2, and (iii) being hospitalized or dying with COVID-19 disease.

Methods: We included individuals prescribed OAT in Scotland from 2015 to 2020. We performed record linkage to SARS-CoV-2 PCR testing, vaccination, hospitalization, and mortality data, and followed up from March 2020 to December 2021. We used proportional hazards analysis and multivariate logistic regression to estimate associations between recent OAT prescription (in the previous 2 months), compared with past exposure (off treatment for over a year), and COVID-19 outcomes. Models were adjusted for confounders.

Results: Among 36 093 individuals prescribed OAT, 19 071 (52.9%) were tested for SARS-CoV-2; 2896 (8.3%) tested positive; and 552 (1.5%) were hospitalized or died with COVID-19. Recent OAT, compared with past exposure, was associated with lower odds of testing positive among those tested (aOR, 0.63; 95% CI, 0.57–0.69). However, among those testing positive, recent OAT was associated with two-fold higher odds of hospitalization or death (aOR, 2.04; 95% CI, 1.60–2.59).

Discussion: We found that recent OAT was associated with lower odds of SARS-CoV-2 infection, but with higher odds of disease once diagnosed. Clinical studies are needed to unravel the role of OAT in these associations. An enhanced effort is warranted to increase vaccine coverage among OAT patients to mitigate the severe consequences of COVID-19. **Megan Glancy, Clin Microbiol Infect 2024;■:1**

Introduction

Injecting drug use is a significant driver of morbidity and premature mortality. Globally, there are an estimated 14.8 million people who inject drugs [1]. Among people who inject drugs, the risk of SARS-CoV-2 infection and associated severe outcomes due to COVID-19 disease may be higher than the general population owing to complex underlying health problems and vulnerable social circumstances.

Large retrospective studies from the United States and Europe have demonstrated that people diagnosed with opioid use disorder have increased odds of infection and worse COVID-19 outcomes when compared with people without opioid use disorder [2–5]. A high prevalence of comorbidities has been highlighted as a key contributing factor [2,5]. Conversely, findings from cross-sectional studies among people who use or inject drugs have been mixed

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in relation to COVID-19 incidence when compared with the general population [6–10]. Where a lower risk has been observed, some have suggested this may be specific to those receiving opioid-agonist treatment (OAT) to treat opioid dependence [10–12].

In Scotland, the risk of hospitalization or death after diagnosis with COVID-19 was two-fold higher among people who had received OAT for their opioid dependence in the past 5 years when compared with those in the wider general population who had not received OAT [13]. This higher risk remained after controlling for comorbidity and vaccination status, suggesting that other factors may explain the difference in risk. Thus, we aimed to examine this further and investigate whether COVID-19 outcomes were related to recent as opposed to past treatment with OAT. Our objectives were to determine whether individuals in Scotland with recent exposure to OAT, when compared with those with past exposure, had different odds of: (i) testing for SARS-CoV-2, (ii) testing positive for SARS-CoV-2, and (iii) being hospitalized or dying after diagnosis with COVID-19 disease. We also aimed to describe other key factors associated with these COVID-19 outcomes.

Methods

Study design

We assessed the effect of COVID-19 among people treated for opioid dependence in Scotland through a retrospective cohort study using linked health care data held by Public Health Scotland, from March 1, 2020 (the start of the COVID-19 pandemic in Scotland) to December 31, 2021.

Approval for the linkage of National Health Service (NHS) data was provided by the NHS Public Benefit and Privacy Panel for Health and Social Care (PBPP-2021-0203).

Cohort

Entry to the cohort was based on having a prescription of OAT for opioid dependence—methadone, buprenorphine, or buprenorphine-naloxone—from January 1, 2015, to December 31, 2020 in the Scottish prescribing information system (PIS). PIS is a nationwide, individual-level dataset of NHS prescriptions dispensed in pharmacy and community settings in Scotland [14]. Cohort exclusions are detailed in Fig. S1.

Data linkage

Prescription records were available from January 2015 to December 2021. We used the community health index (CHI) number, a unique identifier of patients accessing NHS health care in Scotland [15], to deterministically link records to other administrative and health care datasets. Laboratory testing (ECOSS), hospital admissions (SMR01), and mortality data (National Records of Scotland) were used to define COVID-19 outcomes. The CHI number was available for ~75–80% of OAT prescription records from 2015 to 2020 [16]. Details on data sources and variables are in Table S1.

Outcomes and exposures

The following outcome measures were assessed during March 1, 2020 to December 31, 2021: (i) first test for SARS-CoV-2 among all OAT recipients; (ii) tested positive for SARS-CoV-2 among those tested; (iii) hospitalized or died after being diagnosed with COVID-19 among those who tested positive (cohort flowchart in Fig. S1).

Aligned to previous studies [13,17], hospitalization or death after diagnosis with COVID-19 was defined as: an admission where the specific cause was COVID-19 (ICD-10 codes U07.1, U07.2, or U07.5), any hospitalization or death that occurred within 28 days of a positive test, individuals having first tested positive for SARS-CoV-2 while in hospital, or a death certificate with COVID-19 as the underlying cause. Using this definition ensures the ascertainment of all cases resulting in hospitalization or death.

The key exposure was recency of OAT, categorized as: <2 months ago, 2–12 months ago, or >12 months ago (see statistical analysis below for further detail). Where the date of the OAT prescription was unavailable from PIS, the date of reimbursement (occurring on average 6 weeks after prescription date) was substituted (as previously described [18,19]). OAT exposure was determined based on the most recent prescription or reimbursement in relation to the date of outcome.

We considered the following covariates: age-group (as of March 2020), sex, health board of residence, deprivation, comorbidity status, and vaccination status (the number of doses received at least 14 days before the outcome). Comorbidities regarded as risk conditions for COVID-19 disease were determined from linkage to hospital admissions data (SMR01) going back 5 years and prescribing data (PIS) going back nine months [20]. We identified those who were clinically extremely vulnerable (CEV) using records of shielding and CEV individuals [17]. We categorized comorbidity status as the following: (i) CEV, (ii) other comorbidities, and (iii) no known comorbidities.

Statistical analyses

For outcome (i), we used Cox proportional hazards regression to examine the association between time to first SARS-CoV-2 test and recency of OAT. The time at risk was from March 1, 2020 (or the date of first OAT prescription if this occurred later) until the earlier date of the first test, death, or study end (December 31, 2021). The OAT exposure was a time-dependent covariate categorized according to time since most recent prescription, as: (i) < 2 months (relating to period on treatment), (ii) 2 to 12 months (relating to period recently stopped treatment), and (iii) > 12 months (relating to period off treatment for longer). We report unadjusted and adjusted hazard ratios and 95% CIs.

To assess outcomes (ii) testing positive among those tested and (iii) hospitalization or death among those testing positive, we used multivariate logistic regression, allowing for repeated testing among individuals by including an individual identifier variable as a random effect. The OAT exposure was based on the most recent prescription before the date of the test or positive test and was categorized as above. We report unadjusted and adjusted odds ratios and 95% CIs.

For all outcomes, we repeated each analysis stratified by epidemic wave periods to account for changes in testing guidelines and SARS-CoV-2 variants. Epidemic waves were based on Scottish case data, and defined as: wave 1, March 2020 to July 2020; wave 2, August 2020 to April 2021 (alpha-variant dominant); and wave 3, May 2021 to December 2021 (delta-variant dominant) [21]. Individuals could be included in each stratified analysis.

R version 4.1.1 was used for analyses.

Results

Cohort description

Our cohort included 36 083 individuals who received at least one CHI-identified OAT prescription from 2015 to 2020 (Table 1). Most received OAT in 2021 (69.9%; 25 217 of 36 083), whereas the minority were last prescribed from 2015 to 2020 (10 866 of 36 083; 30.1%). Two thirds were male (67.3%; 24 295 of 36 083), aged over 40 years (66.6%; 24 095 of 36 083), and half (52.6%; 18 975 of

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Table 1
Distribution of covariates among the study population by (i) ever tested for SARS-CoV-2, (ii) ever tested positive for SARS-CoV-2, and (iii) ever hospitalized or died with COVID-19 from March 2020 to December 2021 (n = 36 083 individuals prescribed OAT from 2015 to 2020)

	Total (% in group)	Number tested (% of total)	Number tested positive (% of those tested)	Number with COVID-19 admission or death (% of those tested positive)
Total	36 083 (100%)	19 071 (52.9%)	2986 (15.7%)	552 (18.5%)
Age group (y) at December 2020				
18–29	1948 (5.4%)	1168 (60.0%)	217 (18.6%)	22 (10.1%)
30–39	10 110 (28.0%)	5759 (57.0%)	992 (17.2%)	129 (13.0%)
40–49	15 870 (44.0%)	8070 (50.9%)	1240 (15.4%)	216 (17.4%)
50–59	7095 (19.7%)	3514 (49.5%)	485 (13.8%)	154 (31.8%)
60+	1060 (2.9%)	560 (52.8%)	52 (9.3%)	31 (59.6%)
Sex				
Female	11 788 (32.7%)	6657 (56.5%)	969 (14.6%)	192 (19.8%)
Male	24 295 (67.3%)	12 414 (51.1%)	2017 (16.2%)	360 (17.8%)
NHS health board of residence[a]				
Grampian	3649 (10.1%)	1723 (47.2%)	187 (10.9%)	18 (9.6%)
Greater Glasgow and Clyde	10 563 (29.3%)	5692 (53.9%)	932 (16.4%)	216 (23.2%)
Lothian	5962 (16.5%)	2937 (49.3%)	419 (14.3%)	66 (15.8%)
Tayside	2946 (8.2%)	1773 (60.2%)	280 (15.8%)	48 (17.1%)
Rest of Scotland	12 963 (35.9%)	6946 (53.6%)	1168 (16.8%)	204 (17.5%)
Deprivation (Scottish Index of Multiple Deprivation quintile)[a]				
1 (most deprived)	18 975 (52.6%)	10 018 (52.8%)	1624 (16.2%)	325 (20%)
2	9206 (25.5%)	4913 (53.4%)	775 (15.8%)	135 (17.4%)
3	4453 (12.3%)	2279 (51.2%)	296 (13.0%)	51 (17.2%)
4	2369 (6.6%)	1270 (53.6%)	189 (14.9%)	28 (14.8%)
5 (least deprived)	1080 (3.0%)	591 (54.7%)	102 (17.3%)	13 (12.7%)
Comorbidity status				
None	21 441 (59.4%)	10 017 (46.7%)	1722 (17.2%)	179 (10.4%)
Other comorbidities	12 367 (34.3%)	7531 (60.9%)	1064 (14.1%)	279 (26.2%)
Clinically extremely vulnerable	2275 (6.3%)	1523 (66.9%)	200 (13.1%)	94 (47.0%)
SARS-CoV-2 vaccination status[b]				
0 doses	13 460 (37.3%)	6005 (44.6%)	953 (15.9%)	222 (23.3%)
1 dose	5403 (15.0%)	3114 (57.6%)	504 (16.2%)	100 (19.8%)
2+ doses	17 220 (47.7%)	9952 (57.8%)	1529 (15.4%)	230 (15.0%)
Most recent OAT prescription[b]				
2015 to 201	4881 (13.5%)	2480 (50.8%)	551 (22.2%)	60 (10.9%)
2019 to 2020	5985 (16.6%)	3256 (54.4%)	575 (17.7%)	104 (18.1%)
2021	25 217 (69.9%)	13 335 (52.9%)	1860 (13.9%)	388 (20.9%)

OAT, opioid-agonist treatment.
[a] Missing NHS board values combined with Rest of Scotland (538, 1.5%); missing SIMD quintile values combined with SIMD 1 (156, 0.4%).
[b] Relative to December 31, 2021.

Table 2
Crude rate, unadjusted and adjusted hazard ratios (HR) for time to first SARS-CoV-2 PCR test, with time since most recent OAT prescription included as a time-varying covariate

	Time (person-y)	Number tested (rate per 100 person-y)	HR (95% CI)	p	aHR (95% CI)[a]	p
Most recent OAT at time of test						
12+ mo	10 533	5005 (47.5)	1 (ref)		1 (ref)	
2–12 mo	5291	3989 (75.4)	1.57 (1.51–1.64)	<0.001	1.52 (1.46–1.59)	<0.001
<2 mo	32 266	10 068 (331.2)	0.72 (0.70–0.75)	<0.001	0.71 (0.68–0.73)	<0.001
Age group (y)						
18–29	2453	1168 (47.6)	1 (ref)		1 (ref)	
30–39	13 233	5757 (43.5)	0.90 (0.85–0.96)	<0.001	0.93 (0.87–0.99)	0.015
40–49	21 527	8064 (37.5)	0.77 (0.72–0.82)	<0.001	0.79 (0.74–0.84)	<0.001
50–59	9540	3514 (36.8)	0.76 (0.71–0.81)	<0.001	0.71 (0.66–0.76)	<0.001
60+	1338	559 (41.8)	0.87 (0.78–0.96)	<0.001	0.72 (0.65–0.80)	<0.001
Sex						
Female	15 210	6655 (43.8)	1 (ref)		1 (ref)	
Male	32 880	12 407 (37.7)	0.85 (0.83–0.88)	<0.001	0.91 (0.89–0.94)	<0.001
Deprivation (Scottish Index of Multiple Deprivation quintile)						
1 (most deprived)	25 224	10 012 (39.7)	1 (ref)		1 (ref)	
2 or 3	18 295	7190 (39.3)	0.99 (0.96–1.02)	0.445	1.03 (1.00–1.06)	0.080
4 or 5	4572	1860 (40.7)	1.02 (0.98–1.08)	0.335	1.06 (1.01–1.12)	0.020
Comorbidity status						
Neither	30 820	10 010 (32.5)	1 (ref)		1 (ref)	
Other comorbidities	14 808	7529 (50.8)	1.63 (1.58–1.68)	<0.001	1.68 (1.63–1.73)	<0.001
Clinically extremely vulnerable	2462	1523 (61.9)	2.02 (1.92–2.13)	<0.001	2.22 (2.10–2.35)	<0.001

[a] Adjusted for all covariates presented and for health board of residence.Hazard ratios are presented with 95% CI. N = 36 083 people prescribed OAT from 2015 to 2020. OAT, opioid-agonist treatment.

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36 083) resided in an area ranked among the most deprived in Scotland (Scottish Index of Multiple Deprivation (SIMD) quintile 1). Health conditions were prevalent among the cohort; 34.3% (12 367 of 36 083) had one or more pre-existing comorbidities, and 6.3% (2275 of 36 083) were considered CEV. As of December 2021, just under half (47.7%; 17 220 of 36 083) had received two or more doses of SARS-CoV-2 vaccination.

Factors associated with being tested for SARS-CoV-2

From March 2020 to December 2021, just over half (52.9%; 19 071 of 36 083) of the cohort had been tested for SARS-CoV-2, and 60 500 tests were carried out overall (Table 1). During this time, 1094 individuals died of other causes and were censored from the analysis. Relative to those who had not received OAT in over 12 months, the adjusted hazard ratio for OAT exposure within 2–12 months was 1.52 (1.46–1.59), whereas for OAT exposure within <2 months was 0.71 (0.68–0.73) (Table 2). We found similar trends in analyses stratified by wave period (Table S2).

Other factors associated with testing for SARS-CoV-2 were being CEV (aHR = 2.22 [2.10–2.35]) or having other comorbidities (aHR = 1.68 ([1.63–1.73]). Negative predictors were being male (aHR = 0.91 [0.89, 0.94]) and older in age, most evident among those aged 50–59 and 60+ years (aHR = 0.71 [0.66–0.76] and aHR = 0.72 [0.65–0.80], respectively, when compared with the 18–29 age group).

Factors associated with testing positive for SARS-CoV-2

Of those ever tested, 15.7% (2986 of 19 071) tested positive for SARS-CoV-2 during the study period (relating to 3292 positive tests) (Table 1). Recent exposure to OAT (i.e. prescription <2 months before date of test) was associated with reduced odds of testing positive (aOR = 0.63 (0.57–0.69)) when compared with those with past exposure (>12 months since last prescription) (Table 3). The association between recent OAT exposure and reduced odds of testing positive was consistent across all epidemic waves (wave 1, aOR = 0.66 [0.38–1.12]; wave 2, aOR = 0.53 [0.44–0.]; wave 3, aOR = 0.71 [0.63–0.79]) (Table S3).

Being aged 50+ years was associated with lower odds of testing positive when compared with the 18–29 age group (60+, aOR = 0.49 [0.36–0.69]; 50–59, aOR = 0.77 [0.64–0.94]), whereas vaccination was associated with increased odds of testing positive (one dose, aOR = 1.13 [1.02–1.27]); two or more doses (aOR = 1.37 [1.25–1.50]) (Table 3).

Factors associated with hospitalization/death after diagnosis with COVID-19

Among those who tested positive for SARS-CoV-2, 18.5% (552 of 2986) were hospitalized or died due to COVID-19, relating to 1.5% (552 of 36 083) of the total cohort (Table 1). Recent OAT exposure was associated with two-fold higher odds of COVID-19 hospitalization or death (aOR = 2.04 [1.60–2.59]) (Table 4); consistent across epidemic waves 2 and 3 (wave 2, aOR = 2.40 [1.54–3.73]; wave 3, aOR = 1.94 [1.42–2.66]) (Table S4).

Increased odds of hospitalization or death were seen among older individuals (60+ aOR = 6.06 [2.97–12.36]; 50–59 aOR = 2.77 [1.67–4.60]), and those with comorbidities (CEV, aOR = 3.52 [2.53–4.91]; other comorbidities, aOR = 2.46 [1.99–3.04]). Receiving one dose of vaccine was significantly associated with reduced odds of hospitalization or death (aOR = 0.69 (0.52–0.92), and further reduced with two or more doses (aOR = 0.34 [0.27–0.45]) (Table 4).

Discussion

Based on a large nationwide linkage study of people with opioid dependence in Scotland, we identified that individuals with recent exposure to OAT, when compared with those off treatment for at least a year, had a lower rate of testing, and a lower risk of testing positive for SARS-CoV-2 among those tested. However, among

Table 3
Factors associated with ever testing positive for SARS-CoV-2 among those tested

	Number of tests (% in group)	Number of positive tests (% of tests)	OR (95% CI)	p	aOR (95%)[a]	p[a]
Most recent OAT at time of test						
12+ mo	15 966 (26%)	1095 (6.9%)				
2–12 mo	8275 (14%)	516 (6.2%)	0.87 (0.77–0.99)	0.03	0.90 (0.79–1.01)	0.08
<2 mo	36 259 (60%)	1681 (4.6%)	0.59 (0.53–0.64)	<0.001	0.63 (0.57–0.69)	<0.001
Age group (y)						
18–29	3675 (6%)	228 (6.2%)				
30–39	17 207 (28%)	1069 (6.2%)	0.99 (0.83–1.17)	0.864	1.01 (0.85–1.20)	0.99
40–49	25 384 (42%)	1361 (5.4%)	0.85 (0.72–1.00)	0.06	0.89 (0.75–1.06)	0.194
50–59	12 080 (20%)	569 (4.7%)	0.71 (0.59–0.85)	<0.001	0.77 (0.64–0.94)	0.09
60+	2154 (4%)	65 (3.0%)	0.42 (0.31–0.58)	<0.001	0.49 (0.36–0.69)	<0.001
Sex						
Female	23 419 (39%)	1079 (4.6%)				
Male	37 081 (61%)	2213 (6.0%)	1.24 (1.14–1.35)	<0.001	1.19 (1.09–1.30)	<0.001
Deprivation (Scottish Index of Multiple Deprivation quintile)						
1 (most deprived)	31 391 (52%)	1806 (5.8%)				
2 or 3	23 044 (38%)	1165 (5.1%)	0.88 (0.81–0.96)	0.004	0.87 (0.79–0.95)	0.002
4 or 5	6065 (10%)	321 (5.3%)	0.94 (0.81–1.08)	0.381	0.90 (0.78–1.05)	0.170
Comorbidity status						
Neither	27 365 (45%)	1832 (6.7%)				
Other comorbidities	26 334 (44%)	1195 (4.5%)	0.62 (0.57–0.67)	<0.001	0.67 (0.61–0.73)	<0.001
Clinically extremely vulnerable	6801 (11%)	265 (3.9%)	0.49 (0.42–0.57)	<0.001	0.56 (0.47–0.66)	<0.001
Vaccine status at time of test						
0 doses	35 749 (59%)	1821 (5.1%)				
1 dose	9274 (15%)	502 (5.4%)	1.14 (1.02–1.27)	0.022	1.13 (1.02–1.27)	0.025
2+ doses	15 477 (26%)	969 (6.3%)	1.40 (1.28–1.53)	<0.001	1.37 (1.25–1.50)	<0.001

Unadjusted and adjusted OR and 95% CI from multivariate logistic regression model are presented. N = 19 071 people tested and 60 500 tests. OAT, opioid-agonist treatment.
[a] Adjusted for all covariates presented and for health board of residence.

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Table 4
Factors associated with hospitalization or death after diagnosis with COVID-19 disease among those who tested PCR positive for SARS-CoV-2

	Number of positive tests (% in group)	Number hospitalized or died (% of positive tests)	OR (95% CI)	p	aOR (95%)[a]	p[a]
Most recent OAT before positive test						
12+ mo	1095 (33%)	118 (10.8%)				
2–12 mo	516 (16%)	77 (14.9%)	1.45 (1.07–1.98)	0.02	1.54 (1.11–2.14)	0.009
<2 mo	1681 (51%)	357 (21.2%)	2.23 (1.78–2.79)	<0.001	2.04 (1.60–2.59)	<0.001
Age group (y)						
18–29	228 (7%)	22 (9.6%)				
30–39	1069 (32%)	129 (12.1%)	1.29 (0.80–2.07)	0.302	1.29 (0.79–2.11)	0.305
40–49	1361 (41%)	216 (15.9%)	1.77 (1.11–2.81)	0.02	1.72 (1.07–2.79)	0.03
50–59	569 (17%)	154 (27.1%)	3.47 (2.16–5.60)	<0.001	2.77 (1.67–4.60)	<0.001
60+	65 (2%)	31 (47.7%)	8.54 (4.43–16.45)	<0.001	6.06 (2.97–12.36)	<0.001
Sex						
Female	1079 (33%)	192 (17.8%)				
Male	2213 (67%)	360 (16.3%)	0.9 (0.74–1.09)	0.271	1.02 (0.83–1.26)	0.824
Deprivation (Scottish Index of Multiple Deprivation quintile)						
1 (most deprived)	1806 (55%)	325 (18%)				
2 or 3	1165 (35%)	186 (16%)	0.87 (0.71–1.05)	0.153	1.07 (0.86–1.32)	0.56
4 or 5	321 (10%)	41 (12.8%)	0.67 (0.47–0.95)	0.023	0.88 (0.60–1.30)	0.520
Comorbidity status						
Neither	1832 (56%)	179 (9.8%)				
Other comorbidities	1195 (36%)	279 (23.3%)	2.81 (2.29–3.45)	<0.001	2.46 (1.99–3.04)	<0.001
Clinically extremely vulnerable	265 (8%)	94 (35.5%)	5.08 (3.78–6.82)	<0.001	3.52 (2.53–4.91)	<0.001
Vaccine status at time of positive test						
0 doses	1821 (55%)	390 (21.4%)				
1 dose	502 (15%)	72 (14.3%)	0.61 (0.47–0.81)	<0.001	0.69 (0.52–0.92)	0.013
2+ doses	969 (29%)	90 (9.3%)	0.38 (0.29–0.48)	<0.001	0.34 (0.27–0.45)	<0.001

Unadjusted and adjusted OR and 95% CI from multivariate logistic regression model are presented. N = 2986 people who tested positive for SARS-CoV-2 and 3292 positive tests. OAT, opioid-agonist treatment.

[a] Adjusted for all covariates presented and for health board of residence.

those who tested positive, the risk of hospitalization or death after diagnosis with COVID-19 was two-fold higher for those recently on OAT. These results highlight the vulnerability of people with opioid dependence to severe COVID-19 outcomes.

Our finding of a lower rate of testing and lower risk of testing positive for SARS-CoV-2 among those recently on OAT when compared with those with past exposure could be due to behavioural differences between these populations or may indicate that being on OAT offers a protective effect against infection. Lower than expected incidences among people who use drugs have also been reported elsewhere [7,9,10].

Environmental factors, such as increased levels of cross-immunity to SARS-CoV-2 among OAT patients, have been suggested to account for the differences [9]. Behavioural differences between those recently on OAT may also explain the difference in risk of testing positive compared to those without recent treatment. Among people with opioid dependence, OAT reduces the urgency to source illicit opioids. Qualitative research from Scotland and the United Kingdom found that many used the pandemic as an opportunity to reduce contacts with drug dealers or peers and take advantage of remotely delivered harm reduction services (including take-home doses of OAT), which may have reduced their need to test or their exposure to SARS-CoV-2 [22,23]. It has also been speculated that a lower than anticipated incidence among drug-treatment populations could be due to opioids or opioid antagonists interacting with the immune system to affect COVID-19 pathogenesis [10,11,24]. It is also possible that not all cases were detected in this study among those who seldom tested, and these individuals (along with those who never tested) may differ in terms of their risk of infection. For example, those more recently treated with OAT, when compared with those off longer term treatment, may be more likely to get tested regularly, regardless of symptoms, if they are in regular contact with services.

In our analysis, restricted to those who did test positive for SARS-CoV-2, we found that the risk of hospitalization or death after diagnosis with COVID-19 was increased among people recently on OAT. An increased risk of severe COVID-19 outcomes among people with opioid dependence has been reported in other highly-powered cohort studies from the United States and Europe [2–5,13].

Plausible biological pathways by which opioids may worsen COVID-19 outcomes have been highlighted [24,25]. These include immune modulation that may impair response to SARS-CoV-2 infection, an increased risk of adverse respiratory outcomes because of respiratory depression caused by opioid use, and potentially harmful effects of drug–drug interactions in patients being treated for both opioid dependence and COVID-19.

The presence of chronic conditions such as lung, cardiovascular, kidney, and liver disease, type 2 diabetes, obesity, and cancer are determinants of COVID-19 risk [20,26]. In our multivariable analyses, recent OAT recipients had a significantly increased risk after adjustment for comorbidities. Although the presence of comorbidities increases the risk of severe COVID-19 disease, there may be other pharmacological factors that contribute. In a case–control study in Scotland restricted to those without predisposed comorbidities, severe COVID-19 was associated with polypharmacy, and in particular, medications that caused sedation and respiratory depression, such as opioid analgesics and gabapentinoids [27]. Co-prescription of such medications are common among individuals receiving OAT in Scotland and elsewhere [28,29].

Vaccination mitigates the risk of severe COVID-19 disease [30]. However, COVID-19 vaccine uptake has lagged among people who use drugs in comparison to the general population in some regions, including Scotland, based on self-reported status and linked surveillance data [13,31]. This follows concerns that the uptake among these populations would be lower, potentially because of challenges in health care access [23,32] or vaccine hesitancy [33,34]. In our analyses, there was a moderate association between receiving one or more vaccine doses and testing positive for SARS-CoV-2,

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potentially due to behaviour changes among those vaccinated (e.g. more social contacts) or a higher risk of testing positive during the third wave when more of this cohort were vaccinated. However, when we restricted the analysis to those who tested positive, one or more vaccination doses were strongly associated with reduced risk of hospitalization or death after diagnosis with COVID-19. Although suboptimal vaccine uptake and worse COVID-19 outcomes have been noted among ethnic minorities, this is unlikely to have affected results as nearly all drug users presenting at drug-treatment services in Scotland are White [35]. By the end of the study in December 2021—around one year after the vaccine campaign began in Scotland — over one-third of the cohort had not received a vaccine dose. Understanding and addressing lagging vaccine coverage among at-risk populations, such as people who use drugs, is crucial to mitigate severe COVID-19 outcomes.

There were limitations in this study. (i) We were unable to determine whether individuals had recently used illicit drugs, which may be a confounding factor. However, in public health surveillance of clients accessing injecting equipment provision sites for needle exchange, 66% reported receipt of OAT in the last 6 months, thus we can assume illicit drug use was common for those in treatment [36]. Other OAT cohort studies suggest that individuals remain opioid dependent for several years and cycle in and out of treatment, with many re-initiating within 2 years [19,37]. There may be other social factors associated with opioid dependence that we were unable to control for. (ii) We inferred recent OAT exposure based on date of reimbursement, but were not able to establish start or stop dates or adherence [19]. (iii) COVID-19 studies may be limited by the fact that not all with SARS-CoV-2 infection access testing. We addressed this limitation by comparing the odds of testing positive and hospitalization or death among those who were tested. The proportion tested during each wave was comparable with that of the general Scottish population at the time. Despite limitations, our study captures the majority of people who prescribed treatment for opioid dependence across Scotland from 2015 to 2020.

We found evidence to suggest that recent exposure to OAT (within <2 months), when compared with past exposure (>12 months), was associated with a reduced risk of SARS-CoV-2 infection among those tested. However, among those diagnosed with infection, recent exposure to OAT was associated with an increased risk of hospitalization or death. Understanding the role of OAT in COVID-19 progression warrants further clinical study, as these potentially pharmacologically mediated results may be relevant in the management of patients or prescribing guidelines. An enhanced effort is warranted to increase vaccine coverage among people receiving OAT to help mitigate the severe consequences of COVID-19.

Author's contributions

Conceptualization: SH; data curation: AY, JB, BT, JL, LB, and SH; methodology: MG, AY, and SH; formal analysis: MG; supervision: AM, NP, and SH; validation: AY; writing—original draft: MG; writing—review & editing: MG, AY, AM, NP, JB, BT, JL, LB, SP, and SH.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.06.019.

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