Original research

Association of clinically significant obstructive sleep apnoea with risks of contracting COVID-19 and serious COVID-19 complications: a retrospective population-based study of health administrative data

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ABSTRACT

Rationale/objectives Despite plausible pathophysiological mechanisms, more research is needed to confirm the relationship between obstructive sleep apnoea (OSA) and the risk of COVID-19 infection or COVID-19-related serious complications.

Methods We conducted a retrospective population-based cohort study using provincial health administrative data (Ontario, Canada). Adults with physician-diagnosed OSA who received positive airway pressure therapy in the 5 years prepandemic (*OSA group*) were propensity score matched by baseline characteristics to individuals in the general population at low risk of OSA (*non-OSA group*) using inverse probability of treatment weighting. Weighted HRs of (1) a positive COVID-19 test and (2) COVID-19-related emergency department (ED) visits, hospitalisations, intensive care unit (ICU) admissions and mortality, within 12 months of pandemic onset, were compared between groups. We also evaluated the impact of comorbid cardiometabolic or chronic airways disease.

Results We identified and matched 324 029 individuals in the OSA group to 4 588 200 individuals in the non-OSA group. Compared with the non-OSA group, those in the OSA group were at a greater hazard of testing positive for COVID-19 (HR=1.17, 95% CI 1.13 to 1.21), having a COVID-19-related ED visit (HR=1.62, 95% CI 1.51 to 1.73), hospitalisation (HR=1.50, 95% CI 1.37 to 1.65) or ICU admission (HR=1.53, 95% CI 1.27 to 1.84). COVID-19-related 30-day mortality was not different (HR=0.98, 95% CI 0.82 to 1.16).

We found that for the OSA group, comorbid airways disease but not cardiometabolic conditions increased the hazards of COVID-19-related outcomes, including mortality.

Conclusion In this large population-based study, we demonstrated that a recent diagnosis of OSA requiring treatment was associated with an increased hazard of testing positive for COVID-19 and serious COVID-19-related complications, particularly in those with co-existing chronic airways disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite a plausible pathophysiological basis for obstructive sleep apnoea (OSA) increasing the risk of COVID-19-related outcomes, more research is needed to confirm this relationship.

WHAT THIS STUDY ADDS

⇒ We conducted a large, real-life, longitudinal population study and demonstrated that recently diagnosed clinically significant OSA is associated with an increased risk of contracting COVID-19 and serious COVID-19-related complications, such as emergency department visits, hospitalisations or intensive care unit admissions, but not COVID-19-related mortality compared with the general population without OSA. Our study enhances published evidence by incorporating the entire first year of the COVID-19 pandemic with a large number of events, propensity score weighting to properly adjust for confounders and validated definitions for OSA in health administrative data.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support consideration of OSA as a high-risk condition for adverse COVID-19 outcomes and warrant higher prioritisation of patients with OSA for public health protection. Furthermore, screening for undiagnosed OSA and subsequent treatment should be made a priority—not halted during periods of high COVID-19 in the community—to reduce this risk.

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INTRODUCTION

Obstructive sleep apnoea (OSA) is the most prevalent sleep-related breathing disorder and is characterised by repeated episodes of upper airway obstruction during sleep associated with sleep fragmentation and intermittent hypoxaemia. Globally, 425 million middle-aged adults are estimated to have moderate to severe OSA.[1] OSA is an important modifiable risk factor for several chronic diseases.[2–4] Positive airway pressure (PAP) therapy is the treatment of choice for clinically significant OSA.[5 6]

Previous studies have shown OSA to be associated with an increased risk of influenza infection[7] and hospitalisation from influenza infection.[8] Untreated

OSA may increase risks of COVID-19 infection and associated complications through the following postulated mechanisms: (1) pathophysiological downstream phenomenon of OSA that may predispose to more severe disease, such as intermittent hypoxia, oxidative stress, sympathetic activation, inflammation or endothelial dysfunction; (2) associated obesity, cardiometabolic comorbidities and lung disease that present risks for more severe COVID-19 outcomes; (3) ACE-2 receptor (the entry receptor for COVID-19), which may be overexpressed in individuals with OSA; and (4) higher risk of pneumonia via microaspiration, acute respiratory distress syndrome and thromboembolic phenomena associated with OSA.[9 10]

A recent meta-analysis, which used data from 15,835 COVID-19-positive individuals, including 1294 individuals with OSA, demonstrated that OSA was significantly associated with COVID-19 hospitalisations after adjusting for age, sex, and ethnic background, but this association became non-significant when additionally controlling for obesity.[11] Another meta-analysis conducted on 54 276 individuals with COVID-19 demonstrated that OSA was associated with severe COVID-19, intensive care unit (ICU) admissions, need for mechanical ventilation, and mortality; however, adjustment for covariates was not performed.[12] Most published studies are limited by focusing on the early stages of the pandemic, lack of a validated health administrative data case definition for OSA (for health administrative data studies),[13–15] self-reported OSA (for survey studies),[16] a relatively small number of individuals with OSA, a poorly characterised non-COVID-19 group, and limited or no adjustment for covariates. Many of those studies were also published as research letters, providing minimal information on data quality and analytical approaches. Thus, more research is still needed to determine whether individuals with OSA should be added to the list of vulnerable groups for public health management of COVID-19.

Our study investigated relationships between OSA requiring PAP treatment and the risk of COVID-19 infection or serious complications from COVID-19. As a secondary objective, we further evaluated whether the presence of comorbid cardiometabolic or chronic airways disease affects the relationship between OSA and COVID-19-related outcomes. We hypothesised that OSA requiring PAP treatment (ie, clinically significant) is associated with a greater risk of COVID-19-related outcomes and that the presence of comorbid cardiometabolic or chronic airways disease modifies the relationship between OSA and COVID-19-related outcomes.

METHODS

Study design

We conducted a retrospective population-based study using provincial health administrative data (Ontario, Canada) from adults alive at the start of the pandemic and living in Ontario in the 5 years before the COVID-19 pandemic (March 2015–March 2020). We considered *17 March 2020*, when a state of emergency was declared in Ontario, as the start of the pandemic (*index date*). Individuals were followed up until 31 March 2021, or death, whichever came first.

ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement.

Data sources

Residents of Ontario have universal public health insurance under the Ontario Health Insurance Plan (OHIP), the single-payer for all medically necessary services. OHIP provides full coverage for sleep physicians' visits and in-laboratory sleep studies and partial coverage for PAP therapy if prescribed by a sleep physician registered with the Assistive Devices Program (ADP).[17] Details on outpatient and inpatient services are held in large, individually linked, high-quality and regularly updated population-based administrative databases housed at ICES (formerly Institute for Clinical Evaluative Sciences).[18–20] The main databases used for this study were the Registered Persons Database (demographics), the Discharge Abstract Database (hospital admissions), the National Ambulatory Care Reporting System Database (emergency room and urgent care visits), the OHIP database (all physician billing and technical fees for procedures), the Canadian Census (socioeconomic details) and the ADP database (claims for PAP devices). Further, the COVID-19 Integrated Testing Dataset was created by ICES and is a comprehensive dataset of all available COVID-19 diagnostic laboratory results in Ontario. It is derived from three data sources: (1) Ontario Laboratories Information System (OLIS) (COVID-19 testing episodes using standard PCR tests, from January 2020 to present); (2) distributed testing data from laboratories within the COVID-19 Diagnostic Network (results only up to 13 April 2020, before a requirement to report all test results in OLIS); and (3) Public Health Case & Contact Management Solution, formerly known as the integrated Public Health Information System (client-level dataset (not testing episodes) for individuals who are confirmed positive for COVID-19 based on the provincial case definition, from January 2020 to present). These datasets were linked using unique encoded identifiers and analysed at ICES. See further details on databases and variables' definitions in the online supplemental tables E1 and E2 and at www.data-dictionary.ices.on.ca.

Exposure: recent clinically significant OSA

Given that information on OSA severity based on the Apnoea–Hypopnoea Index (AHI) is not available in health administrative data, we used two (not mutually exclusive) definitions to identify individuals with clinically significant OSA from health administrative data to show the robustness of our findings.

Primary definition

Individuals who purchased PAP through the ADP in the 5 years before the COVID-19 pandemic (March 2015–March 2020) were considered to have *physician-diagnosed OSA requiring PAP treatment* (*PAP group*). A 5-year look-back window was predefined as recommended for chronic conditions.[21 22] Previously, a PAP purchase through the ADP within a year since the diagnostic sleep study yielded a sensitivity of 50% (95% CI 49% to 51%), specificity of 91% (95% CI 90 to 91), and positive predictive value of 0.81 (95% CI 0.80 to 0.83) to identify individuals with moderate to severe OSA (AHI ≥15).[23]

Secondary definition

We used a validated case ascertainment algorithm[23] to identify individuals with at least a 50% probability of having moderate to severe OSA in the last 5 years before the pandemic (March 2015–March 2020) (*moderate/severe OSA group*). The best model contained six variables in relation to an index sleep study: an outpatient visit for OSA from a specialist physician, a repeated sleep study and a PAP treatment claim within 1 year

of the index sleep study, patient sex and age at the index sleep study and hospitalisations with hypertension in the last 3 years prior to the sleep study. This definition yielded a sensitivity of 59% (95% CI 58% to 60%), specificity of 87% (95% CI 0.87% to 0.88%) and positive predictive value of 0.79 (95% CI 0.78 to 0.80). While this definition yielded higher sensitivity than the primary definition, it also included individuals with moderate/severe OSA who may not have initiated PAP therapy.

Non-OSA group: general adult population presumably at low risk of OSA

To ensure a low probability of OSA, we selected adults who have never been referred for OSA care since 1991, defined as the absence of the following: (1) prior sleep study, (2) a claim for PAP treatment, (3) surgery for OSA or (4) inpatient or outpatient visits with a diagnostic code for OSA.

Outcomes

We used established definitions to define two major COVID-19-related outcomes:[24] (1) contracting COVID-19 and (2) serious complications from COVID-19. *Contracting COVID-19* was defined by a receipt of a positive test result for SARS-CoV-2 infection, ascertained by real-time reverse transcription-polymerase chain reaction (RT-PCR) tests on respiratory specimens, including samples from the nasopharynx (most common), nose, throat, saliva, and turbinates. For cases with multiple positive test results, we used the date of the first positive test result. Several outcomes were considered as *serious complications from COVID-19*: COVID-19-related emergency department (ED) visits (International Classification of Diseases, 10th Revision with Canadian Enhancements (ICD-10-CA) code U071 U072); COVID-19-related hospitalisations (ICD-10-CA code U071 U072); COVID-19-related ICU admissions; and COVID-19-related mortality, defined as death within 30-days of the positive test.

Given limited access to testing at the beginning of the pandemic, for the primary analysis, we focused on serious complications from the COVID-19 regardless of the COVID-19 test results. COVID-19-related ED visits, hospitalisations and ICU admissions defined by ICD-10-CA code U071 and U072 were less affected by testing availability at the beginning of the pandemic because the hospitals were testing everyone for COVID-19 and because the diagnosis of the COVID-19 was based on both COVID-19 testing and a clinical diagnosis if the test was inconclusive or not available.[25] For the secondary analysis, only COVID-19-related ED visits, hospitalisations and ICU admissions within 30 days of a positive test were considered.

Baseline covariates

The following variables were considered as potential covariates in the analysis: (1) demographic characteristics at the index date: age, sex, neighbourhood income quintile, rural residence and allocation by a local health integration network (LHIN or home and community care support services) where the health authorities are responsible for regional administration of public healthcare services in Ontario; (2) comorbidities: prevalent comorbidities at index date: diabetes,[26] hypertension,[27] chronic heart failure (CHF),[28] asthma,[29] chronic obstructive pulmonary disease (COPD),[30] immunocompromising conditions[31] and cancer; in the prior 2 years: Charlson Comorbidity Index[32] and non-psychotic mood and anxiety disorders; in the prior 5 years: any cardiovascular (CV) hospitalisation including for atrial fibrillation,[33] end-stage renal disease/hemodialysis, neuromuscular disease, alcohol use disorder, and obesity or bariatric surgery.

To address our secondary objective, the presence of *cardiometabolic morbidity* was defined using validated definitions for prevalent diabetes,[26] hypertension[27] or CHF,[28] or hospitalisations for CV conditions[33] in the last 5 years. The presence of *chronic airways disease* was defined using validated definitions for prevalent COPD[30] or asthma.[29]

Details on the definitions for exposures, outcomes and covariates are provided in the online supplemental table E2.

Analysis

Descriptive statistics were used to characterise the study population by exposure status. Incidence rates per person-year and 95% Wald CIs were calculated for the first event only (for each outcome separately).

Primary analyses

To address potential confounding, we modelled propensity scores—the probability of an individual having physician-diagnosed OSA requiring PAP treatment in the last 5 years before the pandemic, given their unique characteristics—using all covariates mentioned previously. To be included in the propensity score, the age variable was transformed using a five-knot restricted cubic spline at evenly spaced percentile knot locations. Inverse probability of treatment weighting (IPTW) using propensity scores was used to minimise the effect of confounding.[34–36] An advantage of using IPTW is that by assigning different weights, we can estimate both the average treatment effect on the treated (ATT) and the average treatment effect (ATE).[36] ATT estimates the average effect of treatment (ie, OSA exposure in our study) on those individuals who were exposed. Thus, the distribution of baseline covariates of those at low risk of OSA (ie, *non-OSA group*) is standardised to match that of the clinically significant OSA population (figure 1 and online supplemental figures E1 and E2). ATE estimates how outcomes would differ if everyone in the sample were exposed versus everyone that were not, for example, if a population health standard is to consider everyone, even at low risk of OSA, to be managed as an individual with a clinically significant OSA. Since we were interested in the effect of recently diagnosed clinically significant OSA on COVID-19-related outcomes, that is, to standardise the covariate distribution of the PAP group to the non-OSA group, we chose the ATT as our primary focus; ATE was explored in a sensitivity analysis. The balance between variables by exposure was assessed using the standardised difference of the effect size[37]; a threshold of >10% was used as an indicator of a meaningful difference between groups. To improve residual imbalance across age and sex for the ATE weight allocation, we included an age–sex interaction.

We fit the weighted cause-specific Cox proportional hazards model with robust SEs to compare COVID-19-related outcomes between groups while accounting for all-cause mortality as a competing risk when applicable. The primary models used the ATT weights. To examine the ATE, we used stabilised ATE weights to guard against the undue influence of individuals with extreme weights on the analysis.

Secondary analyses

In the secondary analysis, we used the approaches described above to estimate the marginal effect of a high probability of

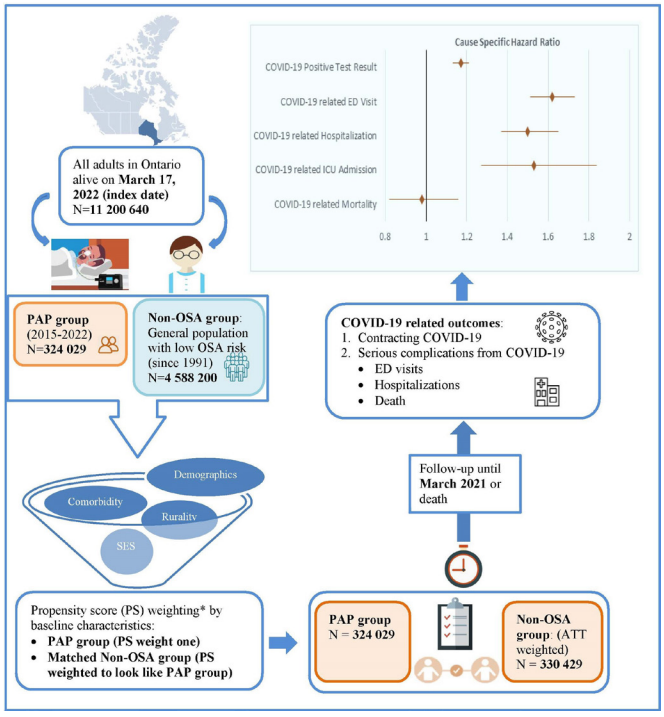

Figure 1 Study design and main findings. *Groups were matched using inverse probability of treatment weighting; for the primary analysis, weights were assigned to estimate the ATT (shown in figure); the average treatment effect weights (not shown) were estimated in the sensitivity analysis. ATT, average treatment effect on the treated; ED, emergency department; OSA, obstructive sleep apnoea; PAP, positive airway pressure.

moderate/severe OSA (secondary definition of exposure) on COVID-19-related outcomes.

We evaluated whether the presence of comorbid cardiometabolic and chronic airways disease affects the relationship between OSA and COVID-19-related outcomes through statistical interaction terms. Given the exploratory nature of this analysis, it was performed using the primary definition of the exposure and the primary analytic approach (ATT weighting) only.

Finally, we used logistic regression using the ATT weights to investigate the relationship between the primary definition of OSA and COVID-19-related ED visits, hospitalisations and ICU admissions within 30 days of a positive test.

To be able to use the full sample postweighting, we imputed missing values using a simple mode imputation (ie, from the most common/prevalent group), given a relatively small number of missing values: income status (14 217, 0.3%), rural status (12 363, 0.3%) and LHIN (<5). All statistical analyses were performed in the secure environment at ICES following Ontario privacy standards using SAS Enterprise Guide V.7.1 and SAS V.9.4.

RESULTS

We identified 324 029 individuals (median age of 58 years, 65% male) in the PAP group using the primary definition of OSA and 4 588 200 individuals in the non-OSA general population group (median age of 47 years, 52% male) (figure 2).

In unadjusted comparison, individuals in the PAP group were more likely to be older, male, with a higher level of comorbidities, including cardiometabolic morbidity and chronic airways disease, than the non-OSA group (table 1). Unadjusted incident rates of all COVID-19-related outcomes were higher in the PAP group compared with the non-OSA group (table 2).

Primary analyses

Propensity score weighting achieved excellent balance in baseline characteristics between the PAP and non-OSA groups (online supplemental figures E1 and E2 and online supplemental tables E3–E5). On a weighted sample, compared with the non-OSA group, those in the PAP group had a greater hazard of having a positive test for COVID-19 (cause-specific HR (csHR)=1.17, 95% CI 1.13 to 1.21), COVID-19-related ED visit (csHR=1.62, 95% CI 1.51 to 1.73), COVID-19-related hospitalisations (csHR=1.50, 95% CI 1.37 to 1.65) and COVID-19-related ICU admissions (csHR=1.53, 95% CI 1.27 to 1.84), but not COVID-19-related 30-day mortality (csHR=0.98, 95% CI 0.82 to 1.16) (table 2). The results were consistent across differently weighted populations (ATT and ATE).

Secondary analyses

Secondary definition of OSA exposure

We identified 191 447 individuals (median age of 57, 68% male) in the moderate/severe OSA group (online supplemental tables E4 and E5). Details on the overlap between primary and secondary definitions of OSA are presented in online supplemental table E6. On a weighted sample, compared with the non-OSA group, those in the moderate/severe OSA group were at a greater hazard of having tested positive for COVID-19, COVID-19-related ED visits, hospitalisations or ICU admissions, but not COVID-19-related 30-day mortality (online supplemental table E7).

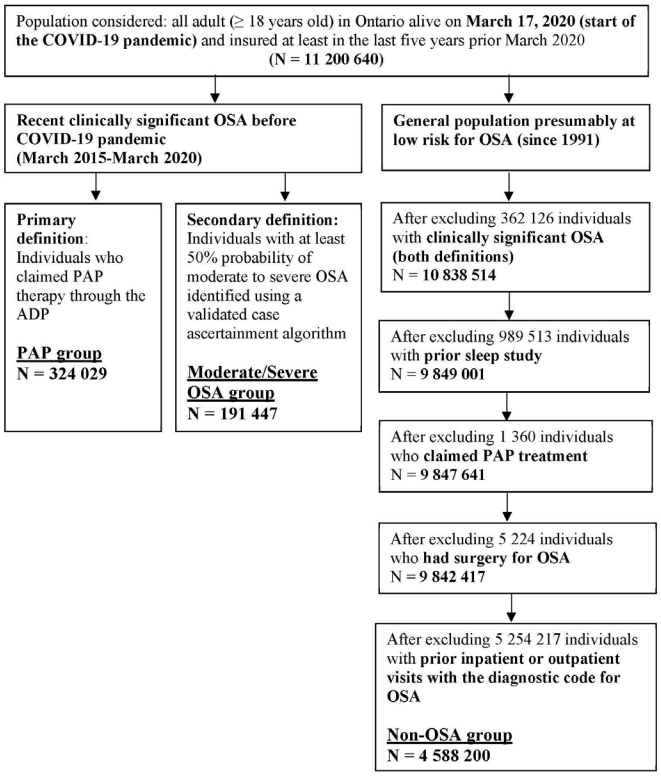

Figure 2 Study flow diagram to define two comparison groups. OSA, obstructive sleep apnoea; PAP, positive airway pressure.

Table 1 Cohort characteristics by exposure status

Cohort characteristics	Non-OSA (unweighted) N=4 588 200	PAP group (unweighted) N=324 029	Standardised difference (unweighted comparison)	Non-OSA (ATT weighted)* N=330 429	Standardised difference (comparison on an ATT weighted sample)
Demographics at the index date					
Age, median (IQR)	47 (33–61)	58 (49–67)	0.67	57.68	0.005
Sex, male, n (%)	2 368 385 (51.6)	211 379 (65.2)	0.28	65.64	0.008
Rural status: yes, n (%)	547 452 (11.9)	40 449 (12.5)	0.02	12.76	0.008
Neighbourhood income, n (%)					
Quintile 1	883 936 (19.3)	54 792 (16.9)	0.06	16.95	0.004
Quintile 2	898 281 (19.6)	62 000 (19.1)	0.01	19.04	0.002
Quintile 3	918 096 (20.0)	66 746 (20.6)	0.01	20.78	0.004
Quintile 4	924 562 (20.2)	69 379 (21.4)	0.03	21.59	0.004
Quintile 5	949 776 (20.7)	70 444 (21.7)	0.03	21.65	0.002
Comorbidities, n (%)					
Prevalent conditions					
Diabetes	408 683 (8.9)	96 277 (29.7)	0.55	30.36	0.014
Hypertension	899 553 (19.6)	178 511 (55.1)	0.79	56.03	0.019
CHF	42 050 (0.9)	20 756 (6.4)	0.30	6.49	0.004
Asthma	394 682 (8.6)	67 988 (21.0)	0.35	21.1	0.003
COPD	184 450 (4.0)	56 689 (17.5)	0.45	17.74	0.007
Immunocompromising conditions	82 839 (1.8)	14 537 (4.5)	0.15	4.57	0.004
Cancer	219 899 (4.8)	31 551 (9.7)	0.19	9.93	0.006
In the last 2 years					
CCI score					
High (≥3)	13 577 (0.3)	5387 (1.7)	0.14	1.62	0.003
Moderate (2)	19 522 (0.4)	7020 (2.2)	0.15	2.16	0.000
Low (1)	24 926 (0.5)	8580 (2.6)	0.17	2.81	0.010
None (0)	240 723 (5.2)	30 429 (9.4)	0.16	9.86	0.016
Non-psychotic mood or anxiety disorders	476 419 (10.4)	83 515 (25.8)	0.41	27.01	0.028
In the past 5 years					
Any CV hospitalisation	142 505 (3.1)	49 293 (15.2)	0.43	16.01	0.022
Prior end-stage renal disease/haemodialysis	8549 (0.2)	3480 (1.1)	0.11	1.04	0.003
Neuromuscular disease	75 316 (1.6)	16 382 (5.1)	0.19	5.25	0.009
Alcohol dependence/intoxication	78 073 (1.7)	6672 (2.1)	0.03	2.12	0.004
Obesity/bariatric surgery	1425 (0.0)	5786 (1.8)	0.19	2.28	0.035
Cardiometabolic morbidity (prevalent diabetes, hypertension or CHF, or hospitalisations for CV conditions in the last 5 years)	1 108 647 (24.2)	209 593 (64.7)	0.89		

Continued

Table 1 Continued

	Non-OSA (unweighted)	PAP group (unweighted)	Standardised difference (unweighted comparison)	Non-OSA (ATT weighted)*	Standardised difference (comparison on an ATT weighted sample)
Cohort characteristics	**N=4 588 200**	**N=324 029**		**N=330 429**	
Chronic airway disease (COPD or asthma)	550 303 (12.0)	103 729 (32.0)	0.50		

Individuals with a low probability of OSA (control group) are presented as unweighted (original) and weighted† on the propensity score.
*Estimates presented as mean or prevalence (percentage) as applicable.
†In weight allocation using the ATT approach (used in the main analysis), the exposure group has weight 1, and only the controlled group is weighted. Weight allocation using the average treatment effect approach (used in sensitivity analysis) is presented in online supplemental table E3.
ATT, average treatment effect on the treated; CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; IQR, *interquartile range*; OSA, obstructive sleep apnoea; PAP, positive airway pressure.

Effect of the presence of cardiometabolic or chronic airways disease

Statistically significant interactions between primary exposure and chronic airways disease on COVID-19-related outcomes were noted (table 3). Specifically, individuals in the PAP group with comorbid chronic airways disease had a higher hazard of developing COVID-19-related outcomes, including mortality, than those without comorbid chronic lung conditions.

In contrast, individuals in the PAP group with comorbid cardiometabolic conditions had a lower hazard of developing COVID-19-related outcomes, compared with those without comorbid cardiometabolic conditions, with only significant interactions noted for COVID-19-positive test results and COVID-19-related hospitalisation or ICU admissions.

Population with a positive COVID-19 test

On an ATT weighted sample, we found a significant association between the primary definition of OSA and COVID-19-related ED visits, hospitalisations or ICU admissions within 30 days of a positive test (online supplemental table E8), confirming the robustness of our primary analysis.

DISCUSSION

We conducted a large, real-life, longitudinal population study and demonstrated that recently diagnosed clinically significant OSA is associated with an increased risk of contracting COVID-19 and serious COVID-19-related complications, such as ED visits, hospitalisations or ICU admissions, but not COVID-19-related mortality compared with the general population without OSA. We demonstrated the robustness of our findings using multiple definitions of OSA and outcomes and different propensity score weighting methods. We also found that comorbid cardiometabolic and airways disease may modify this relationship. Importantly, greater hazards of all COVID-19-related outcomes, including mortality, were associated with clinically significant OSA (vs no OSA) in individuals with comorbid airway disease compared with those without airway disease. Our study enhances published evidence by incorporating the entire first year of the COVID-19 pandemic with a large number of events, propensity score weighting to properly adjust for confounders and validated definitions for OSA in health administrative data. These findings support consideration of OSA as a high-risk condition for adverse COVID-19 outcomes and warrant higher prioritisation of patients with OSA for public health protections. Furthermore, screening for undiagnosed OSA and subsequent treatment should be made a priority—not halted during periods of high COVID-19 in the community—to reduce this risk.

Our findings are consistent with studies showing that OSA was significantly associated with COVID-19-related hospitalisations and/or ICU admissions adjusting for confounders.[11–13 16 38] In a study conducted by Cade *et al*, using health administrative

Table 2 Unadjusted rates of COVID-19-related outcomes by exposure status on the unweighted subgroups and adjusted association between clinically significant OSA (primary definition) and COVID-19-related outcomes

	Non-OSA group (unweighted)		PAP group (unweighted)		Cause-specific HR (95% CI)	
	N=4 588 200		N=324 029			
Outcomes	**N (%)**	**Rate per 1000 person-year (95% CI)**	**N (%)**	**Rate per 1000 person-year (95% CI)**	**ATT weighted samples (primary analysis)**	**ATE weighted samples (sensitivity analysis)**
Contracting COVID-19						
COVID-19-positive test result	83 373 (1.82)	17.7 (17.5 to 17.8)	6855 (2.12)	20.6 (20.2 to 21.1)	1.17 (1.13 to 1.21)	1.18 (1.11 to 1.25)
Serious complications from COVID-19						
COVID-19-related ED visit	16 138 (0.35)	3.4 (3.4 to 3.5)	2476 (0.76)	7.4 (7.1 to 7.7)	1.62 (1.51 to 1.73)	1.68 (1.54 to 1.82)
COVID-19-related hospitalisation	4095 (0.09)	0.9 (0.8 to 0.9)	967 (0.30)	2.9 (2.7 to 3.1)	1.50 (1.37 to 1.65)	1.60 (1.43 to 1.79)
COVID-19-related ICU admission	1028 (0.02)	0.2 (0.2 to 0.2)	300 (0.09)	0.9 (0.8 to 1.0)	1.53 (1.27 to 1.84)	1.84 (1.52 to 2.22)
COVID-19-related mortality*	1566 (0.03)	0.3 (0.3 to 0.3)	244 (0.08)	0.7 (0.6 to 0.8)	0.98 (0.82 to 1.16)	0.83 (0.68 to 1.02)

*Death within 30 days of the positive test.
ATE, the average treatment effect; ATT, the average treatment effect on the treated; ED, emergency department; ICU, intensive care unit; OSA, obstructive sleep apnoea; PAP, positive airway pressure.

Table 3 Adjusted* association between the exposure of the interest, primary definition (a physician-diagnosed OSA requiring PAP treatment), as compared with the no-OSA group and COVID-19-related outcomes by a presence of cardiometabolic or chronic airways disease. estimates presented as cause-specific HRs and 95% CI

	Cardiometabolic morbidity			Chronic airways disease		
Outcome	No	Yes	P value for the interaction term†	No	Yes	P value for the interaction term†
COVID-19-positive test result	1.24 (1.18 to 1.30)	1.14 (1.09 to 1.18)	0.0108	1.10 (1.06 to 1.14)	1.34 (1.25 to 1.44)	<0.0001
COVID-19-related ED visit	1.71 (1.50 to 1.95)	1.58 (1.46 to 1.71)	0.3106	1.48 (1.39 to 1.57)	1.89 (1.62 to 2.21)	0.0036
COVID-19-related hospitalisation	2.12 (1.76 to 2.56)	1.41 (1.27 to 1.56)	0.0001	1.21 (1.09 to 1.35)	1.99 (1.67 to 2.37)	<0.0001
COVID-19-related ICU admission	2.29 (1.63 to 3.22)	1.43 (1.17 to 1.74)	0.0195	1.32 (1.08 to 1.61)	1.85 (1.31 to 2.62)	0.0918
COVID-19-related mortality‡	1.47 (0.81 to 2.67)	0.95 (0.80 to 1.14)	0.1676	0.71 (0.57 to 0.90)	1.37 (1.04 to 1.82)	0.0004

*Weight allocation using the ATT approach (primary analysis).
†We incorporated in the Cox regression on an ATT weighted sample an interaction between OSA exposure and cardiometabolic morbidity and OSA exposure and chronic lung disease, separately.
‡Death within 30-days of a positive COVID-19 test.
ATT, average treatment effect on the treated; ED, emergency department; ICU, intensive care unit; OSA, obstructive sleep apnoea; PAP, positive airway pressure.

data, the association between OSA and COVID-19-related inpatient admissions and a composite outcome of death, mechanical ventilation or ICU admission became non-significant adjusting for body mass index (BMI) and comorbidities[14]; however, this study was limited by only median 31 days of follow-up, the lack of a validated definition for OSA and a relatively small number of events. One of the potential explanations was also overadjustment bias,[39] when a variable considered for adjustment in a statistical model is an intermediate variable on the causal path from the exposure variable (ie, OSA) to the COVID-19-related outcomes. In our study, we also cannot exclude the possibility of overadjustment bias, especially when investigating the impact of cardiometabolic morbidity.

The evidence on the association between OSA and COVID-19-related mortality remains controversial: while some studies found significant associations,[38 40] others did not.[14 15 41] Potential explanations for discrepancies between studies are misclassification bias in the ascertainment of COVID-19-related mortality, relatively small sample size, differences in definitions for COVID-19-related mortality and OSA and limited adjustment for confounders. Similarly, conflicting evidence exists on the association between OSA and COVID-19 positivity.[16 38] Limitations in COVID-19 testing administration and accuracy at the beginning of the pandemic may be a potential explanation for the lack of association found in early studies.

It has been suggested that OSA may increase the risk of COVID-19 infection and complications from COVID-19 through intermittent hypoxia, oxidative stress, sympathetic activation, inflammation, endothelial dysfunction and associated comorbidities.[9 10] To refine hypothesised mechanisms, one study reported an association between sleep-related hypoxaemia, but not AHI, and increased severity of COVID-19-related complications.[38] The authors suggested that baseline sleep-related hypoxaemia may be associated with hypoxia-related injury due to COVID-19.[38] COVID-19-related hospitalisations or ICU admissions are often driven by hypoxaemia,[42 43] which may be exacerbated by OSA due to lower baseline oxygen saturation, upper airway obstruction and desaturation during sleep, disease-related gas exchange deficits, obesity-related restricted lung volumes and hypoventilation.[44 45] At the same time, it has been hypothesised that COVID-19 exposure in individuals with pre-existing OSA puts them at increased risk of morbidity and mortality through the inflammatory response as they both involve and affect the respiratory system.[46]

We found that comorbid airway disease like COPD and asthma modified the risk of COVID-19 outcomes among patients with OSA. This finding may be due to impaired ventilation and perfusion matching in airway disease, further aggravated by upper airway obstruction during sleep leading to further desaturation. During wakefulness, the effect of obesity on lung volumes and proinflammatory state worsens control of these conditions. A reciprocal interaction has been suggested previously,[47] with chronic lung disease predisposing to OSA and OSA worsening outcomes from lung disease. The combination of sleep and wake respiratory conditions can create an overlap syndrome with unique pathophysiological, diagnostic and therapeutic concerns. We previously found that concurrent OSA and physician-diagnosed asthma or COPD are associated with higher mortality than asthma or COPD alone.[48]

Our findings from exploratory analysis on the interaction between OSA exposure and cardiometabolic morbidity did not confirm the potential synergistic clinical relevance of the combined effect of OSA and cardiometabolic conditions. One of the potential explanations for a negative statistical interaction is that due to the significant effect of cardiometabolic disease on COVID-19-related outcomes, the contribution/incremental value of OSA became smaller but still significant. However, we could not exclude the risk of the statistical model overcontrolling, misclassification bias and unmeasured confounding impacting our results. In addition, a healthy user effect or healthcare bias, where individuals with cardiometabolic morbidity are more aware of their health issues or get more attention in terms of COVID-19 prevention and management as well as early OSA diagnosis and maybe use their PAP therapy more, was unmeasured.

Our study has several strengths, including the use of high-quality, real-life population-level databases, nearly complete follow-up, and access to comprehensive definitions of COVID-19-related outcomes and validated definitions of OSA.

Our study has several limitations, such as (1) unmeasured residual confounding, (2) misclassification bias, (3) selection, including referral bias, and (4) lack of information on PAP use. For example, clinical characteristics such as smoking or BMI cannot be measured using health administrative data. In addition, obesity tends to be highly under-reported in health administrative databases.[49] We minimise this limitation by using IPTW, which mimics attributes of a randomised clinical trial, to adjust for confounders; however, like all propensity score methods, IPTW cannot adjust for characteristics that are not measured. Second,

our study used a surrogate marker to identify individuals with clinically significant OSA; however, we previously validated these definitions for OSA against AHI derived from sleep studies.[23] Third, there is no validated definition of COVID-19-related mortality; therefore, we were unable to differentiate between death due to COVID-19 and death with COVID-19. The latter is also applicable to the COVID-19-related hospitalisations and ICU admissions; however, non-differential misclassification of a dichotomous outcome should bias our results towards the null. While we cannot exclude that selection bias may affect our results, given limited testing in Ontario at the start of the pandemic and the highly selective group of individuals tested, this was mitigated by focusing on serious complications from the COVID-19 regardless of the COVID-19 test results in the primary analysis, long follow-up and using IPTW to balance comparison groups on characteristics associated with having COVID-19 testing probability. If a selection bias is equal between comparison groups due to IPTW, it should bias our results likely toward the null. We tried to minimise referral bias by incorporating a comprehensive definition of the non-OSA group; however, we still missed individuals with undiagnosed OSA.[50] The aforementioned biases differentially impact financially and socially disadvantaged populations who tend to be under-represented and, at the same time, are at the highest risk from COVID-19-related outcomes.[51] This bias is mitigated by social assistance support for PAP and the location of sleep clinics in lower-income areas in Ontario, and the ATE weighting approach used in a sensitivity analysis. In addition, we calculated the E-value to adjust for unmeasured confounders (online supplemental table E9). For example, the E-value of 2.6 tells us that a confounder, or set of confounders, would have to be associated with a 2.6-fold increase in the risk of COVID-19-related ED visits and must be 2.6 times more prevalent in OSA versus non-OSA group, after adjustment for all covariates considered in the propensity score weighting, which is not impossible but unlikely. Finally, our study lacked information on PAP use; however, treatment effects were not the focus of this study. The lack of the effect of PAP therapy for OSA on COVID-19-related outcomes was previously explained by suboptimal adherence,[52] potentially the lesser degree of hypoxaemia in non-PAP users compared with PAP users and residual hypoxaemia despite treatment,[38] and could be a potential reason for poor outcomes reported in patients with treated OSA.[40]

CONCLUSION

In our large, real-life, longitudinal population study, using data during the first year of the pandemic, we demonstrated that recent clinically significant OSA was associated with an increased hazard of contracting COVID-19 or serious complications from COVID-19, such as ED visits, hospitalisations or ICU visits, but not COVID-19-related mortality; furthermore, the presence of a chronic airways disease in individuals with OSA was associated with a greater hazard of COVID-19-related outcomes, including mortality. The increased vulnerability to poor COVID-19 outcomes may warrant additional preventive care and adapted treatments among individuals with OSA. Future studies are required to assess putative mechanisms via which the pathophysiology of OSA, alone and in combination with lung and cardiometabolic conditions, may interact with COVID-19, and the effect of adhering to PAP on the COVID-19-related outcome.

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Contributors All coauthors were involved in the following: study conception and design, interpretation of the data, critical revision of the manuscript for accuracy and important intellectual content, and final approval of the version to be published. TK was additionally involved in obtaining administrative data, analyses of data and drafting the manuscript. RT was additionally involved in data analyses, visual data presentation and drafting the Methods section. SRP was additionally involved in drafting of the manuscript. **Guarantor Statement**: Together, TK and RT had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. They affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had full access to statistical reports and tables.

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Patient consent for publication Not applicable.

Ethics approval ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of anonymised data in this project was authorised under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

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Data availability statement Data may be obtained from a third party and are not publicly available. In Ontario, the dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytical code are available from the authors upon request, understanding that the computer programs may rely

upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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