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 pre-pandemic (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).

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.

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 infection7 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-registry.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 algorithm24–25 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 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 CHF 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: (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, ascertainment 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. 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, hypertension, CHF, chronic heart failure (CHF), asthma, chronic obstructive pulmonary disease (COPD), immunocompromising conditions and cancer; in the prior 2 years: Charlson Comorbidity Index and non-psychotic mood and anxiety disorders; in the prior 5 years: any cardiovascular (CV) hospitalisation including for atrial fibrillation, 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, hypertension or CHF, or hospitalisations for CV conditions in the last 5 years. The presence of chronic airways disease was defined using validated definitions for prevalent COPD or asthma.

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.

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). 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 status 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
Sleep

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.


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.
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cohort characteristics by exposure status</th>
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</thead>
<tbody>
<tr>
<td><strong>Cohort characteristics</strong></td>
<td><strong>Non-OSA (unweighted)</strong></td>
</tr>
<tr>
<td>Demographics at the index date</td>
<td>N=4 588 200</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>47 (33–61)</td>
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<tr>
<td>Sex, male, n (%)</td>
<td>2 368 385 (51.6)</td>
</tr>
<tr>
<td>Rural status: yes, n (%)</td>
<td>547 452 (11.9)</td>
</tr>
<tr>
<td>Neighbourhood income, n (%)</td>
<td></td>
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<tr>
<td>Quintile 1</td>
<td>883 936 (19.3)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>898 281 (19.6)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>918 060 (20.0)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>924 562 (20.2)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>949 776 (20.7)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
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</tr>
<tr>
<td>Prevalent conditions</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>408 683 (8.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>899 553 (19.6)</td>
</tr>
<tr>
<td>CHF</td>
<td>42 050 (0.9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>394 682 (8.6)</td>
</tr>
<tr>
<td>COPD</td>
<td>184 450 (4.0)</td>
</tr>
<tr>
<td>Immunocompromising conditions</td>
<td>82 839 (1.8)</td>
</tr>
<tr>
<td>Cancer</td>
<td>219 899 (4.8)</td>
</tr>
<tr>
<td>In the last 2 years</td>
<td></td>
</tr>
<tr>
<td>CCI score</td>
<td></td>
</tr>
<tr>
<td>High (≥3)</td>
<td>13 577 (0.3)</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>19 522 (0.4)</td>
</tr>
<tr>
<td>Low (1)</td>
<td>24 926 (0.5)</td>
</tr>
<tr>
<td>None (0)</td>
<td>240 723 (5.2)</td>
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<tr>
<td>Non-psychotic mood or anxiety disorders</td>
<td>476 419 (10.4)</td>
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<tr>
<td>In the past 5 years</td>
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</tr>
<tr>
<td>Any CV hospitalisation</td>
<td>142 505 (3.1)</td>
</tr>
<tr>
<td>Prior end-stage renal disease/haemodialysis</td>
<td>8549 (0.2)</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>75 316 (1.6)</td>
</tr>
<tr>
<td>Alcohol dependence/intoxication</td>
<td>78 073 (1.7)</td>
</tr>
<tr>
<td>Obesity/bariatric surgery</td>
<td>1425 (0.0)</td>
</tr>
<tr>
<td>Cardiometabolic morbidity (prevalent diabetes, hypertension or CHF, or hospitalisations for CV conditions in the last 5 years)</td>
<td>1 108 647 (24.2)</td>
</tr>
</tbody>
</table>

Continued...
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. In a study conducted by Cade et al, using health administrative

Table 1  Continued

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

Individuals with a low probability of OSA (control group) are presented as unweighted (original) and weighted† on the propensity score.

†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.

ATE, 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.
data, the association between OSA and COVID-19-related inpa-
tient admissions and a composite outcome of death, mechanical
ventilation or ICU admission became non-significant adjusting
for body mass index (BMI) and comorbidities; 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 overad-
justment bias, 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, others did not. Potential
explanations for discrepancies between studies are misclassifica-
tion bias in the ascertainment of COVID-19-related outcomes and validated definitions of OSA. Our study has several limitations, such as (1) unmeasured
variables that are not measured. Second, we cannot adjust for characteristics that are not measured. Third, we cannot confirm the potential synergistic clinical relevance of the
denticated mortality and OSA and limited adjustment
for confounders. Similarly, conflicting evidence exists on the association between OSA and COVID-19 positivity. 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. To refine hypothesised mechanisms, one study reported an association between sleep-related hypoxaemia, but
not AHI, and increased severity of COVID-19-related complica-
tions. The authors suggested that baseline sleep-related hypoxaemia may be associated with hypoxia-related injury due to
COVID-19. COVID-19-related hospitalisations or ICU admissions are often driven by hypoxaemia, which may be exacer-
bated 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. 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.

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 perfu-
sion 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, 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. 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,
missclassification 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 healthcare administrative data. In addition, obesity tends to be highly under-reported in healthcare
administrative databases. 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. 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. 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. 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, potentially the lesser degree of hypoxaemia in non-PAP users compared with PAP users and residual hypoxaemia despite treatment, and could be a potential reason for poor outcomes reported in patients with treated OSA.

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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