Title: Association of Clinically Significant Obstructive Sleep Apnea with Risks of Contracting COVID-19 and Serious COVID-19 Complications: A Retrospective Population-Based Study of Health Administrative Data

Authors: T Kendzerska, M Povitz, A.S. Gershon, C. Ryan, R. Talarico, D.A. Franco Avecilla, R. Robillard, N. Ayas, S.R. Pendharkar

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Table E1. Details on ICES databases used.

General comments: Since 1991, ICES (www.ices.on.ca) has housed high-quality administrative datasets on publicly funded services provided, including individual-level information on demographics, physician claims, procedures, hospitalization, and emergency visits within Ontario.[1, 2] Using health administrative databases limits information biases such as recall bias, observation bias, and reporting bias. The accuracy of these datasets has been previously validated. [3, 4] A unique provincial personal health number helps to ensure reliable linkages between databases.[5] A description of the ICES datasets is available at https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx. However, health administrative databases in Ontario initially were created for administration purposes, thus, are prompt to misclassification bias, less detailed in their clinical contents, and provide a limited ability to control confounding.[2, 5-7]

Database	Available from	Description	Update frequency	Specific database-related limitations
Registered Persons Database (RPDB)	1991	RPDB includes information on every individual who has been ever issued an Ontario Health Insurance Plan (OHIP) card. RPDB captures almost all of Ontario's 13.4 million residents. Raw data updates are provided to ICES by the Ontario Ministry of Health and Long-Term Care (MOHLTC) under a specific data sharing agreement. The RPDB file contains the individual health card number, as well as demographics and personally identifiable information (e.g., surname, given names, sex, date of birth, the earliest date of coverage, last date of contact with the health care system and residential postal code). The RPDB forms the spine for ICES record linkage. Using a highly confidential and secure proprietary algorithm, each OHIP number in RPDB and any other health data with an OHIP number is uniquely converted to an anonymous ICES Identifier.	Monthly	Individuals without OHIP are not captured; however, Ontario has universal health coverage.
Discharge Abstract Database (DAD)*	1988	Submission of information to the DAD is mandatory in Ontario. The Canadian Institute for Health Information (CIHI) periodically re-abstracts data from charts to assess the quality of DAD. The high validity of the DAD is related to many factors, including the extensive training of coders in colleges, rigourous and comprehensive coding guidelines, and the case mix-based hospital funding model. This database includes data on up to 16 diagnoses and procedures based on ICD-9 codes (up to March 2002) and 25 diagnoses and procedures based on ICD-10-CA (April 1, 2002, and onward) performed for each hospital admission, including ICU. All diagnosis codes listed on the DAD abstract are classified according to type. Multiple types of diagnoses are recorded in the DAD abstract, including most responsible diagnosis, preadmit comorbidity, postadmit comorbidity, secondary diagnoses, and admitting diagnosis.	Quarterly	# of digits used were three for ICD-9 (up to March 31, 2002) and five for ICD-10-CA (April 1, 2002, and onward). All hospital diagnoses are based on exact codes; thus, they can be affected by misclassification bias due to errors in coding.
National Ambulatory Care Reporting System (NACRS)	ED: 2002	This database includes data on up to 10 diagnoses and procedures for emergency room (ED) and urgent care visits. The Canadian Emergency Department Diagnoses Shortlist includes more than 800 diagnoses in common terms, which are mapped to ICD-10-CA codes. The Emergency	Quarterly	All diagnoses and procedures are based on exact codes; thus, they can be affected by

		Department Intervention Value Set includes a list of 173 clinical (common) terms for interventions that are most common/relevant to ED encounters. The terms are mapped to Canadian Classification of Health Interventions (CCI) codes.		misclassification bias due to errors in coding.
OHIP Claims Database	1991	The OHIP is the universal health insurance system that provides almost all Ontario residents with health care services free at the point of delivery based on an OHIP card and its unique 10-digit identifier.[2] The data cover all healthcare providers who can claim under OHIP (this includes physicians, groups, laboratories, and out-of-province providers). Approximately 95% of specialists and 50% of primary care physicians receive most of their income through fee-for-service (FFS) billings to OHIP. To ensure that OHIP data accurately reflect the utilization of physician services in Ontario, all physicians (except the few hundred family physicians working in Community Health Centres) must submit shadow billings for their non-FFS services. Physicians are often provided with cash incentives to encourage them to shadow bills. This database includes data on all physician billing and technical fees for procedures such as polysomnography.	Monthly	All physician claims diagnoses are based on three-digit modified ICD-8 codes. Some health services are not universal and are paid for by OHIP based on eligibility criteria, such as prescription drugs which are publicly funded for those under the age of 25, those over the age of 64, those living in a long-term care home or receiving social assistance.
Canadian Census	1991	It contains aggregated data for Ontario and Canada that describe the general demographic information on 100% of the population, including neighborhood socioeconomic details and the remaining information for a 20% sample of the population.	Every 5 years	Relatively infrequent updates; self-reported data
Assistive devises program (ADP) database	2000	For all insured Ontario residents diagnosed with sleep apnea by a sleep physician, funding is provided for positive airway pressure (PAP) systems and documented in the ADP database from 2000 onwards.[8]	Annual	Information on PAP adherence is unavailable; individuals could obtain PAP devices from other sources, but given partial coverage of PAP cost, it is unlikely affected by a large proportion of individuals.
ICES Physician Database (IPDB)	1992	ICES Physician database. It contains information about physician demographics, specialty training and certification and practice location.	Annual	
ICES disease-specific databases		Those databases are based on the combination of OHIP, DAD and NACRS	Annual	Limitations associated with separate databases included and with the sensitivity and specificity of validated algorithms.
The Ontario Diabetes Database (ODD) [9]	Prevalence : 1991 Incidence: 1994	This data set is a validated registry of all people in Ontario diagnosed with diabetes. It contains all Ontario individuals identified as having diabetes based on OHIP, CIHI/SDS, and RPDB data. Once included, a person remains in the ODD until death or relocation outside Ontario.		

		The best algorithm to identify diabetes cases was the presence at any time of one hospitalization or physician claim for diabetes AND either one prescription for an anti-diabetic medication or one physician claim with a diabetes-specific fee code (sensitivity 84.2%, specificity 99.2%, positive predictive value 92.5%)[10]		
Ontario Hypertension Database [11]	1988	It contains all Ontario hypertension patients based on OHIP, CIHI/SDS, and RPDB data. A case-definition algorithm employing 2 outpatient physician billing claims for hypertension over 3 years had a sensitivity of 73%, a specificity of 95%, a positive predictive value of 87%, and a negative predictive value of 88% for detecting hypertensive adults compared with physician-assigned diagnoses. Compared with self-reported survey data, the algorithm had a sensitivity of 64%, a specificity of 94%, a positive predictive value of 77%, and a negative predictive value of 89%.[12]		
Congestive Heart Failure (CHF) database [13]	Prevalence : 1991 Incidence: 1994	It contains all Ontario individuals identified as having CHF based on OHIP/NACRS, CIHI, and RPDB data. One hospital record or one physician billing followed by a second record from either source within one year had the best result, with a sensitivity of 84.8% and a specificity of 97.0%.[13]		
Ontario Asthma dataset	1996	It contains all Ontario patients with asthma based on OHIP, CIHI, and RPDB data. One or more asthma hospital discharges and/or two or more asthma ambulatory care visits within two years (specificity of 81.4%, sensitivity of 80.6% compared to evaluation by a physician) [14]		
COPD	Prevalence : 1991 Incidence: 1996	It contains all Ontario COPD patients based on OHIP, CIHI, and RPDB data. One or more COPD ambulatory claims and/or one or more COPD hospitalizations (sensitivity of 85.0% and specificity of 78.4%) [15]		
Ontario Cancer Registry [16]	1964	It contains information on all Ontario residents who have been newly diagnosed with cancer or died of cancer, except non-melanoma skin cancer. It includes cancer site, diagnostic date, and cancer stage. Data is collected from: CIHI/DAD; Pathology Reports (paper); Pathology Data (PIMS); Registered Person Database (MOHLTC); Registrar General (Mortality Data); Chemo/Radiation Clinic visits (Integrated Cancer Programs & Princess Margaret Hospital); Data from Other Provincial Registries.	Annual	Limitations associated with separate databases included; information on non-melanoma skin cancer not collected.
Ontario Mental Health Reporting System (OMHRS)	2006	The OMHRS is a data holding at CIHI that includes information on all adult inpatient mental health beds in Ontario for adults. It is based on the Resident Assessment Instrument-Mental Health and includes information about mental and physical health, social support and service use.	Quarterly	
COVID-19-specific datasets#				
COVID19 Integrated Testing Data (C19INTGR)	Jan 2020	ICES-derived comprehensive dataset of all available COVID-19 diagnostic laboratory results in Ontario.[17] The C19INTGR is derived from 3 data sources: 1) Ontario Laboratories Information System (OLIS) contains COVID-19 testing episodes using standard PCR tests from January 2020 to current; 2) Distributed testing data from laboratories within the COVID-19 Diagnostic Network, with results only up to April 13, 2020 (prior to a requirement to report all test results in OLIS, the results of tests performed by laboratories that were part of this	Monthly	

		network were compiled by PHO in a separate database); and 3) Public Health Case & Contact Management (CCM) Solution, formerly known as the integrated Public Health Information System (iPHIS), a 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 current.		
OLIS COVID-19 Laboratory Data (OLISC19)	Jan 2020	OLIS provides lab results of patients from all Public Health Ontario laboratories and a number of hospitals and community laboratories.[18] Variables included in this dataset include province, postal code, date of birth, sex, encrypted health card number, specimen collection date, result release date, whether a COVID test was done, COVID-19 test result (Positive/Presumptive > Indeterminate > Negative > Pending > Cancelled > Rejected).	Monthly	The number of individuals who tested positive in OLIS is ~90% of the cases reported by the Ministry of Health, which uses the iPHIS. Earlier in the pandemic, not all laboratories contributed their lab results to the OLIS, resulting in under-reporting COVID-19 tests and positive COVID-19 cases. Due to the time required for the transportation and processing of specimens, it takes up to six days for approximately 95% of the results to be finalized and reported for a given testing date.
Case and Contact Management System (CCM)	Jan 2020	The Case and Contact Management System (CCM) is a central data repository for COVID-19 case and contact management and reporting in Ontario.[19] This information is used for local, provincial and national surveillance. Between July and August 2020, CCM replaced the iPHIS for COVID-19 for most health units in the province. COVID-19 cases in iPHIS were migrated over to CCM with key reporting elements. iPHIS is used for collecting information on all other reportable diseases in Ontario.	Weekly	The number of cases of COVID-19 in CCM is an underestimate of the actual numbers since not all people with COVID-19 develop symptoms, seek medical treatment or testing, and therefore, the disease goes unreported.

* The Discharge Abstract Database (DAD) is a national database established by the Canadian Institute for Health Information (CIHI) to compile data from acute care institutions across the country

#COVID-19-specific datasets: Initially, only a few laboratories in Ontario were performing SARS-CoV-2 testing, and test results were not stored in a centralized repository. Eventually, testing became more widespread, and results were centralized, and on **April 7, 2020**, ICES started receiving a daily feed of SARS-CoV-2 real-time polymerase chain reaction test results contained in the Ontario Laboratories Information System (OLIS). ICES collaborated closely with teams at the Ministry of Health, Public Health Ontario, and clinical subject matter experts to interpret, validate, and develop an algorithm to transform these data into a research-friendly format. The code to parse relevant test results from these data was published under an open-source license and was subsequently used by the Ministry of Health and Ontario Health for their COVID-19 analytics. Adoption of this code by other organizations that were receiving the same OLIS data feed enabled consistent interpretation of SARS-CoV-2 test results and facilitated uniform reporting

of COVID-19 metrics. Information on COVID-19 cases, such as symptoms, epidemiological contacts and risk factors, are not complete in the OLIS data nor are captured in other health administrative databases. Thus, to enable more descriptive reporting on COVID-19 cases, ICES started receiving daily feeds of the Public Health Case and Contact Management (CCM) Solutions database. CCM was used in combination with OLIS to identify all individuals confirmed positive for SARS-CoV-2 because there were differences in capture rates between the two data sources: OLIS captures approximately ~90% of all confirmed cases that are reported in CCM, but approximately ~6% of cases in CCM are not linkable to other ICES data holdings.

ADP, Assistive devises program; CCI, Canadian Classification of Health Interventions; CIHI, Canadian Institute for Health Information; CCM, Case and Contact Management System; DAD, Discharge Abstract Database; FFS, fee-for-service; IPDB, ICES Physician Database; iPHIS, Integrated Public Health Information System; OHIP, Ontario Health Insurance Plan; OLIS, Ontario Laboratories Information System; OMHRS, Ontario Mental Health Reporting System; RPDB, Registered Persons Database; ODD, the Ontario Diabetes Database.

Table E2. Details on the definition of the variables derived from health administrative data.

COVID-19-related outcomes [20]	
Confirmed COVID-19	ICD-10-CA code and code title: U07.1 COVID-19, virus identified Coding instructions: Assign U07.1 (mandatory) when the patient is diagnosed with an acute infection with the COVID-19 virus (SARS-CoV-2), confirmed by a positive COVID-19 lab test result, or when the physician or primary care provider or infection control staff documented a COVID-19 positive lab test result.
Suspected COVID-19	ICD-10-CA code and code title: U07.2 COVID-19, virus not identified Coding instructions: Assign U07.2 (mandatory) when the patient is diagnosed, clinically or epidemiologically, with an acute infection with the COVID-19 virus (SARS-CoV-2) and the COVID-19 lab test results are inconclusive or not available, or COVID-19 testing is not performed.
Exposure: recent clinically significant OSA diagnosis within 5 years before the COVID-19 pandemic (between March 2015 and March 2020)	Primary definition: recent obstructive sleep apnea (OSA) requiring positive airway pressure (PAP) treatment: those who claimed PAP through the assistive device program (ADP) within the last 5 years prior to the pandemic. Secondary definition: At least 50% probability of having moderate to severe OSA as defined by apnea-hypopnea index≥15/h derived from a diagnostic sleep study (gold standard).[21] 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 hospitalizations with hypertension in the last 3 years prior to the sleep study. In adults who underwent a diagnostic sleep study to identify individuals with an estimated probability of 0.5 or greater of moderate to severe OSA, this definition, when validated on the external cohort, yielded a sensitivity of 59% (95% CI: 58–60), specificity of 87% (95% CI: 0.87–0.88), the positive predictive value of 0.79 (95% CI: 0.78–0.80) and negative predictive value of 0.73 (95% CI: 0.72–0.74).
Income Status	Ontario neighbourhoods are classified into one of the five approximately equal-sized income quintiles, ranked from poorest (Q1) to wealthiest (Q5) and these have been shown to be related to population health status and health care utilization.[22] Each patient was assigned to the income quintile based on the patient's postal code at the time of index date and Statistics Canada's Postal Code Conversion File.[23, 24]
Prevalent conditions	
Diabetes	Prevalent diabetes from the Ontario Diabetes Database [9]
Hypertension	Prevalent hypertension from the Hypertension Database [11]
CHF (chronic heart failure)	Prevalent CHF from the CHF database [13]
Asthma	One or more asthma hospital discharges and/or two or more asthma ambulatory care visits within two years (specificity of 81.4%, sensitivity of 80.6% compared to evaluation by a physician) [14]

COPD	One or more COPD ambulatory claims and/or 1 or more COPD hospitalizations (sensitivity of 85.0% and specificity of 78.4%) [15]
Immunocompromising Conditions [25]	ICD-10 and OHIP codes for the following conditions: Immune system disorders, HIV, Transplant (solid organ and hematopoietic stem cell transplant), cancer (total), solid tumor malignancy, hematologic malignancies, other hematologic diseases.
Cancer	Prevalent cancer from the Ontario Cancer Registry [16]
In the last two years	
Measure of Comorbidity	The Charlson comorbidity index (CCI) [26] 2 years prior to index, aggregated, n (%): • none (CCI score = 0) • low (score = 1) • moderate (score = 2) • high (score ≥ 3)
Non-psychotic mood or anxiety disorders	Inpatient hospital diagnostic codes (at least 1 from DAD) or outpatient physician billing codes (at least 2 from OHIP within a 2-year period)
In the past 5 years	
Prior cardiovascular-related hospitalizations (in the last 5 years)	• Ischemic heart disease: two OHIP codes in 1 year or one hospitalization using CIHI-DAD [27] – ICD-9: 410, 411, 412, 413, 414, 4802, 4803, 4809, 481 – ICD-10: I20, I21, I22, I23, I24, I251, I258, I259, 1IJ50, 1IJ57, 1IJ76 – OHIP codes: 410, 412, 413, R742, R743, Z434, G298 • Stroke hospitalizations – ICD-9: 433, 434, 435, 436 – ICD-10: G45, G46, I63, I64 • Any hospitalization for dysrhythmias – ICD-9: 427 except 427.6 ICD-10: I47, I48, I49
Prior End Stage Renal Disease/Hemodialysis (from CIHI, NACRS, and/or OHIP)	• Any hospitalization or same day record from CIHI/DAD, CIHI/NACRS – ICD-9: 4031, 4039, 585, V45.1 – ICD-10: I12, I13, N18.3, 18.4, 18.5, 18.6, 18.9, E08.22, E09.22, E10.22, E11.22, E13.22, Z99.2 • OHIP codes: G860, G861, G862, G863, G864, G865, G866
Neuromuscular Disease [28] (from CIHI/DAD, OHIP)	• ICD-10 and OHIP codes for the following conditions: Amyotrophic lateral sclerosis, Cerebral palsy, Guillain-Barre syndrome, Metabolic disorders, Multiple sclerosis, Muscular dystrophy, Myasthenia gravis, Neuromuscular disorders (other), Neuropathy, Post-polio syndrome, Spina bifida, Spinal muscular atrophy • For patients identified with OHIP dx349, including only those with subsequent or previous NMD-related ED, hospitalization visit or with subsequent or previous neurologist visit and EMG
Alcohol Dependence/intoxication (from CIHI, NACRS, and/or OHIP)	• Any hospitalization or same day record from CIHI/DAD, CIHI/NACRS • ICD-10: E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721 • OHIP code: 303
Obesity/Bariatric Surgery	Inpatient Bariatric Procedures: • ICD-10-CA – E66, obesity; AND • CCI codes: 1NF78 repair by decreasing size, stomach Outpatient bariatric procedures:

	• OHIP fee codes: S120 for gastric bypass with Roux-en-Y anastomosis; S114 for sleeve gastrectomy; S189 for intestines-intestinal bypass for morbid obesity
Local Health Integration Network (LHIN)	1 = Erie St. Clair 2 = South West 3 = Waterloo Wallington 4 = Hamilton Niagara Haldimand Brant 5 = Central West 6 = Mississauga Halton 7 = Toronto Central 8 = Central 9 = Central East 10 = South East 11 = Champlain 12 = North Simcoe Muskoka 13 = North East 14 = North West

DAD, the Discharge Abstract Database (Canadian Institute for Health Information); NACRS, the National Ambulatory Care Reporting System Metadata (Canadian Institute for Health Information); COPD, chronic obstructive pulmonary disease; ED, emergency department; ICD, International Classification of Diseases; OHIP, the Ontario Health Insurance Plan Database; OMHRS, the Ontario Mental Health Reporting System; RPDB, the Registered Persons Database; SDS, Same Day Surgery

Table E3. Cohort characteristics by exposure status (primary definition of obstructive sleep apnea [OSA]) presented as unweighted (original) and the ATE (average treatment effect) weighted* on the propensity score.

Cohort Characteristics	**Non-OSA (unweighted)** N=**4,588,200**	**PAP group (unweighted)** N=**324,029**	**Standardized Difference (unweighted comparison)**	**PAP group (ATE weighted) #** N=**299,564**	**Non-OSA (ATE weighted)#** N=**4,594,179**	**Standardized Difference (comparison on an ATE weighted sample)**
Demographics at the index date						
Age, median (IQR)	47 (33-61)	58 (49-67)	0.67	49.80	48.44	0.08
Sex, Male, n (%)	2,368,385 (51.6)	211,379 (65.2)	0.28	55.50	52.56	0.06
Rural Status: Yes, n (%)	547,452 (11.9)	40,449 (12.5)	0.02	13.18	11.99	0.04
Neighborhood Income, n (%)						
Quintile 1	883,936 (19.3)	54,792 (16.9)	0.06	20.01	19.39	0.02
Quintile 2	898,281 (19.6)	62,000 (19.1)	0.01	20.10	19.54	0.01
Quintile 3	918,096 (20.0)	66,746 (20.6)	0.01	20.24	20.06	0.00
Quintile 4	924,562 (20.2)	69,379 (21.4)	0.03	19.87	20.25	0.01
Quintile 5	949,776 (20.7)	70,444 (21.7)	0.03	19.78	20.76	0.02
Comorbidities, n (%)						
Prevalent conditions						
Diabetes	408,683 (8.9)	96,277 (29.7)	0.55	12.10	10.35	0.06
Hypertension	899,553 (19.6)	178,511 (55.1)	0.79	24.45	22.05	0.06
CHF	42,050 (0.9)	20,756 (6.4)	0.30	1.42	1.29	0.01
Asthma	394,682 (8.6)	67,988 (21.0)	0.35	9.81	9.44	0.01
COPD	184,450 (4.0)	56,689 (17.5)	0.45	5.52	4.94	0.03
Immunocompromising Conditions	82,839 (1.8)	14,537 (4.5)	0.15	2.27	1.99	0.02
Cancer	219,899 (4.8)	31,551 (9.7)	0.19	5.80	5.14	0.03
In the last two years						
Charlson Comorbidity Index (CCI)						
High (CCI score ≥ 3)	13,577 (0.3)	5,387 (1.7)	0.14	0.42	0.38	0.01
Moderate (CCI score = 2)	19,522 (0.4)	7,020 (2.2)	0.15	0.63	0.54	0.01
Low (CCI score = 1)	24,926 (0.5)	8,580 (2.6)	0.17	0.79	0.70	0.01
None (CCI score = 0)	240,723 (5.2)	30,429 (9.4)	0.16	5.68	5.56	0.01

Cohort Characteristics	**Non-OSA (unweighted)** N=**4,588,200**	**PAP group (unweighted)** N=**324,029**	**Standardized Difference (unweighted comparison)**	**PAP group (ATE weighted) #** N=**299,564**	**Non-OSA (ATE weighted)#** N=**4,594,179**	**Standardized Difference (comparison on an ATE weighted sample)**
Non-psychotic mood or anxiety disorders	476,419 (10.4)	83,515 (25.8)	0.41	13.52	11.5	0.06
In the past 5 years						
Any CV Hospitalization	142,505 (3.1)	49,293 (15.2)	0.43	4.73	3.97	0.04
Prior End Stage Renal Disease/Hemodialysis	8,549 (0.2)	3,480 (1.1)	0.11	0.27	0.24	0.01
Neuromuscular Disease	75,316 (1.6)	16,382 (5.1)	0.19	2.43	1.88	0.04
Alcohol Dependence/intoxication	78,073 (1.7)	6,672 (2.1)	0.03	2.11	1.73	0.03
Obesity/Bariatric Surgery	1,425 (0.0)	5,786 (1.8)	0.19	0.16	0.18	0.00

*In weight allocation using the average treatment effect (ATE) approach both groups are weighted. The groups were also perfectly weighted on 14 Local Health Integration Network (LHIN) (data are not shown).

#Estimates presented as mean or prevalence (percentage) as applicable.

CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; OSA, obstructive sleep apnea.

Table E4. Cohort characteristics by exposure status (secondary definition of obstructive sleep apnea [OSA]). Individuals with a low probability of obstructive sleep apnea (control group) are presented as unweighted (original) and ATT (average treatment effect on the treated) weighted* on the propensity score.

Cohort Characteristics	**Non-OSA (unweighted)** N=**4,588,200**	**Moderate/Severe OSA group (unweighted)** N=**191,447**	**Standardized Difference (unweighted comparison)**	**Non-OSA (ATT weighted)#** N=**193,807**	**Standardized Difference (comparison on an ATE weighted sample)**
Demographics at the index date					
Age, median (IQR)	47 (33-61)	57 (48-67)	0.64	57.33	0.00
Sex, Male, n (%)	2,368,385 (51.6)	129,772 (67.8)	0.33	67.92	0.00
Rural Status: Yes, n (%)	547,452 (11.9)	23,072 (12.1)	0.00	12.21	0.00
Neighborhood Income, n (%)					
Quintile 1	883,936 (19.3)	33,439 (17.5)	0.05	17.55	0.00
Quintile 2	898,281 (19.6)	37,327 (19.5)	0.00	19.43	0.00
Quintile 3	918,096 (20.0)	39,245 (20.5)	0.01	20.63	0.00
Quintile 4	924,562 (20.2)	40,443 (21.1)	0.02	21.23	0.00
Quintile 5	949,776 (20.7)	40,593 (21.2)	0.01	21.16	0.00
Comorbidities, n (%)					
Prevalent conditions					
Diabetes	408,683 (8.9)	48,433 (25.3)	0.45	25.71	0.01
Hypertension	899,553 (19.6)	99,921 (52.2)	0.72	52.84	0.01
CHF	42,050 (0.9)	11,704 (6.1)	0.29	6.28	0.01
Asthma	394,682 (8.6)	35,760 (18.7)	0.30	18.82	0.00
COPD	184,450 (4.0)	30,742 (16.1)	0.41	16.27	0.01
Immunocompromising Conditions	82,839 (1.8)	8,185 (4.3)	0.14	4.33	0.00
Cancer	219,899 (4.8)	17,906 (9.4)	0.18	9.49	0.01
In the last two years					
Charlson Comorbidity Index (CCI)					
High (CCI score ≥ 3)	13,577 (0.3)	2,939 (1.5)	0.13	1.50	0.00
Moderate (CCI score = 2)	19,522 (0.4)	3,795 (2.0)	0.14	2.00	0.00
Low (CCI score = 1)	24,926 (0.5)	4,465 (2.3)	0.15	2.44	0.01
None (CCI score = 0)	240,723 (5.2)	17,728 (9.3)	0.16	9.64	0.01
Non-psychotic mood or anxiety disorders	476,419 (10.4)	45,937 (24.0)	0.37	24.9	0.02
In the past 5 years					
Any CV Hospitalization	142,505 (3.1)	29,972 (15.7)	0.44		
Prior End Stage Renal Disease/Hemodialysis	8,549 (0.2)	2,121 (1.1)	0.12	1.08	0.00
Neuromuscular Disease	75,316 (1.6)	8,928 (4.7)	0.17	4.79	0.01
Alcohol Dependence/intoxication	78,073 (1.7)	4,185 (2.2)	0.04	2.23	0.00
Obesity/Bariatric Surgery	1,425 (0.0)	2,711 (1.4)	0.16	1.72	0.02

*In weight allocation using the average treatment effect on the treated (ATT) approach (used in the main analysis), the exposure group has weight one, and only the controlled group is weighted. The groups were also perfectly weighted on 14 Local Health Integration Network (LHIN) (data are not shown).

#Estimates presented as mean or prevalence (percentage) as applicable.

CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; OSA, obstructive sleep apnea.

Table E5. Cohort characteristics by exposure status (secondary definition of obstructive sleep apnea [OSA]) presented as unweighted (original) and ATE (average treatment effect) weighted* on the propensity score.

Cohort Characteristics	**Non-OSA (unweighted)**	**Moderate/Severe OSA group (unweighted)**	**Standardized Difference (unweighted comparison)**	**Non-OSA (ATE weighted)#**	**Moderate/Severe OSA group (ATE weighted)#**	**Standardized Difference (comparison on an ATE weighted sample)**
	N=**4,588,200**	N=**191,447**		N= **4,590,000**	N= **174,167**	
Demographics at the index date						
Age, median (IQR)	47 (33-61)	57 (48-67)	0.64	48.16	49.93	0.10
Sex, Male, n (%)	2,368,385 (51.6)	129,772 (67.8)	0.33	52.28	55.29	0.06
Rural Status: Yes, n (%)	547,452 (11.9)	23,072 (12.1)	0.00	11.94	12.98	0.03
Neighborhood Income, n (%)						
Quintile 1	883,936 (19.3)	33,439 (17.5)	0.05	19.48	20.25	0.02
Quintile 2	898,281 (19.6)	37,327 (19.5)	0.00	19.57	19.94	0.01
Quintile 3	918,096 (20.0)	39,245 (20.5)	0.01	20.03	20.15	0.00
Quintile 4	924,562 (20.2)	40,443 (21.1)	0.02	20.19	19.89	0.01
Quintile 5	949,776 (20.7)	40,593 (21.2)	0.01	20.72	19.76	0.02
Comorbidities, n (%)						
Prevalent conditions						
Diabetes	408,683 (8.9)	48,433 (25.3)	0.45	9.59	11.88	0.07
Hypertension	899,553 (19.6)	99,921 (52.2)	0.72	20.95	23.84	0.07
CHF	42,050 (0.9)	11,704 (6.1)	0.29	1.13	1.29	0.01
Asthma	394,682 (8.6)	35,760 (18.7)	0.30	9.02	9.44	0.01
COPD	184,450 (4.0)	30,742 (16.1)	0.41	4.52	5.16	0.03
Immunocompromising Conditions	82,839 (1.8)	8,185 (4.3)	0.14	1.91	2.19	0.02
Cancer	219,899 (4.8)	17,906 (9.4)	0.18	4.98	5.75	0.03
In the last two years						
Charlson Comorbidity Index (CCI)						
High (CCI score ≥ 3)	13,577 (0.3)	2,939 (1.5)	0.13	0.34	0.37	0.00
Moderate (CCI score = 2)	19,522 (0.4)	3,795 (2.0)	0.14	0.49	0.57	0.01
Low (CCI score = 1)	24,926 (0.5)	4,465 (2.3)	0.15	0.62	0.77	0.02
None (CCI score = 0)	240,723 (5.2)	17,728 (9.3)	0.16	5.42	5.40	0.00
Non-psychotic mood or anxiety disorders	476,419 (10.4)	45,937 (24.0)	0.37	10.97	13.40	0.07

Cohort Characteristics	**Non-OSA (unweighted)**	**Moderate/Severe OSA group (unweighted)**	**Standardized Difference (unweighted comparison)**	**Non-OSA (ATE weighted)#**	**Moderate/Severe OSA group (ATE weighted)#**	**Standardized Difference (comparison on an ATE weighted sample)**
	N=**4,588,200**	N=**191,447**		N= **4,590,000**	N= **174,167**	
In the past 5 years						
Any CV Hospitalization	142,505 (3.1)	29,972 (15.7)	0.44	3.64	4.45	0.04
Prior End Stage Renal Disease/Hemodialysis	8,549 (0.2)	2,121 (1.1)	0.12	0.22	0.25	0.00
Neuromuscular Disease	75,316 (1.6)	8,928 (4.7)	0.17	1.77	2.14	0.03
Alcohol Dependence/intoxication	78,073 (1.7)	4,185 (2.2)	0.04	1.72	2.00	0.02
Obesity/Bariatric Surgery	1,425 (0.0)	2,711 (1.4)	0.16	0.1	0.1	0.00

*In weight allocation using the average treatment effect (ATE) approach both groups are weighted. The groups were also perfectly weighted on 14 Local Health Integration Network (LHIN) (data are not shown).

#Estimates presented as mean or prevalence (percentage) as applicable.

CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; OSA, obstructive sleep apnea.

Table E6. Overlap between primary and secondary definitions of obstructive sleep apnea (OSA).

	Primary definition of OSA	**Secondary definition of OSA**	**Standardized Difference**
	N=324,029	N=191,447	
OSA-Primary	324,029 (100%)	153,350 (80.1%)	
OSA-Secondary	153,350 (47.3%)	191,447 (100%)	
VARIABLES			
Demographics at the index date			
Age at index date, Median (IQR)	58 (49-67)	57 (48-67)	0.04
Sex, Male, n (%)	211,379 (65.2%)	129,772 (67.8%)	0.05
Rural Status: Yes, n (%)	40,449 (12.5%)	23,072 (12.1%)	0.01
Neighborhood Income, n (%)			
Quintile 1	54,792 (16.9%)	33,439 (17.5%)	0.01
Quintile 2	62,000 (19.1%)	37,327 (19.5%)	0.01
Quintile 3	66,746 (20.6%)	39,245 (20.5%)	0
Quintile 4	69,379 (21.4%)	40,443 (21.1%)	0.01
Quintile 5	70,444 (21.7%)	40,593 (21.2%)	0.01
Comorbidities, n (%)			
Prevalent conditions			
Diabetes	96,277 (29.7%)	48,433 (25.3%)	0.10
Hypertension	178,511 (55.1%)	99,921 (52.2%)	0.06
CHF	20,756 (6.4%)	11,704 (6.1%)	0.01
Asthma	67,988 (21.0%)	35,760 (18.7%)	0.06
COPD	56,689 (17.5%)	30,742 (16.1%)	0.04
Immunocompromising Conditions	14,537 (4.5%)	8,185 (4.3%)	0.01
Cancer	31,551 (9.7%)	17,906 (9.4%)	0.01
In the last two years			
Charlson Comorbidity Index (CCI)			
High (CCI score ≥ 3)	5,387 (1.7%)	2,939 (1.5%)	0.01
Moderate (CCI score = 2)	7,020 (2.2%)	3,795 (2.0%)	0.01
Low (CCI score = 1)	8,580 (2.6%)	4,465 (2.3%)	0.02
None (CCI score = 0)	30,429 (9.4%)	17,728 (9.3%)	0
Non-psychotic mood or anxiety disorders	83,515 (25.8%)	45,937 (24.0%)	0.04
In the past 5 years			
Any CV Hospitalization	49,293 (15.2%)	29,972 (15.7%)	0.01
Prior End Stage Renal Disease/Hemodialysis	3,480 (1.1%)	2,121 (1.1%)	0
Neuromuscular Disease	16,382 (5.1%)	8,928 (4.7%)	0.02
Alcohol Dependence/intoxication	6,672 (2.1%)	4,185 (2.2%)	0.01
Obesity/Bariatric Surgery	5,786 (1.8%)	2,711 (1.4%)	0.03
Cardiometabolic Morbidity (prevalent diabetes, hypertension or CHF, or hospitalizations for CV conditions in the last 5 years)	209,593 (64.7%)	117,282 (61.3%)	0.07

Chronic Airways Disease (COPD or asthma)	103,729 (32.0%)	56,133 (29.3%)	0.06

CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; OSA, obstructive sleep apnea.

Table E7. Unadjusted rates of COVID-19-related outcomes by exposure status on the unweighted subgroups, and adjusted associations between clinically significant obstructive sleep apnea (OSA, secondary definition) and COVID-19-related outcomes.

Outcomes	**Non-OSA group (unweighted)**		**Moderate/Severe OSA group (unweighted)**		**Hazard Ratio (95% Confidence Interval)**	
	N=4,588,200		N=191,447		**ATT weighted samples**	**ATE weighted samples**
	N (%)	Rate per 1,000 Person-Year (95% CI)	N (%)	Rate per 1,000 Person-Year (95% CI)		
Contracting COVID-19						
COVID-19 Positive Test Result	83,373 (1.82)	17.7 (17.5-17.8)	4,454 (2.33)	22.7 (22.0-23.4)	1.26 (1.22-1.30)	1.26 (1.16-1.37)
Serious complications from COVID-19						
COVID-19 related ED Visit	16,138 (0.35)	3.4 (3.4-3.5)	1,573 (0.82)	8.0 (7.6-8.4)	1.74 (1.62-1.86)	1.77 (1.59-1.97)
COVID-19 related Hospitalization	4,095 (0.09)	0.9 (0.8-0.9)	592 (0.31)	3.0 (2.8-3.3)	1.54 (1.39-1.71)	1.74 (1.51-2.00)
COVID-19 related ICU Admission	1,028 (0.02)	0.2 (0.2-0.2)	181 (0.09)	0.9 (0.8-1.1)	1.60 (1.31-1.96)	1.67 (1.33-2.11)
COVID-19 related Mortality*	1,566 (0.03)	0.3 (0.3-0.3)	155 (0.08)	0.8 (0.7-0.9)	1.00 (0.83-1.21)	0.86 (0.67-1.11)

*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.

Table E8. Adjusted* associations between clinically significant obstructive sleep apnea (OSA, primary definition) and COVID-19-related outcomes (secondary definition). Estimates are presented as odds ratio and 95% confidence intervals (N=90,228).

Outcome	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit
Covid-19 related ED Visit within 30 days of Positive Test (Events=11,478)	1.50	1.38	1.64
Covid-19 related Hospitalization within 30 days of Positive Test (Events=4,659)	1.40	1.27	1.55
Covid-19 related ICU Admission within 30 days of Positive Test (Events=1,247)	1.41	1.16	1.70

*On the ATT (average treatment effect on the treated) weighted samples.

Table E9: Adjusted statistically significant association between clinically significant obstructive sleep apnea (primary definition) and COVID-19-related outcomes and relevant E values.

Outcomes	**ATT weighted samples (primary analysis) Cause Specific Hazard Ratio (95% Confidence Interval)**	**E Values***
COVID-19 Positive Test Result	1.17 (1.13-1.21)	1.62
COVID-19-related ED Visit	1.62 (1.51-1.73)	2.62
COVID-19-related Hospitalization	1.50 (1.37-1.65)	2.37
COVID-19-related ICU Admission	1.53 (1.27-1.84)	2.43

*The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates. 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 vs. non-OSA group, after adjustment for all covariates considered in the PS weighting (i.e., demographics [age, sex, neighborhood income quintile, rural residence, and allocation by a local health integration network], comorbidities [diabetes, hypertension, chronic heart failure (CHF), asthma, COPD, immunocompromising conditions, Charlson Comorbidity Index, non-psychotic mood and anxiety disorders, cardiovascular (CV) hospitalization including for atrial fibrillation, end-stage renal disease/ hemodialysis, neuromuscular disease, alcohol use disorder, and obesity or bariatric surgery), to explain the observed risk ratio, which is not impossible but unlikely, given the current evidence.[29]

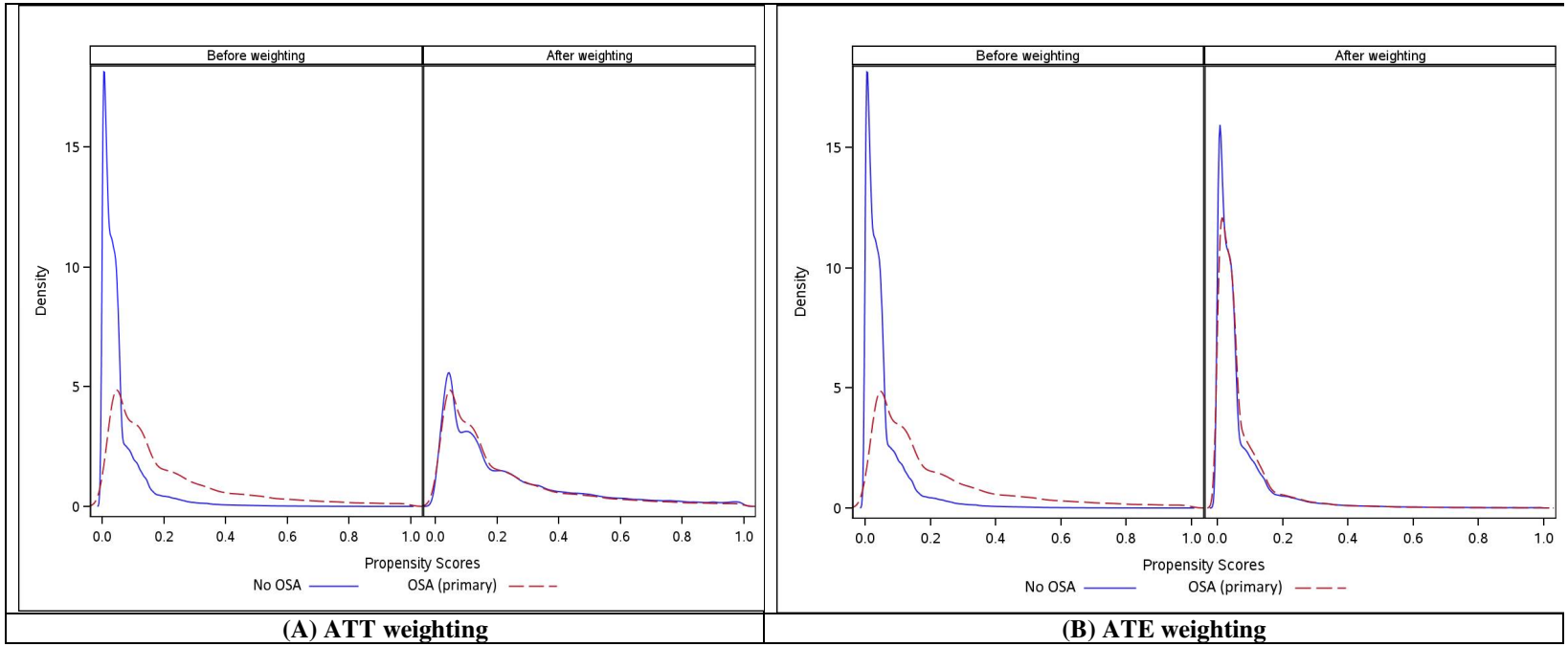

Figure E1. Density plot: The effect of weights on the magnitude of differences between obstructive sleep apnea (OSA, primary definition) vs. No-OSA groups (before and after weighting) while applying ATT weights (A) and ATE weights (B). In these plots, substantial reductions in effect sizes are observed before and after weighting. ATE, average treatment effect; ATT, average treatment effect on the treated; OSA, obstructive sleep apnea.

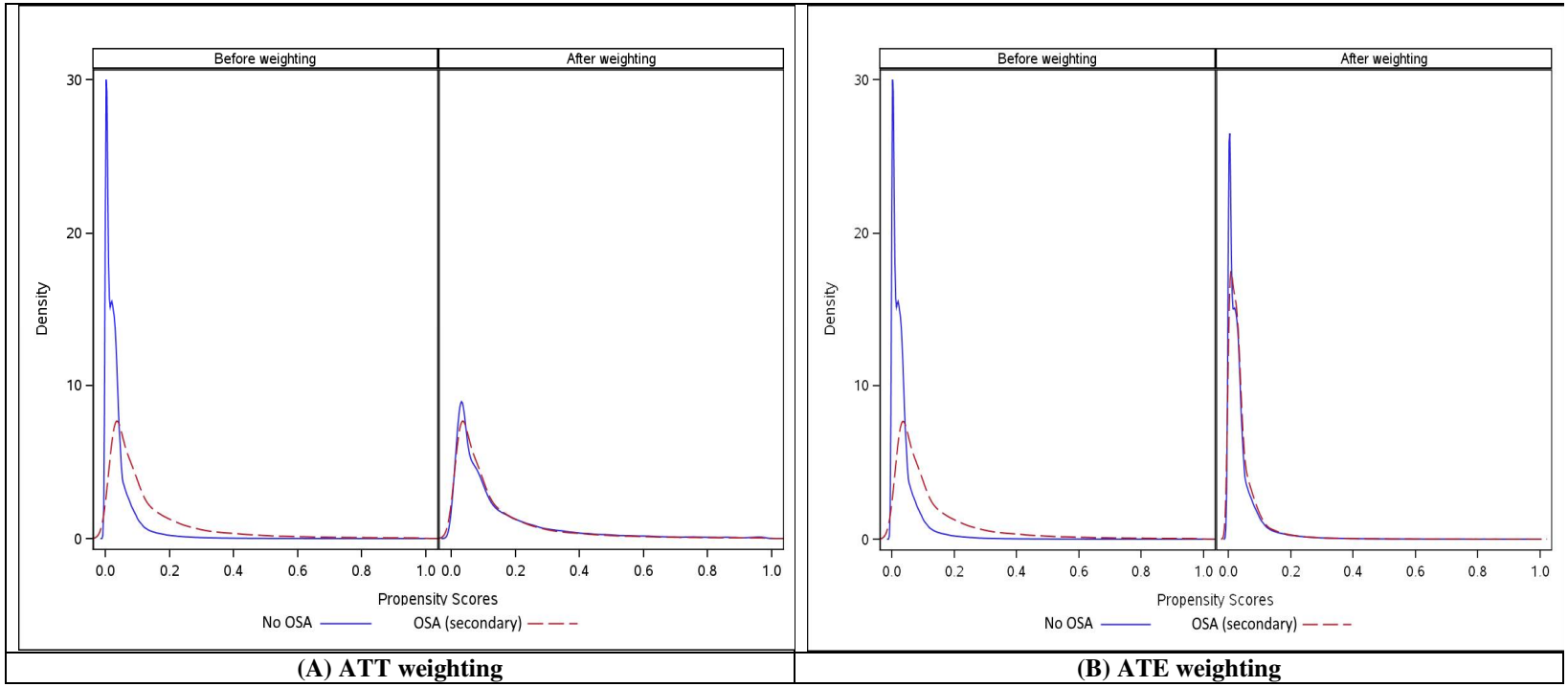

Figure E2. Density plot: The effect of weights on the magnitude of differences between obstructive sleep apnea (OSA, secondary definition) vs. No-OSA groups (before and after weighting) while applying ATT weights (A) and ATE weights (B). In these plots, substantial reductions in effect sizes are observed before and after weighting. ATE, average treatment effect; ATT, average treatment effect on the treated; OSA, obstructive sleep apnea.

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