SUPPLEMENT

FOR

CANNABIS USE AND RISKS OF RESPIRATORY AND ALL-CAUSE MORBIDITY AND MORTALITY: A POPULATION-BASED, DATA-LINKAGE, COHORT STUDY

Running title: Cannabis and respiratory health

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Section 1: List of ICD-10 codes identifying the primary outcome respiratory-related ER visit or hospitalization

ICD-10 code	Description
Asthma	
J45	Asthma
J46	Status asthmaticus
J82	Eosinophilic asthma
COPD	
J41	Simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J44	Other chronic obstructive pulmonary disease
Respiratory tract infection	
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J05	Acute obstructive laryngitis [croup] and epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J11	Influenza, virus not identified
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J20	Acute bronchitis
J21	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection
J40	Bronchitis, not specified as acute or chronic
J85	Abscess of lung and mediastinum

J86	Pyothorax
Respiratory failure	
J96	Respiratory failure, not elsewhere classified

Section 2: List of all variables included in the propensity score

Variable in propensity score	Database source, definition, and rationale for selection
Age at index date	CCHS. Age was a potential confounder in our analysis, because cannabis use is known to be more prevalent among younger age groups and younger (versus older) individuals were anticipated to be less likely to experience our selected adverse health outcomes.
Sex	CCHS. Sex was a potential confounder in our analysis, because cannabis use is known to be more prevalent among men and men were anticipated to more likely to experience some of our selected adverse health outcomes.
Urban versus rural residence at index date	RPD. Rural residence was a potential confounder in our analysis, because cannabis use was anticipated to be more prevalent among individuals residing in rural areas and such persons would also be greater risk for adverse health outcomes.
Income quintile	RPD. Lower income was a potential confounder in our analysis, because cannabis use was anticipated to be more prevalent among lower income individuals and such persons would also be greater risk for adverse health outcomes.
Any-cause ER visit or hospitalization within the year prior to the index date	CIHI-DAD and NACRS. This variable was included in the propensity score model to potentially adjust for a behaviour of recurrent health care access, which may be associated both with the exposure and outcomes of interest.
Respiratory-related ER visit or hospitalization within the year prior to the index date	CIHI-DAD and NACRS. This variable was included in the propensity score model to potentially adjust for a behaviour of recurrent health care access, which may be associated both with the exposure and outcomes of interest.
Had an outpatient physician visit (any specialty, for any reason) in the 12 months prior to the index date	OHIP. This variable was included in the propensity score model to potentially adjust for a behaviour of recurrent health care access, which may be associated both with the exposure and outcomes of interest.
Tobacco smoking status	CCHS. Responses categorized as current or

	former smoker, versus never smoker or not available. Tobacco smoking was a potential confounder in our analysis, because it is known to be associated with cannabis use and it would also increase the risk for adverse health outcomes.
Mean number of cigarettes smoked per day among current or former smokers	CCHS. Responses categorized as <=12/day (with 12 cigarettes per day being equivalent to about half a pack per day), versus >12day, versus not applicable/available. Rationale for inclusion in propensity score model is the same as outlined above.
Any self-reported illicit substance use (including cocaine, speed, ecstasy, hallucinogens, solvents or heroin) in the past year	CCHS. Illicit substance use was a potential confounder in our analysis, because it was anticipated that this behaviour would be more commonly encountered among cannabis users and it would also increase the risk for adverse health outcomes.
Self-reported history of problem drinking.	CCHS. Problem drinking was defined as >=14 drinks in the past week if the survey respondent was a man and >=7 drinks in the past week if the survey respondent was a woman. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of asthma or COPD diagnosis at any time prior to the index date	ICES Asthma and ICES COPD databases. Validated asthma case definition: one hospitalisation in CIHI-DAD, or two or more ambulatory care visits in OHIP, for asthma within a 2-year period (age ≥18 years: sensitivity=84%, specificity=76%).[1] Validated COPD case definition: one hospitalisation in CIHI-DAD or one ambulatory care visit in OHIP for COPD (sensitivity=85.0%, specificity=78.4%).[2] Asthma and COPD diagnoses were included in the propensity score model, since cannabis smoking may contribute to the development of these conditions and the presence of these conditions would increase the risk for our adverse health outcomes.

Presence of other pulmonary disease diagnosis based on 3 year look back from the index date	Any one claim for either bronchiectasis, occupational lung diseases, pleural effusion, pulmonary fibrosis, pneumothorax, pulmonary embolus/infarction, atelectasis, or other disease in either OHIP or CIHI-DAD: OHIP codes: 41.5, 49.4, 50.1, 50.2, 51.1, 51.2, 51.5, 51.8, 51.9. CIHI-DAD ICD-10 codes: I26, J47, J60-J70.9, J84.0-J84.9, J85.0-J86.9, J90-J94.9, J95.0-J95.9, J98.0- J99.8. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of gastroesophageal reflux disease diagnosis based on 3 year look back from the index date	Any of the following CIHI ICD-10 codes in CIHI-DAD: R12, K20, K21.0, K21.9, K22. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of hypertension diagnosis at any time prior to the index date	ICES Hypertension Database. Validated case definition: two outpatient physician billing claims in OHIP for hypertension over a 3-year period (sensitivity=73%, specificity 95%).[3] Rationale for inclusion in propensity score model is the same as outlined above.
Presence of acute myocardial infarction diagnosis at any time prior to the index date	ICES OMID database. Validated case definition: a hospitalisation with acute myocardial infarction as the most responsible diagnosis (sensitivity=92.8%, specificity=88.8%).[4] Rationale for inclusion in propensity score model is the same as outlined above.
Presence of CHF diagnosis at any time prior to the index date	ICES CHF database Validated case definition: One hospitalisation in CIHI-DAD for CHF, or one ambulatory care or ER visit in OHIP or NACRS for CHF, followed by one hospitalisation, ambulatory care, or ER visit with a CHF claim within 2 years (sensitivity=84.8%, specificity=97.0%).[5]

	Rationale for inclusion in propensity score model is the same as outlined above.
Presence of any cancer diagnosis at any time prior to the index date	Ontario Cancer Registry (a validated provincial cancer registry, using information from hospital discharge data, reports from cancer treatment centres, pathology reports, and death certificates).[6] Cancer diagnosis was a potential confounder in our analysis, because it is known to be associated with cannabis use and its presence would also increase the risk for our adverse health outcomes.
Presence of diabetes diagnosis at any time prior to the index date	ICES Ontario Diabetes Database Validated case definition for individuals ≥ 19 years old: one hospitalisation in CIHI-DAD or two or more ambulatory care visits in OHIP for diabetes within a 2-year period (age ≥19 years: sensitivity=86%, specificity=97%).[7] Diabetes diagnosis was a potential confounder in our analysis, because it may be associated with cannabis use (e.g., cannabis may be used to manage diabetic neuropathy pain) and its presence would also increase the risk for our adverse health outcomes.
Presence of any psychotic mental health disease diagnosis based on 3 year look back from the index date	Any one of the following codes for either schizophrenia, bipolar disorder or paranoid states in either OHIP, CIHI-DAD, or OMHRS[8]: OHIP codes: 295, 296, 297, 298. CIHI-DAD ICD-10 codes: F20.0-20.6, F20.8-20.9, F21, F23.2, F25.0-25.2, F25.8, F25.9, F22.0, F22.8, F22.9, F23.0, F23.1, F23.3, F23.8, F23.9, F24, F28, F29, F30.0, F30.1, F30.2, F30.8-31.9, F33.3, R41.0. OMHRS DSM4 codes: 295.10, 295.20, 295.30, 295.40, 295.60, 295.70, 295.90, 296.00-296.06, 296.24, 296.34 296.40-289.46, 296.50-296.56, 296.60-296.66, 296.70, 296.80, 296.89, 296.90, 297.10, 297.30, 298.80, 298.90. Psychotic mental health disease diagnosis

	was a potential confounder in our analysis, because it was anticipated to be associated with cannabis use and its presence would also increase the risk for our adverse health outcomes.
Presence of depression disorder diagnosis based on 3 year look back from the index date	Any one of the following codes in either OHIP, CIHI-DAD, or OMHRS[8]: OHIP codes: 311. CIHI-DAD ICD-10 codes: F32.0, F32.1-F32.3, F32.8, F32.9, F33.0-33.4, F33.8-F39, F34.0, F34.1, F34.8-34.9, F38.0-38.1, F38.8, F39. OMHRS DSM4 codes: 296.20-296.26, 296.30-296.36, 300.40, 301.13, 311.00. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of anxiety disorder diagnosis based on 3 year look back from the index date	Any one of the following codes in either OHIP, CIHI-DAD, or OMHRS[8]: OHIP codes: 300, 309. CIHI-DAD ICD-10 codes: F40.0-40.2, F40.8-F41.3, F41.8-42.2, F42.8-F43.2, F43.8-F45.4, F45.8, F45.9. OMHRS DSM4 codes: 300.00-300.02, 300.11-300.16, 300.19, 300.21-300.23, 300.29-300.30, 300.60, 300.70, 300.81-300.82, 308.30, 309.00, 309.21, 309.24, 309.28, 309.30, 309.40, 309.81, 309.90. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of mental or behavioural disorder due to substance use diagnosis based on 3 year look back from the index date	Any one of the following codes in either OHIP, CIHI-DAD, or OMHRS[8]: OHIP codes: 303, 304, 305. CIHI-DAD ICD-10 codes: F10.0-10.2, F11.1-11.2, F12.1-12.2, F13.1-13.2, F14.1-14.2, F15.1-15.2, F16.1-16.2, F17.1-17.2, F18.1-18.2, F19.1-19.2, F55. OMHRS DSM4 codes: 303.90, 304.00, 304.10, 304.20, 304.30, 304.40, 304.50, 304.60, 304.80, 304.90, 305.00, 305.10, 305.20, 305.30, 305.40, 305.50, 305.60, 305.70, 305.90. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of personality disorder diagnosis based on 3 year look back from the index date	Any one of the following codes in either OHIP, CIHI-DAD, or OMHRS[8]: OHIP codes: 301.

	CIHI-DAD ICD-10 codes: F60.0-60.9, F61, F62.0, F62.1, F62.8, F62.9, F68.0, F68.1, F68.8, F69. OMHRS DSM4 codes: 301.00, 301.20, 301.22, 301.40, 301.50, 301.60, 301.70, 301.81-301.83, 301.90. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of other mental health disorder diagnosis based on 3 year look back from the index date	Any one of the following codes in either OHIP, CIHI-DAD, or OMHRS[8]: OHIP codes: 306, 307. CIHI-DAD ICD-10 codes: F48.0-F81, F48.8, F48.9, F50.0-F50.5, F50.8, F50.9, F53.0, F53.1, F53.8, F53.9, F59, F84.5, F93.0, F95.0-95.2, F95.8-95.9, F98.0-98.6, F98.8, F98.9, F99, G44.2. OMHRS DSM4 codes: 299.80, 300.90, 306.51, 307.00, 307.10, 307.20-307.23, 307.30, 307.50- 307.53, 307.59, 307.60, 307.70, 307.80, 307.89-307.90. Rationale for inclusion in propensity score model is the same as outlined above.
Presence of any sleep disorder diagnosis based on 3 year look back from the index date	Any one of the following codes in either OHIP, CIHI-DAD, or OMHRS: OHIP codes: 307, 786. CIHI-DAD ICD-10 codes: F51.0, F51.1, F51.3, F51.4, F51.5, F51.8, F51.9, G47.0-47.3, G47.4, G47.8-47.9, Z72.8, Z73.8. OMHRS DSM4 codes: 307.42, 307.44, 307.45, 307.46, 307.47. Rationale for inclusion in propensity score model is the same as outlined above.
Respirologist outpatient visit in the past 12 months prior to the index date	OHIP. This variable was included in the propensity score model to potentially adjust for a health care utilization behaviour, which may be associated both with the exposure and outcomes of interest.
Receipt of spirometry or bronchoprovocation challenge testing or exercise oximetry testing in the 12 months prior to index date	OHIP. Rationale for inclusion in propensity score model is the same as outlined above.
Self-reported respiratory-related medication use within the year prior to the index date	CCHS. Based on the following question: "In the past 12 months, have you taken any medicine for asthma such as inhalers, nebulizers, pills, liquids or injections?" (with possible responses including yes and

	no). Respiratory-related medication use was a potential confounder in our analysis, because individuals using cannabis may be more likely to receive such medications as a result of having respiratory-related symptoms from cannabis consumption and use of respiratory pharmacotherapy may in turn influence risk adverse health outcomes.
Self-reported influenza vaccination within the year prior to the index date	CCHS. Based on the following two questions: "Have you ever had a seasonal flu shot?" (with possible responses including yes and no) and "When did you last have your seasonal flu shot?" (with possible responses including less than one year ago, one year to less than two years ago, and more than two years ago). Influenza vaccination receipt was a potential confounder in our analysis, because individuals using cannabis may be more likely (or not) to receiving this treatment and this factor may in turn influence risk adverse health outcomes.
Year of CCHS interview (i.e., year of cohort entry)	CCHS.

CCHS= Canadian Community Health Survey; CHF= congestive heart failure; CIHI-DAD= Canadian Institutes for Health Information Discharge Abstract Database; COPD= chronic obstructive pulmonary disease; DSM4= Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition; ER= emergency room; NACRS= National Ambulatory Care Reporting System; OHIP= Ontario Health Insurance Plan; OMHRS= Ontario Mental Health Reporting Database; OMID= Ontario Myocardial Infarction Database; RPD= Registered Persons Database.

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Section 3: Additional sensitivity analysis.

Our outcomes were also estimated over a 3-year period following the index date, in order to assess if a different pattern of outcomes might be observed after considering a potentially longer duration of cannabis use. In order to account for potentially more variable follow-up time periods among individuals as a result of death, Cox proportional hazard regression (rather than logistic regression) was instead used for this specific sensitivity analysis, estimating hazard ratios [HR] with 95% confidence intervals (CI).

Similar to our main cohort results, there were no significant differences in respiratory-related ER visit or hospitalization, or all-cause mortality, between cannabis users and controls, but cannabis users were observed to have significantly elevated odds of all-cause ER visit or hospitalization (HR 1.16, 95% CI 1.11-1.21, number needed to harm [NNH] 20) (eTable 1).

eTable 1. Hazard ratios and confidence intervals for outcomes in the overall propensity-score matched cohort, considering a 3-year follow-up period

Outcomes	Cannabis use status	Number of events (%)	HR (95% CI), *P*-value
Respiratory-related ER visit or hospital admission	Cannabis users	442 (9.2)	0.98 (0.88-1.09), *P*=0.70
	Control group	997 (9.4)	1.00
All-cause ER visit or hospital admission	Cannabis users	2668 (55.5)	1.16 (1.11-1.21), *P* <0.0001
	Control group	5262 (50.6)	1.00
All-cause mortality	Cannabis users	32 (0.7)	0.90 (0.60-1.35), *P*=0.26
	Control group	77 (0.7)	1.00

CI= confidence interval; ER= emergency room; HR= hazard ratio; N= number