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Primary care-based smoking cessation treatment and subsequent healthcare service utilisation: a matched cohort study of smokers using linked administrative healthcare data

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ABSTRACT

Background No research has assessed the individual-level impact of smoking cessation treatment delivered within a general primary care patient population on multiple forms of subsequent healthcare service use.

Objective We aimed to compare the rate of outpatient visits, emergency department (ED) visits and hospitalisations during a 5-year follow-up period among smokers who had and had not accessed a smoking cessation treatment programme.

Methods The study was a retrospective matched cohort study using linked demographic and administrative healthcare databases in Ontario, Canada. 9951 patients who accessed smoking cessation services between July 2011 and December 2012 were matched to a smoker who did not access services, obtained from the Canadian Community Health Survey, using a combination of hard matching and propensity score matching. Outcomes were rates of healthcare service use from index date (programme enrolment or survey response) to March 2017.

Results After controlling for potential confounders, patients in the overall treatment cohort had modestly greater rates of the outcomes: outpatient visits (rate ratio (RR) 1.10, 95% CI: 1.06 to 1.14), ED visits (RR 1.08, 95% CI: 1.03 to 1.13) and hospitalisations (RR 1.09, 95% CI: 1.02 to 1.18). Effect modification of the association between smoking cessation treatment and healthcare service use by prevalent comorbidity was found for outpatient visits ($p=0.006$), and hospitalisations ($p=0.050$), but not ED visits.

Conclusions Patients who enrolled in smoking cessation treatment offered through primary care clinics in Ontario displayed a modest but significantly greater rate of outpatient visits, ED visits and hospitalisations over a 5-year follow-up period.

INTRODUCTION

Worldwide, smoking remains a leading cause of premature death and disability¹ and billions of dollars in lost productivity and healthcare resource use are related to smoking every year.^{1,2} To combat this burden, the WHO's Framework Convention on Tobacco Control (FCTC) recommends the provision of effective tobacco dependence treatment using existing healthcare infrastructure as much

as possible; integrating cessation support into the primary healthcare system is an essential component of any tobacco control strategy.³ Almost all high-income countries make cessation services available with 90% offering at least partial cost coverage.³

There is a wealth of high quality research on the clinical effectiveness of smoking cessation treatment.^{4–6} Yet, the translation of clinical effectiveness of smoking cessation treatment on healthcare service use using real-world evidence has received limited attention in the literature.⁷

Prior research has largely focused on the effect of smoking cessation treatment provided to hospitalised patients on subsequent re-hospitalisation.^{8–12} Overall, the evidence suggests that hospital-based cessation programmes can lower re-admission rates.¹³ This evidence is limited to the subpopulation of smokers accessing tertiary care due to significant existing comorbidities. To our knowledge, only one study has examined healthcare service use among a broad general patient base of smokers.¹⁴ Patients who accessed a smoking cessation pharmacotherapy benefit experienced a decrease in hospitalisations for acute myocardial infarction and atherosclerosis but not for other cause-specific diagnoses.

Chronic conditions that are more common among people who smoke, such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease, are associated with increased levels of healthcare service use.^{15–19} Although quitting smoking has been shown to provide health benefits for these and other diseases, the degree of health benefits and period of abstinence over which they are observed is variable.²⁰ As such, the impact on healthcare service use following smoking cessation treatment may vary between groups with different comorbidities.

No research to date has assessed the real world individual-level impact of smoking cessation treatment delivered within a general primary care patient population on multiple types of healthcare service use. Therefore, using linked administrative healthcare data, we compared outpatient visits, emergency department (ED) visits and hospitalisations among smokers who had and had not accessed a smoking cessation treatment programme, and interactions with prevalent comorbidities, in Ontario, Canada.



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METHODS

Study design

This retrospective matched cohort study used routinely collected smoking cessation treatment programme data linked to population-based administrative and demographic databases housed at ICES (<https://www.ices.on.ca>). 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. These data sets were linked using unique encoded identifiers and analysed at ICES. The study is reported in accordance with REporting of studies Conducted using Observational Routinely-collect Data (RECORD) guidelines.²¹

Setting

Canada's province of Ontario has a population of 13.5 million,²² with 1.8 million smoking cigarettes daily or occasionally (1.1 million men and 700 000 women).²³ Medically required healthcare services are paid for by the province through the Ontario Health Insurance Plan (OHIP). The Smoking Treatment for Ontario Patients (STOP) programme delivers smoking cessation treatment at partnering healthcare organisations and is also publicly funded. Patients can enrol through either practitioner-referral or self-referral. It is a pragmatic, real-world programme in which treatment, consisting of nicotine replacement therapy for up to 26 weeks and behavioural counselling, is individually tailored. STOP is effective with 26% of patients reporting abstinence at 6-month follow-up.²⁴ Additional details are provided in online supplemental appendix S1.

Study population

The treatment cohort initiated smoking cessation treatment with the STOP programme between 01 July 2011 and 31 December 2012. Patient-level data were previously linked to ICES data holdings using probabilistic and deterministic linkage with a 96% linkage rate.²⁵ Ninety per cent of patients who enrolled during the study time frame consented to linkage. For any patient who enrolled more than once, data related to their first enrolment was used. A treated patient's index date was the date of enrolment. Patients accessed treatment at one of three organisation types with greater than 99% attending a primary care clinic.

The control cohort of Ontario smokers, not using STOP services, was assembled using the Canadian Community Health Survey (CCHS), that has been linked to ICES databases. The CCHS is a cross-sectional survey conducted by Statistics Canada that collects self-reported health-related data from about 130 000 Canadians in every 2-year cycle.²⁶ It is representative of approximately 98% of the Canadian population aged 12 and older residing in private households; detailed survey methodology is reported elsewhere.²⁷ Approximately 84.7% of respondents residing outside the province of Quebec agreed to linkage of their data, with variation across survey years.²⁸ We used three cycles of the CCHS to increase sample size^{29 30}: 2007/2008, 2009/2010 and 2011/2012. For any respondent in multiple cycles, data from their most recent survey was used to better align with the time frame for the treatment cohort. A respondent's index date was the date they completed the survey. The study time frame was selected because it marked initiation of these STOP models, had linked CCHS data from which to select controls and allowed up to 5 years of follow-up time.

In both cohorts, individuals were excluded if sex was missing, they had an invalid record, they were ineligible for OHIP

coverage, did not reside in Ontario at index date, had a date of death that preceded index date, were not smoking daily or occasionally, age was less than 12 or greater than 105 years or lacked a full 2-year lookback window. Additionally, individuals in the potential treatment cohort that also completed the CCHS were excluded if they reported not smoking in the survey.

Each treated individual was matched to one control individual using hard (sex and age at index ± 2 years) and propensity score matching. The propensity score was obtained using multivariable logistic regression with the following covariates: age at index date (continuous with linear and quadratic terms), education quintile, household income quintile, number of cigarettes smoked per day at index (continuous with linear and quadratic terms), age first started smoking (continuous with linear and quadratic terms), number of Aggregated Diagnostic Groups (ADGs) categorical (0–5, 6–9, 10+) and the rate of ED visits and rate of hospitalisations in the 2 years prior to index date. Missing values of categorical variables were coded as a distinct category and were included in the propensity score. Missing values of continuous variables were not included in the propensity score and patients were not matched. Once propensity scores were estimated, 1:1 matching was completed using a greedy algorithm with no replacement based on a calliper width of 0.2 SD of the logit of the estimated propensity score.³¹

Healthcare service utilisation outcomes

The primary outcomes were the rate of outpatient visits, rate of ED visits and rate of all-cause hospital admissions. For each outcome, every individual could experience multiple occurrences throughout their observation period. Times to each occurrence were measured in years from index date until 31 March 2017, death or loss of OHIP eligibility, whichever occurred first. Online supplemental table S1 describes the derivation of outcome variables.

Baseline characteristics

The following self-reported descriptive characteristics were measured at index in the treatment programme intake data or CCHS survey: frequency of smoking, number of cigarettes smoked per day and age first tried smoking. Duration of smoking was calculated using an individual's age at index, from ICES data sets, and age of smoking initiation, from STOP and CCHS surveys.

Additional individual-level characteristics measured at index were derived via linkage to ICES data sets: age at index, sex and migrant status. The following prevalent comorbidities were obtained from existing ICES-derived data sets built by applying standardised algorithms: diabetes, hypertension, COPD, asthma, congestive heart failure and myocardial infarction. Ecological-level measures of neighbourhood educational, employment and income quintiles, and rurality were estimated using data from the 2006 Canadian census³² and were applied to individuals according to the smallest geographical census area in which they resided at index. Prior healthcare utilisation, and comorbidity burden derived from ADG scores, were estimated using a 2-year lookback window from index date. The Johns Hopkins ACG® System Aggregated Diagnosis Groups (Version 10) provide a numeric method for grouping diagnostic codes similar in severity and likelihood of persistence. They have previously been validated for use in the adult Ontario population.³³ Online supplemental table S1 describes derivation of the baseline characteristic variables.

Statistical analyses

Distributions of baseline characteristics were reported using frequencies and percentages for categorical measures and mean and SD for continuous measures. Balance between treated and control groups was assessed using standardised mean differences (SMD), where a SMD of greater than 10%³⁴ implies a meaningful imbalance. Initial crude analyses were conducted by calculating the total number of ED visits, outpatient visits and hospital admissions, and corresponding crude rates (per person-year) with CIs for rates generated under Poisson assumptions.³⁵ Based on a recurrent event and counting process framework, for each outcome, the non-parametric mean cumulative function approach was used to illustrate the mean cumulative number of events as a function of time, along with 95% CIs.³⁶

Multivariable Andersen-Gill (AG) recurrent event regression models were implemented on our matched cohort to examine the association between exposure to smoking cessation treatment and the rate of each outcome.^{37–39} Attained age was used as the time scale. For each outcome, the event times for an individual were the times from their index date to the date of each occurrence. Individuals were right-censored at the end of their observation window. A robust sandwich variance estimation approach was used to account for the matched design. As decided a priori, characteristics that remained unbalanced in our matched cohort at baseline between treated and control groups were included as covariates in multivariable AG regression models to account for possible confounding. Interactions with treatment (our main exposure) and comorbidities (COPD and hypertension) were also examined to determine if the association between exposure to the smoking cessation treatment and outcome rates varied by presence of comorbidity.

All analyses discussed above were conducted on the overall matched cohort and stratified by sex. Analyses were performed using the SAS Enterprise Guide V7.12 (2016, SAS Institute). Statistical tests were two-sided; an alpha of less than 0.05 was considered statistically significant.

RESULTS

Derivation and baseline characteristics by cohort

Between 01 July 2011 and 31 December 2012, 13 561 Ontario smokers used the smoking cessation treatment programme and had data linked to ICES data holdings. After applying the exclusion criteria described above, there were 12 965 individuals in the potential treatment cohort available for matching. Of the 19 771 CCHS respondents who were smokers, 19 260 were in the potential control cohort and available to serve as matches (see online supplemental figure S1).

Prior to matching, the potential treatment and control cohorts were unbalanced on several demographic characteristics: the potential treatment cohort smoked more, had a greater number of comorbidities and a higher rate of prior healthcare utilisation (see online supplemental tables S2 and S3). Of the 12 965 individuals in the potential treatment cohort, 9951 were matched to a control smoker. After matching, the majority of baseline characteristics became well matched (SMD <0.1); differences remained in smoking frequency and comorbidities (see table 1 and online supplemental table S4). The median follow-up time in the treatment cohort and control cohorts were 4.8 and 6.1 years, respectively.

Healthcare service use during follow-up

Of the 9951 individuals in the treatment cohort, 9793 (98.4%), 7944 (79.8%) and 3499 (35.2%) had at least one outpatient visit,

Table 1 Baseline characteristics and prior healthcare service use of matched treatment and control cohorts

	Treatment cohort (n=9951)	Control cohort (n=9951)	SMD
Sociodemographic characteristics			
Age, mean±SD	48.96±14.18	48.98±14.17	0
Sex			
Female	5257 (52.8)	5257 (52.8)	0
Male	4694 (47.2)	4694 (47.2)	0
Education quintile			
Missing	556 (5.6)	541 (5.4)	0.01
Q1 (lowest)	690 (6.9)	661 (6.6)	0.01
Q2	1485 (14.9)	1461 (14.7)	0.01
Q3	1989 (20)	1977 (19.9)	0
Q4	2523 (25.4)	2548 (25.6)	0.01
Q5 (highest)	2708 (27.2)	2763 (27.8)	0.01
Employment quintile			
Missing	556 (5.6)	541 (5.4)	0.01
Q1 (lowest)	2196 (22.1)	2234 (22.5)	0.01
Q2	2013 (20.2)	1876 (18.9)	0.03
Q3	1787 (18)	1915 (19.2)	0.03
Q4	1745 (17.5)	1746 (17.5)	0
Q5 (highest)	1654 (16.6)	1639 (16.5)	0
Rurality + neighbourhood income quintile			
Missing	19 (0.2)	19 (0.2)	0
Rural	2381 (23.9)	2383 (23.9)	0
Urban Q1 (lowest)	2196 (22.1)	2166 (21.8)	0.01
Urban Q2	1579 (15.9)	1597 (16)	0
Urban Q3	1431 (14.4)	1477 (14.8)	0.01
Urban Q4	1336 (13.4)	1321 (13.3)	0
Urban Q5 (highest)	1009 (10.1)	988 (9.9)	0.01
Migrant status			
Immigrant*	262 (2.6)	267 (2.7)	0
Non-immigrant	9689 (97.4)	9684 (97.3)	0
Smoking characteristics			
Frequency of smoking			
Daily	9745 (97.9)	9133 (91.8)	0.28
Occasional	206 (2.1)	818 (8.2)	0.28
Cigarettes per day, mean±SD	17.82±9.77	17.56±9.56	0.03
Age first tried smoking, mean±SD	15.82±4.81	15.69±4.67	0.03
Duration smoking (years), mean±SD	33.14±14.41	33.29±14.20	0.01
Health comorbidities			
Prevalent comorbidities			
COPD	2985 (30)	2018 (20.3)	0.23
Hypertension	2863 (28.8)	2694 (27.1)	0.04
Diabetes	1515 (15.2)	1146 (11.5)	0.11
Asthma	1882 (18.9)	1474 (14.8)	0.11
Cancer	448 (4.5)	400 (4)	0.02
Myocardial infarction	332 (3.3)	248 (2.5)	0.05
Congestive heart failure	235 (2.4)	193 (1.9)	0.03
No. ADG comorbidities, mean±SD	5.84±3.43	5.45±3.63	0.11
0–5	5149 (51.7)	5177 (52)	0.01
6–9	3314 (33.3)	3355 (33.7)	0.01
10+	1488 (15)	1419 (14.3)	0.02

Continued

Table 1 Continued

	Treatment cohort (n=9951)	Control cohort (n=9951)	SMD
Rate of healthcare service use ppy†			
Outpatient visits (mean±SD)	6.61±8.62	6.16±7.64	0.06
ED visits (mean±SD)	0.89±1.40	0.83±1.50	0.04
Hospitalisations (mean±SD)	0.13±0.38	0.12±0.37	0.02

Number (%) are reported unless otherwise noted.

*Includes immigrants and refugees.

†During 2-year period up to index date.

ADG, Aggregated Diagnostic Groups; COPD, chronic obstructive pulmonary disease; ED, emergency department; ppy, per person year; Q, quintile; SMD, standardised mean difference.

ED visit or hospitalisation, respectively. Similarly, of the 9951 individuals in the control cohort, 9606 (96.5%), 7844 (79.8%) and 3815 (38.3%) had at least one outpatient visit, ED visit or hospitalisation, respectively. Table 2 shows the crude rates of outpatient visits, ED visits and hospitalisations in the matched treatment and control cohorts, overall and by sex. Patterns were similar for outpatient and ED visits: the rates were higher in the treatment cohort than in the control cohort. This was observed in the overall and sex-stratified cohorts. Within treatment and control cohorts, crude rates were higher in women than in men. For hospitalisations, the overall pattern observed was similar to that for outpatient and ED visits, but with differences attenuated. These findings are depicted visually in figure 1, which plots the estimated mean cumulative number of outpatient visits, ED visits and hospitalisations during follow-up (and 95% CIs) for the treatment and matched control cohorts, both overall and by sex. Point estimates at 2 and 5 years are provided; for example, 5 years after index date the cumulative number of outpatient visits in the overall cohorts were 35.02 and 31.16 among the treatment and control cohorts, respectively.

Adjusted association between smoking cessation treatment and healthcare service use

Compared with matched controls, after controlling for potential confounders, patients in the overall treatment cohort had

Table 2 Crude rates and adjusted associations between smoking cessation treatment and healthcare service use outcomes in Ontario, Canada, between 2011 and 2017, in matched treatment and control cohorts, overall and stratified by sex

Outcome	Sex	Unadjusted mean±SD rate ppy		Adjusted rate ratio (95% CI)
		Treatment cohort	Control cohort	
Outpatient visits	Overall	7.52±10.26	6.73±8.42	1.10 (1.06 to 1.14)
	Female	8.03±10.06	7.44±8.40	1.08 (1.03 to 1.12)
	Male	6.95±10.46	5.93±8.38	1.13 (1.07 to 1.19)
ED visits	Overall	1.03±1.78	0.88±1.67	1.08 (1.03 to 1.13)
	Female	1.06±1.77	0.95±1.72	1.05 (0.98 to 1.12)
	Male	0.99±1.80	0.80±1.60	1.13 (1.05 to 1.20)
Hospitalisations	Overall	0.23±0.81	0.21±0.68	1.09 (1.02 to 1.18)
	Female	0.23±0.84	0.21±0.73	1.09 (1.00 to 1.19)
	Male	0.24±0.78	0.20±0.63	1.10 (0.98 to 1.24)

Bolded rate ratios are significant at p<0.05.

ED, emergency department; ppy, per person year.

significantly greater rates of each of the three healthcare service use outcomes. The magnitude of the positive associations was modest. Stratified by sex, a positive association between smoking cessation treatment and healthcare service use was observed for ED visits among men only, and for outpatient visits among women and among men, but the magnitude of association was greater in men. Findings were inconclusive as to whether there was an association observed for hospitalisations among women or among men (see table 2).

Effect modification of the association between smoking cessation treatment and healthcare service use by prevalent comorbidity was found for outpatient visits in the overall cohort (p=0.006), with no difference in rates versus controls in patients with prevalent hypertension (figure 2). These effects were primarily driven by differences in women, among whom rates were significantly greater versus controls in patients with neither hypertension nor COPD. In patients with either one or both conditions, findings were inconclusive as to whether or not there was a difference between treatment and control cohorts. Statistically significant effect modification was also found in the overall cohort for hospitalisations, with greater rates versus controls in patients with neither prevalent hypertension nor COPD, and in patients with COPD only, than among patients with hypertension only or both conditions; p=0.05). The complete multivariable regression estimates are available in online supplemental tables S5–S13.

DISCUSSION

In this study of 19902 matched smokers, we found a slightly greater rate of outpatient visits, ED visits and hospitalisations among smokers who had accessed the smoking cessation treatment programme compared with smokers who did not. In analyses stratified by sex, the increased rate of outpatient visits was observed among men and women, while the increased rate of ED visits was restricted to men only. The increased rate of hospitalisations was observed in the overall cohort but not when stratified by sex.

The difference in healthcare service use between the intervention and matched control groups was greater among those patients who did not have pre-existing comorbid conditions—and lesser among patients who did. The implication is that for patients who are already engaged with the healthcare system for the diagnosis and treatment of chronic disease, the addition of smoking cessation treatment has less impact on the subsequent rate of healthcare use. This is an important finding because COPD and hypertension were common in the matched cohorts and are common in people who smoke generally.

Our findings contrast with prior studies that showed a decrease in healthcare service use associated with smoking cessation treatment.^{8–12 14} A possible explanation for the contradictory findings may lie with differences in treatment setting, patient population and healthcare service outcome measures in our and most prior studies. Patients in primary care settings are less likely to have severe comorbidities requiring hospitalisation; indeed 83.2% of individuals in our matched treatment cohort had not been hospitalised in the 2 years prior to index date. By focusing on hospitalised patients, and re-hospitalisation outcome measures, previous investigations have focused on narrower populations, and possibly ones likely to benefit from an intervention in the short-term during a teachable moment.¹³ In the singular prior study¹⁴ that also had a general population of smoking cessation treatment users, the likelihoods of hospitalisations for two indications (myocardial infarction and atherosclerosis) were

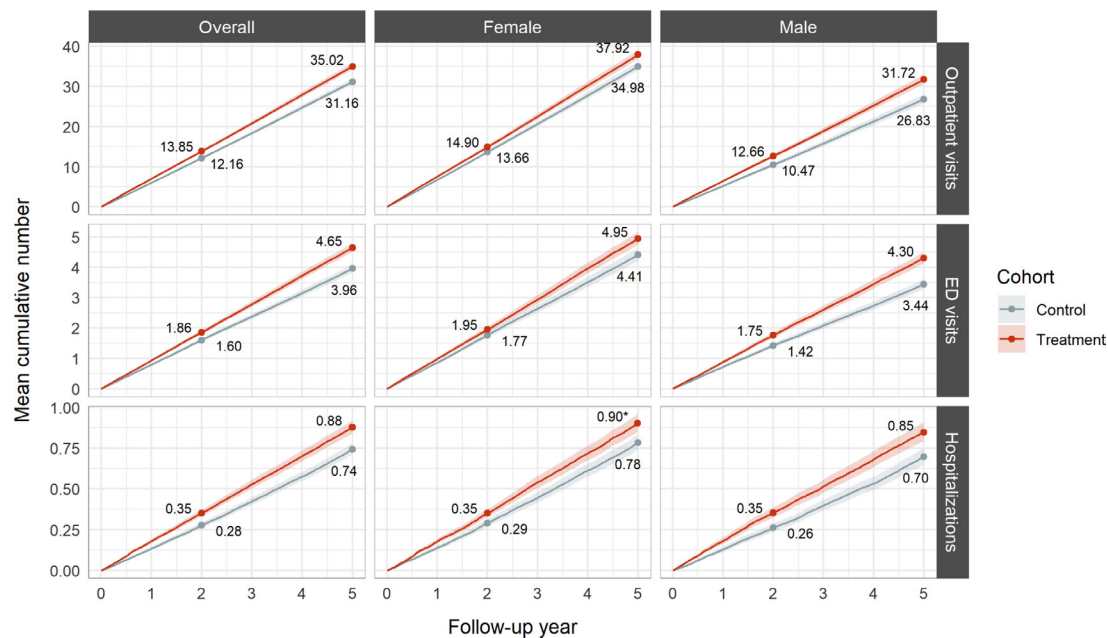


Figure 1 Estimated mean cumulative number of outpatient visits, emergency department visits and hospitalisations in Ontario, Canada, between 2011 and 2017, in matched treatment and control cohorts, overall and stratified by sex. *Mean cumulative number of hospitalisations for women in the Smoking Treatment for Ontario Patients cohort at year 4.99. ED, emergency department.

decreased, but no decrease or increase for 13 other cause-specific hospitalisations or all-cause hospitalisations were observed. The prior literature, with its dearth of directly relevant studies, does not provide a strong context into which to place our results. The related literature, however, linking smoking status itself with healthcare service utilisation is relevant. Relative to never smokers, current smokers have greater healthcare service utilisation in most,^{40–48} but not all,^{41 42 49} analyses. While there is some evidence that healthcare service use is also lower among former smokers relative to current smokers,^{40 43} in various analyses smoking cessation is associated with a short-term increase in usage that remains above that of, similar to, or below that of, current smokers,^{41–43 46 47} or is not associated with any increase or decrease.^{41 43 50} These findings provide conflicting and indirect evidence that smoking cessation may reduce healthcare service use but that reductions may not be realised for some time.

In our study, the rate of healthcare service use in the 2 years prior to the index date was similar in the matched cohorts. Since the number of patients who quit smoking is likely greater in the treatment cohort than the control cohort,^{13 24 51 52} if quitting smoking results in decreased healthcare service use then it follows that healthcare service use should be lower on average in the treatment cohort than the control cohort. As that was not observed, these findings suggest that, in the population of Ontarian smokers, either the beneficial effect of smoking cessation treatment on healthcare service use among those patients who achieve abstinence is outweighed by the lack of such effect among the majority of patients who do not achieve abstinence, or there is no such beneficial effect during the first 5 years following initiation of smoking cessation treatment.

Further research should build on these findings. It is unclear in the observed increased healthcare service use is a positive or negative consequence of smoking cessation treatment and what mechanisms underlie the observed association. Our study lacked longitudinal measures of smoking status or complex smoking cessation trajectories due to the absence of such data in routinely collected administrative healthcare data. Longitudinal studies

of smokers, if linked to administrative healthcare data and of sufficient size to have robust numbers of treatment seeking smokers, could help address these important gaps. Additionally, patients in Ontario do not incur personal costs (eg, service fees or copays) to access ED, outpatient or hospitalisation services; further research is warranted to assess the impact of smoking cessation treatment in jurisdictions where these barriers to healthcare service use exist.

Assessing the healthcare system implications associated with uptake of available smoking cessation treatment services is important for tobacco control experts and healthcare system planners internationally. Relatively few smokers who attempt to quit use available smoking cessation resources.⁵³ However, tobacco control policies, such as increased taxation, anti-smoking media campaigns and comprehensive smoke-free policies, increase the demand for tobacco dependence treatment and therefore, continued capacity building and adoption of FCTC guidelines may both increase interest in smoking cessation treatment and provide guidelines for implementation in primary care settings.⁵³

Strengths of this study include the use of a non-treatment seeking control group. Such a control group cannot be derived from typical administrative healthcare data and was possible due to the prior linkage of very large population based health survey data. Additionally, use of a concurrent control group allowed for avoidance of temporal differences that can impact results when a pre-post design is used. Lastly, all outcomes in both treatment and control groups were ascertained identically using healthcare administrative databases therefore bias resulting from differential missing data are unlikely.

This study also has limitations. First, the exposure, which necessarily requires both motivation to quit smoking and a willingness to engage with smoking cessation treatment, cannot be randomised. Although we accounted for a range of factors through hard and propensity score matching and adjustment for potential confounders, there is potential for unmeasured or residual confounding. Second, the statistical analyses necessarily

Figure 2. Adjusted association between smoking cessation treatment and healthcare service use outcomes in Ontario, Canada between 2011 and 2017, in matched treatment and control cohorts, and interactions with prevalent hypertension and prevalent COPD, overall and stratified by sex.

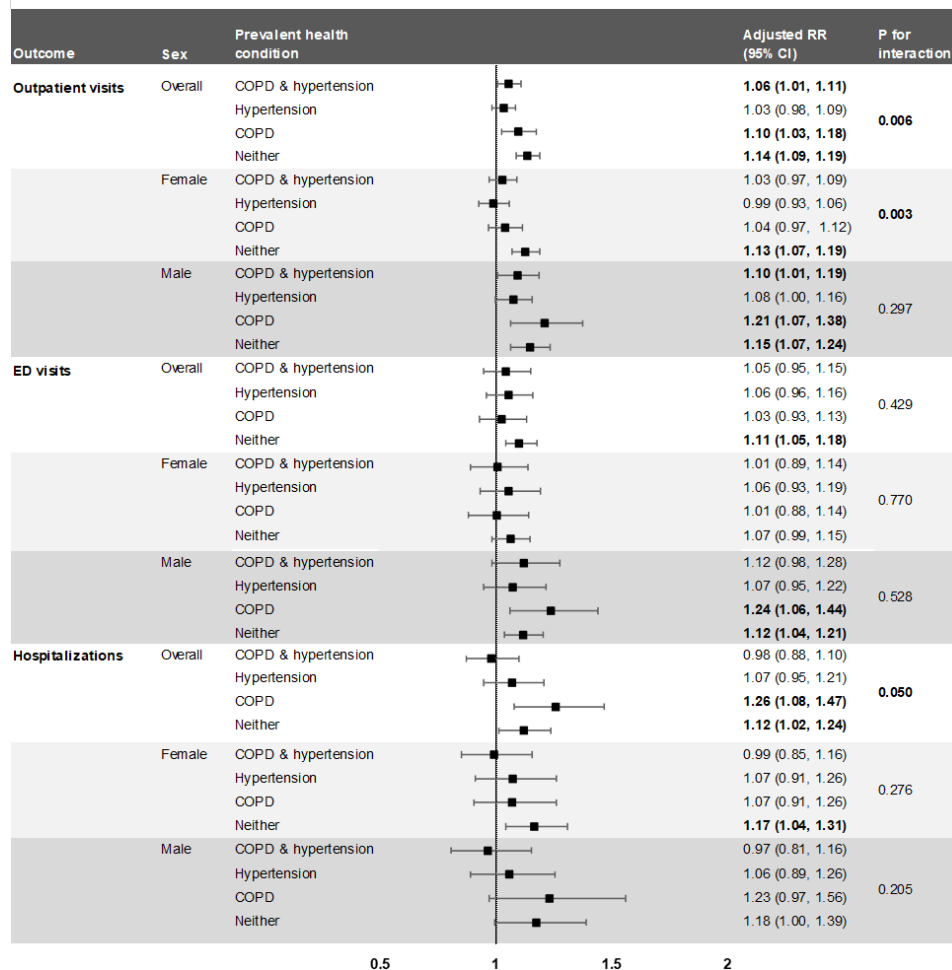


Figure 2 Adjusted association between smoking cessation treatment and healthcare service use outcomes in Ontario, Canada, between 2011 and 2017, in matched treatment and control cohorts, overall and stratified by sex. Bolded RRs are significant at $p < 0.05$. COPD, chronic obstructive pulmonary disease; ED, emergency department; RR, rate ratio.

were restricted to treatment patients who were successfully matched to a control, thus including the majority of, but not all, patients. We combined cycles of the CCHS in order to increase the number of potential matches, but residual differences may have occurred affecting generalisability. Third, the length of follow-up in our study is insufficient to ascertain any long-term impacts of smoking cessation treatment on healthcare service utilisation.

CONCLUSIONS

Primary care-based smoking cessation treatment in Ontario, Canada, was associated with a small but significant increase in the rate of all-cause outpatient visits, ED visits and hospitalisations, but there was significant heterogeneity in some outcomes depending on sex and the presence of comorbid COPD and hypertension.

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Competing interests DB reports receiving grant funding in the past 5 years from Pfizer, Ontario Ministry of Health and Long-Term Care, Canadian Institutes of Health Research (CIHR) and the Canadian Cancer Society Research Institute (CCSRI). PS reports receiving funding in the past 3 years from CCSRI, CIHR, Canadian Partnership Against Cancer, Centre for Addiction and Mental Health (CAMH), Health Canada, Medical Psychiatry Alliance, Ontario Ministry of Health and Long-Term Care, Ontario Neurotrauma Foundation and the Public Health Agency of Canada. PS also reports funding from the following commercial organisations: Patient-Centred Outcome Research Institute and Pfizer. PS has received honoraria in the past 3 years from University of Ottawa Heart Institute, Royal College of Physicians and Surgeons of Canada, Royal Victoria Regional Health Centre, Department of Family and Community Medicine at the University of Toronto, Northern Ontario School of Medicine, Canadian Partnership Against Cancer, Battle River Treaty 6 Healthcare, Lung Association of Nova Scotia, Exchange Summit, Toronto Public Health, Ontario Association of Public Health Dentistry and ECHO. PS has been retained as an expert witness by the Ontario and New Brunswick provincial governments in litigation against the tobacco industry. PS was a member and co-chaired the Ministry of Health's Ontario Smoke Free Strategy cessation subcommittee. Through an open tender process, Johnson & Johnson, Novartis and Pfizer are vendors of record for providing free/discounted smoking cessation pharmacotherapy for research studies in which PS and/or LZ are principal or co-investigator. CdO reports receiving grant funding in the past 5 years from CIHR, University of Toronto, Medical Research Council, National Institutes of Health, CAMH, Alberta Innovates, Ontario Ministry of Health and Long-Term Care, Canadian Centre for Applied Research in Cancer Control and Ontario Mental Health Foundation. PK reports receiving grant funding in the past 5 years from CIHR and the Ontario Ministry of Health and Long-Term Care. LR reports receiving grant funding in the past 5 years from CIHR, New Frontiers in Research Fund, Canada Research Chairs and the Connaught Foundation. LZ reports receiving grant funding in the past 5 years from Pfizer, Ontario Ministry of Health and

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Patient consent for publication Not required.

Ethics approval The Centre for Addiction and Mental Health Research Ethics Board approved this study (#110/2019), data linkage (#027/2016) and smoking cessation treatment models (#058/2011, #154/2012), and patients provided written informed consent.

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Data availability statement The data set from this study, composed of STOP programme data and ICES data sets, is held securely in coded form at ICES. While data sharing agreements and privacy legislation for the province of Ontario prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at <https://www.ices.on.ca/DAS>. Requests to access ICES data may be submitted to ICES Data & Analytic Services at das@ices.on.ca, with information available at <https://www.ices.on.ca/DAS/Submitting-your-request>. One of the authors (LF) had access to the linked databases and conducted all analyses.

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What this paper adds

What is already known on this subject

- Hospital-based smoking cessation programmes, an intervention that takes place during a teachable moment, can lower subsequent hospital re-admission rates.

What important gaps in knowledge exist on this topic

- The translation of the clinical effectiveness of primary-care based smoking cessation programmes, which serve patients less likely to have severe comorbidities requiring hospitalisation, on healthcare service use using real-world evidence has received limited attention in the literature.
- Only one study has examined healthcare service use among a broad general patient base of smokers that accessed smoking cessation treatment. A decrease in hospitalisations for two indications was observed, but no decrease or increase for 13 other cause-specific hospitalisations or all-cause hospitalisations.
- The impact on other healthcare service types has not been assessed.

What this paper adds

- Primary care-based smoking cessation treatment was associated with a small increase in the rate of all-cause outpatient visits, ED visits and hospitalisations
- For patients who are already engaged with the healthcare system for the diagnosis and treatment of chronic disease, the addition of smoking cessation treatment had less impact on the subsequent rate of healthcare use.

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Appendix S1. Smoking cessation treatment description.**Target patient population**

Patients who enroll in the Smoking Treatment for Ontario Patients (STOP) program are cigarette smokers who want help to quit smoking, reduce smoking, or maintain a recent quit attempt. There are no age exclusions and minors may enroll with the consent of their parent or legal guardian. Patients can enroll through either practitioner- or self-referral, provided they are a rostered or registered patient with an organization delivering the STOP program. Prior to receiving treatment, patients must provide informed consent to treatment and complete an initial assessment to collect relevant background information such as smoking history, comorbid conditions and other substance use. Patients are also invited to complete follow-up surveys 3, 6 and 12 months after enrollment, online or via telephone, to assess smoking status and other outcomes.

Centralized model

The Nicotine Dependence Service at the Centre for Addiction and Mental Health acts as a central hub that coordinates and supports implementation of the STOP program, while partnering healthcare organizations deliver smoking cessation treatment services to patients. Centralized components of the program include nicotine replacement therapy (NRT) inventory management, ongoing education for providers, and follow-up with program participants for research and quality improvement purposes. While some key features of treatment remain consistent across sites (e.g., quantity and types of NRT permitted), individual providers or sites are otherwise free to modify delivery of the program so that the program is flexible enough to be implemented by

organizations varying in capacity, priorities and other factors. The patient accesses treatment at the healthcare organization where they are rostered, by their own healthcare provider(s).

Treatment description

Smoking cessation treatment is comprised of NRT and behavioural counseling. The number, frequency or duration of treatment visits is not proscribed and can be adjusted based on patient need, though providers typically meet with patients every 2 to 4 weeks. Patients are eligible to receive up to 26 weeks of NRT in a 12-month period; up to 4 weeks of NRT may be dispensed at a single visit (exceptions may be permitted). Formulation and dose of NRT are tailored based on patient need, preference and previous history of NRT use. Both long-acting (patch) and several types of short-acting NRT (e.g., gum, lozenge, inhaler) are available. Prescribing a combination of nicotine patch and short-acting NRT or patch doses exceeding 21 mg per day are permitted based on the discretion of the health provider. Although counselling is a central component of the smoking cessation treatment provided, the format (i.e., individual or group), content, frequency and duration of counselling provided is not proscribed and may vary.

Program inception and partnering organizations

The STOP program delivers smoking cessation treatment at partnering healthcare and public health organizations across the province of Ontario, Canada. STOP is publicly funded by the province's Ministry of Health, under the auspices of the Smoke-Free Ontario Strategy. Initially launched in 2005, STOP has delivered several different treatment models over time [1-6]. The treatment models available at any given time varies, as the program has evolved iteratively in response to changes in budget, policy, government priorities, and evidence. To date, the STOP

program has had over 270,000 enrollments and is currently available to patients at over 300 healthcare provider organizations across Ontario.

This paper reports on data collected from patients that enrolled in the STOP program at Family Health Teams (FHTs), Community Health Centres (CHCs) and Addiction Agencies (AAs) from initial implementation (FHTs, July 2011; CHCs, February 2012; AAs, October 2012) to December 2012. There were 15,962 enrollments at the 122 FHTs, 39 CHCs and 1 AA that partnered with STOP during this time.

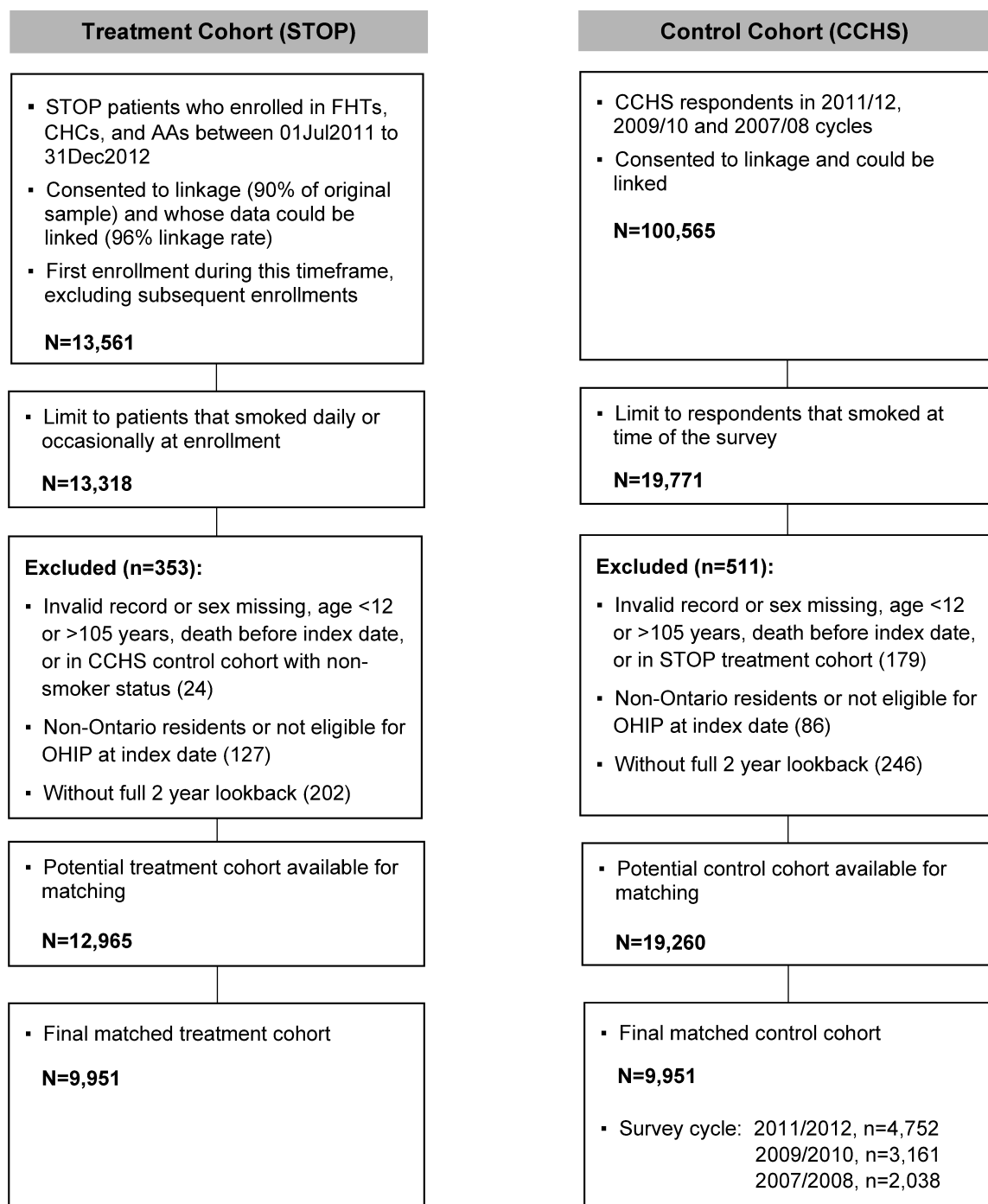
FHTs and CHCs deliver primary care services to patients using a collaborative, interprofessional team approach. CHCs integrate primary care with other health promotion services and community partnerships to foster the health of the local community they serve, including addressing social determinants of health. AAs provide treatment services for substance use problems and addiction. Each of these services are available to Ontarians through the province's universal healthcare system.

Providers implementing the STOP program are trained in cessation counseling and continuing education is available to them through bi-weekly teleconferences and monthly lunch-and-learn webinars. Health providers include nurses, physicians, social workers, and other health professionals.

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Figure S1. Flow chart of derivation of treatment and control cohorts.

Abbreviations: CCHS = Canadian Community Health Survey; STOP = Smoking Treatment for Ontario Patients; AA = Addiction Agency; CHC = Community Health Centre; FHT = Family Health Team; OHIP = Ontario Health Insurance Plan.

Table S1. Variable derivation.

Variable	Source
Individual-level smoking characteristics (self-report)	
Frequency of smoking	STOP intake and CCHS surveys.
Number of cigarettes smoked per day	STOP intake and CCHS surveys.
Age first tried smoking	STOP intake and CCHS surveys.
Duration of smoking	Age at index – age first tried smoking.
Individual-level sociodemographic characteristics (data linkage)	
Age	Registered Persons Database, contains information on all persons registered with the Ontario Health Insurance Plan (OHIP).
Sex	Registered Persons Database, contains information on all persons registered with the Ontario Health Insurance Plan (OHIP).
Immigrant status	Immigration, Refugee and Citizenship Canada Permanent Resident database. Immigrants, refugee and other immigrants collapsed. If not in database, classified as not immigrant.
Prevalent comorbidities	Validated algorithms (see below) were used to determine prevalence of the following comorbidities: asthma, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, hypertension and myocardial infarction. Prior cancer diagnosis was ascertained using the Ontario Cancer Registry.
Comorbidity burden in 2 years up to index	Aggregated Diagnosis Groups (ADGs) score was based on previous health care use captured in the Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan database, and the Canadian Institute for Health Information Same Day Surgery Database.
Ecological-level sociodemographic characteristics (data linkage)	
Neighbourhood educational quintile	Postal code from Registered Persons Database linked to 2011 Canadian Census data on neighbourhood educational attainment.
Neighbourhood employment quintile	Postal code from Registered Persons Database linked to 2011 Canadian Census data on neighbourhood employment status.
Neighbourhood income quintile and rurality	Composite variable composed of neighbourhood income quintile and rurality of the community. To determine neighbourhood income quintile, residential postal code from the Registered Persons Database was linked with 2006 Statistics Canada census data. Rurality was assessed using the Rurality Index of Ontario (RIO 2008) [1] and linked to residential postal code. Rural was defined by a RIO score ≥ 40 and urban was defined by a RIO score < 40 .

Healthcare service utilization (data linkage)		
Outpatient physician visits	Ontario Health Insurance Plan database.	
Hospitalizations	Canadian Institute for Health Information Discharge Abstract Database and Ontario Mental Health Reporting System.	
ED visits	National Ambulatory Care Reporting System.	
Prevalent comorbidity algorithms		
Comorbidity	Algorithm	Validation
Asthma [2]	≥1 hospitalization <i>or</i> ≥2 physician billings in a 2-year period	80.6% sensitivity 81.4% specificity
Congestive heart failure [3]	≥1 hospitalization <i>or</i> 1 physician billing / ED visit, <i>followed by</i> ≥1 hospitalization / ED visit / physician billing within one year	84.8% sensitivity 97.0% specificity
Chronic obstructive pulmonary disease [4]	≥1 hospitalization <i>or</i> ≥1 physician billing	85.0% sensitivity 78.4% specificity
Diabetes mellitus [5]	≥2 physician billings <i>or</i> ≥1 drug claim in a 1-year period <i>or</i> ≥1 hospitalization	90.0% sensitivity 97.7% specificity
Hypertension [6]	≥1 hospitalization <i>or</i> ≥2 physician billings in a 2-year period.	72% sensitivity 95% specificity
Myocardial infarction [7]	≥1 hospitalization	88.8% sensitivity 92.8% specificity

Abbreviations: CCHS = Canadian Community Health Survey; ED = emergency department; STOP = Smoking Treatment for Ontario Patients.

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Table S2. Baseline characteristics and prior healthcare service use of potential treatment and control cohorts (unmatched)

	Potential treatment cohort (n=12,965)	Potential control cohort (n=19,260)	SMD
Sociodemographic characteristics			
Age, mean \pm SD	49.31 \pm 13.56	45.35 \pm 16.71	0.26
Sex			
Female	7,144 (55.1)	9,495 (49.3)	0.12
Male	5,821 (44.9)	9,765 (50.7)	0.12
Education quintile			
Missing	698 (5.4)	1,257 (6.5)	0.05
Q1 (lowest)	796 (6.1)	1,695 (8.8)	0.10
Q2	1,930 (14.9)	2,951 (15.3)	0.01
Q3	2,528 (19.5)	3,962 (20.6)	0.03
Q4	3,285 (25.3)	4,740 (24.6)	0.02
Q5 (highest)	3,728 (28.8)	4,655 (24.2)	0.10
Employment quintile			
Missing	698 (5.4)	1,257 (6.5)	0.05
Q1 (lowest)	2,935 (22.6)	4,058 (21.1)	0.04
Q2	2,617 (20.2)	3,583 (18.6)	0.04
Q3	2,302 (17.8)	3,674 (19.1)	0.03
Q4	2,251 (17.4)	3,444 (17.9)	0.01
Q5 (highest)	2,162 (16.7)	3,244 (16.8)	0.00
Rurality + neighbourhood income quintile			
Missing	28 (0.2)	51 (0.3)	0.01
Rural	3,784 (29.2)	3,269 (17.0)	0.29
Urban Q1 (lowest)	2,809 (21.7)	4,085 (21.2)	0.01
Urban Q2	1,916 (14.8)	3,447 (17.9)	0.08
Urban Q3	1,702 (13.1)	3,063 (15.9)	0.08
Urban Q4	1,552 (12.0)	2,950 (15.3)	0.10
Urban Q5 (highest)	1,174 (9.1)	2,395 (12.4)	0.11
Migrant status			
Immigrant ^a	299 (2.4)	797 (4.1)	0.10
Non-immigrant	12,666 (97.7)	18,463 (95.9)	0.10
Smoking characteristics			
Frequency of smoking			

Daily	12,741 (98.3)	15,384 (79.9)	0.62
Occasional	224 (1.7)	3,876 (20.1)	0.62
Cigarettes per day, mean \pm SD	20.43 \pm 11.53	13.17 \pm 9.39	0.69
Age first tried smoking, mean \pm SD	15.87 \pm 5.30	15.83 \pm 4.44	0.01
Duration smoking (years), mean \pm SD	33.44 \pm 13.97	29.47 \pm 16.47	0.26
Health comorbidities			
Prevalent comorbidities			
COPD	4,206 (32.4)	2,958 (15.4)	0.41
Hypertension	3,902 (30.1)	4,286 (22.3)	0.18
Diabetes	2,218 (17.1)	1,674 (8.7)	0.25
Asthma	2,643 (20.4)	2,708 (14.1)	0.17
Cancer	618 (4.8)	667 (3.5)	0.07
Myocardial infarction	470 (3.6)	390 (2.0)	0.10
Congestive heart failure	356 (2.7)	324 (1.7)	0.07
No. ADG comorbidities, mean \pm SD	6.33 \pm 3.58	4.70 \pm 3.39	0.47
0-5	5,821 (44.9)	12,285 (63.8)	0.39
6-9	4,713 (36.4)	5,102 (26.5)	0.21
10+	2,431 (18.8)	1,873 (9.7)	0.26
Rate of healthcare service use ppy^b			
Outpatient visits (mean \pm SD)	7.22 \pm 9.03	5.15 \pm 6.73	0.26
ED visits (mean \pm SD)	1.17 \pm 2.17	0.64 \pm 1.39	0.29
Hospitalizations (mean \pm SD)	0.17 \pm 0.50	0.09 \pm 0.31	0.18

Note. Number (%) are reported unless otherwise noted. Abbreviations: ADG = Aggregated Diagnosis Group; COPD = chronic obstructive pulmonary disease; SD = standard deviation; ppy = per person year; ED = emergency department; Q = quintile; IQR = interquartile range; SMD = standardized mean difference.

^a Includes immigrants and refugees.

^b During 2 years up to index date.

Table S3. Baseline characteristics and prior healthcare service use of potential treatment and control cohorts (unmatched), stratified by sex.

	Female			Male		
	Potential treatment cohort (n=7,144)	Potential control cohort (n=9,495)	SMD	Potential treatment cohort (n=5,821)	Potential control cohort (n=9,765)	SMD
Sociodemographic characteristics						
Age, mean ± SD	48.79 ± 13.50	46.54 ± 17.20	0.15	49.95 ± 13.61	44.19 ± 16.13	0.39
Education quintile						
Missing	371 (5.2)	586 (6.2)	0.04	327 (5.6)	671 (6.9)	0.05
Q1 (lowest)	408 (5.7)	812 (8.6)	0.11	388 (6.7)	883 (9.0)	0.09
Q2	1,057 (14.8)	1,419 (14.9)	0.00	873 (15.0)	1,532 (15.7)	0.02
Q3	1,366 (19.1)	1,948 (20.5)	0.04	1,162 (20.0)	2,014 (20.6)	0.02
Q4	1,812 (25.4)	2,340 (24.6)	0.02	1,473 (25.3)	2,400 (24.6)	0.02
Q5 (highest)	2,130 (29.8)	2,390 (25.2)	0.1	1,598 (27.5)	2,265 (23.2)	0.10
Employment quintile						
Missing	371 (5.2)	586 (6.2)	0.04	327 (5.6)	671 (6.9)	0.05
Q1 (lowest)	1,616 (22.6)	2,031 (21.4)	0.03	1,319 (22.7)	2,027 (20.8)	0.05
Q2	1,461 (20.5)	1,761 (18.5)	0.05	1,156 (19.9)	1,822 (18.7)	0.03
Q3	1,234 (17.3)	1,797 (18.9)	0.04	1,068 (18.3)	1,877 (19.2)	0.02
Q4	1,253 (17.5)	1,725 (18.2)	0.02	998 (17.1)	1,719 (17.6)	0.01
Q5 (highest)	1,209 (16.9)	1,595 (16.8)	0.00	953 (16.4)	1,649 (16.9)	0.01
Rurality + neighbourhood income quintile						
Missing	18 (0.3)	24 (0.3)	0.00	10 (0.2)	27 (0.3)	0.02
Rural	2,073 (29.0)	1,616 (17.0)	0.29	1,711 (29.4)	1,653 (16.9)	0.30

Urban Q1 (lowest)	1,563 (21.9)	2,042 (21.5)	0.01	1,246 (21.4)	2,043 (20.9)	0.01
Urban Q2	1,100 (15.4)	1,742 (18.3)	0.08	816 (14.0)	1,705 (17.5)	0.09
Urban Q3	940 (13.2)	1,518 (16.0)	0.08	762 (13.1)	1,545 (15.8)	0.08
Urban Q4	843 (11.8)	1,419 (14.9)	0.09	709 (12.2)	1,531 (15.7)	0.10
Urban Q5 (highest)	607 (8.5)	1,134 (11.9)	0.11	567 (9.7)	1,261 (12.9)	0.10
Migrant status						
Immigrant ^a	126 (1.8)	283 (3.0)	0.08	173 (3.0)	514 (5.3)	0.12
Non-immigrant	7,018 (98.2)	9,212 (97.0)	0.08	5,648 (97.0)	9,251 (94.7)	0.12
Smoking characteristics						
Frequency of smoking						
Daily	7,029 (98.4)	7,604 (80.1)	0.62	5,712 (98.1)	7,780 (79.7)	0.61
Occasional	115 (1.6)	1,891 (19.9)	0.62	109 (1.9)	1,985 (20.3)	0.61
Cigarettes per day, mean \pm SD	19.20 \pm 10.70	11.94 \pm 8.48	0.75	21.95 \pm 12.31	14.36 \pm 10.06	0.67
Age first tried smoking, mean \pm SD	16.02 \pm 5.33	16.16 \pm 4.69	0.03	15.69 \pm 5.25	15.52 \pm 4.14	0.04
Duration smoking (years), mean \pm SD	32.78 \pm 13.52	30.32 \pm 16.40	0.16	34.25 \pm 14.47	28.64 \pm 16.50	0.36
Health comorbidities						
Prevalent comorbidities						
COPD	2,407 (33.7)	1,655 (17.4)	0.38	1,799 (30.9)	1,303 (13.3)	0.43
Hypertension	2,011 (28.1)	2,290 (24.1)	0.09	1,891 (32.5)	1,996 (20.4)	0.28
Diabetes	1,107 (15.5)	834 (8.8)	0.21	1,111 (19.1)	840 (8.6)	0.31
Asthma	1,845 (25.8)	1,634 (17.2)	0.21	798 (13.7)	1,074 (11.0)	0.08
Cancer	316 (4.4)	370 (3.9)	0.03	302 (5.2)	297 (3.0)	0.11
Myocardial infarction	152 (2.1)	130 (1.4)	0.06	318 (5.5)	260 (2.7)	0.14
Congestive heart failure	159 (2.2)	172 (1.8)	0.03	197 (3.4)	152 (1.6)	0.12

No. ADG comorbidities, mean \pm SD	6.83 \pm 3.57	5.58 \pm 3.44	0.36	5.71 \pm 3.50	3.84 \pm 3.11	0.57
0-5	2,729 (38.2)	5,033 (53.0)	0.30	3,092 (53.1)	7,252 (74.3)	0.45
6-9	2,827 (39.6)	3,173 (33.4)	0.13	1,886 (32.4)	1,929 (19.8)	0.29
10+	1,588 (22.2)	1,289 (13.6)	0.23	843 (14.5)	584 (6.0)	0.28
Rate of healthcare service use ppy^b						
Outpatient visits (mean \pm SD)	7.82 \pm 9.10	6.27 \pm 7.14	0.19	6.49 \pm 8.89	4.07 \pm 6.11	0.32
ED visits (mean \pm SD)	1.24 \pm 2.14	0.71 \pm 1.35	0.30	1.09 \pm 2.21	0.58 \pm 1.43	0.27
Hospitalizations (mean \pm SD)	0.17 \pm 0.51	0.11 \pm 0.34	0.13	0.16 \pm 0.48	0.07 \pm 0.29	0.22

Note. Number (percent) are reported unless otherwise noted. Abbreviations: ADG = Aggregated Diagnosis Group; COPD = chronic obstructive pulmonary disease; SD = standard deviation; ppy = per person year; ED = emergency department; Q = quintile; IQR = interquartile range; SMD = standardized mean difference.

^a Includes immigrants and refugees.

^b During 2 years up to index date.

Table S4. Baseline characteristics and prior healthcare service use of matched treatment and control cohorts, stratified by sex.

	Female			Male		
	Treatment cohort (n=5,257)	Control cohort (n=5,257)	SMD	Treatment cohort (n=4,694)	Control cohort (n=4,694)	SMD
Sociodemographic characteristics						
Age, mean \pm SD	48.74 \pm 14.30	48.77 \pm 14.32	0.00	49.20 \pm 14.03	49.22 \pm 14.00	0.00
Education quintile						
Missing	276 (5.3)	274 (5.2)	0.00	280 (6.0)	267 (5.7)	0.01
Q1 (lowest)	343 (6.5)	348 (6.6)	0.00	347 (7.4)	313 (6.7)	0.03
Q2	797 (15.2)	767 (14.6)	0.02	688 (14.7)	694 (14.8)	0.00
Q3	1,034 (19.7)	1,048 (19.9)	0.01	955 (20.3)	929 (19.8)	0.01
Q4	1,340 (25.5)	1,346 (25.6)	0.00	1,183 (25.2)	1,202 (25.6)	0.01
Q5 (highest)	1,467 (27.9)	1,474 (28.0)	0.00	1,241 (26.4)	1,289 (27.5)	0.02
Employment quintile						
Missing	276 (5.3)	274 (5.2)	0.00	280 (6.0)	267 (5.7)	0.01
Q1 (lowest)	1,167 (22.2)	1,180 (22.4)	0.01	1,029 (21.9)	1,054 (22.5)	0.01
Q2	1,072 (20.4)	986 (18.8)	0.04	941 (20.0)	890 (19.0)	0.03
Q3	901 (17.1)	1,015 (19.3)	0.06	886 (18.9)	900 (19.2)	0.01
Q4	948 (18.0)	947 (18.0)	0.00	797 (17.0)	799 (17.0)	0.00
Q5 (highest)	893 (17.0)	855 (16.3)	0.02	761 (16.2)	784 (16.7)	0.01
Rurality + neighbourhood income quintile						
Missing	11 (0.2)	13 (0.2)	0.01	8 (0.2)	6 (0.1)	0.01
Rural	1,219 (23.2)	1,238 (23.5)	0.01	1,162 (24.8)	1,145 (24.4)	0.01
Urban Q1 (lowest)	1,161 (22.1)	1,152 (21.9)	0.00	1,035 (22.0)	1,014 (21.6)	0.01
Urban Q2	889 (16.9)	881 (16.8)	0.00	690 (14.7)	716 (15.3)	0.02
Urban Q3	757 (14.4)	787 (15.0)	0.02	674 (14.4)	690 (14.7)	0.01
Urban Q4	707 (13.4)	678 (12.9)	0.02	629 (13.4)	643 (13.7)	0.01
Urban Q5 (highest)	513 (9.8)	508 (9.7)	0.00	496 (10.6)	480 (10.2)	0.01
Migrant status						
Immigrant ^a	106 (2.0)	106 (2.0)	0.00	156 (3.3)	161 (3.4)	0.01
Non-immigrant	5,151 (98.0)	5,151 (98.0)	0.00	4,538 (96.7)	4,533 (96.6)	0.01
Smoking characteristics						
Frequency of smoking						
Daily	5,152 (98.0)	4,794 (91.2)	0.30	4,593 (97.8)	4,339 (92.4)	0.25
Occasional	105 (2.0)	463 (8.8)	0.30	101 (2.2)	355 (7.6)	0.25
Cigarettes per day, mean \pm SD	16.44 \pm 8.99	15.78 \pm 8.63	0.08	19.35 \pm 10.36	19.55 \pm 10.14	0.02
Age first tried smoking, mean \pm SD	15.98 \pm 4.84	16.00 \pm 4.84	0.00	15.64 \pm 4.76	15.35 \pm 4.45	0.06

Duration smoking (years), mean \pm SD	32.75 \pm 14.09	32.77 \pm 13.90	0.00	33.57 \pm 14.76	33.87 \pm 14.51	0.02
Health comorbidities						
Prevalent comorbidities						
COPD	1,654 (31.5)	1,118 (21.3)	0.23	1,331 (28.4)	900 (19.2)	0.22
Hypertension	1,437 (27.3)	1,439 (27.4)	0.00	1,426 (30.4)	1,255 (26.7)	0.08
Diabetes	715 (13.6)	579 (11.0)	0.08	800 (17.0)	567 (12.1)	0.14
Asthma	1,266 (24.1)	988 (18.8)	0.13	616 (13.1)	486 (10.4)	0.09
Cancer	230 (4.4)	210 (4.0)	0.02	218 (4.6)	190 (4.0)	0.03
Myocardial infarction	98 (1.9)	69 (1.3)	0.04	234 (5.0)	179 (3.8)	0.06
Congestive heart failure	108 (2.1)	96 (1.8)	0.02	127 (2.7)	97 (2.1)	0.04
No. ADG comorbidities, mean \pm SD	6.33 \pm 3.46	6.26 \pm 3.61	0.02	5.30 \pm 3.32	4.54 \pm 3.43	0.23
0-5	2,371 (45.1)	2,203 (41.9)	0.06	2,778 (59.2)	2,974 (63.4)	0.09
6-9	1,937 (36.8)	2,076 (39.5)	0.05	1,377 (29.3)	1,279 (27.2)	0.05
10+	949 (18.1)	978 (18.6)	0.01	539 (11.5)	441 (9.4)	0.07
Rate of healthcare service use ppy^b						
Outpatient visits (mean \pm SD)	7.16 \pm 8.62	7.15 \pm 7.87	0.00	6.01 \pm 8.58	5.05 \pm 7.23	0.12
ED visits (mean \pm SD)	0.94 \pm 1.46	0.91 \pm 1.55	0.02	0.84 \pm 1.32	0.75 \pm 1.43	0.07
Hospitalizations (mean \pm SD)	0.13 \pm 0.37	0.14 \pm 0.39	0.02	0.13 \pm 0.38	0.11 \pm 0.35	0.06

Note. Number (%) are reported unless otherwise noted. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; SD = standard deviation; ppy = per person year; ED = emergency department; Q = quintile; IQR = interquartile range; SMD = standardized mean difference.

^a Includes immigrants and refugees.

^b During 2 year period up to index date.

Table S5. Multivariable regression analysis: Outpatient visits – Overall sample

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.22 (1.19, 1.25)	1.100 (1.06, 1.14)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.94 (0.91, 0.97)	0.98 (0.95, 1.01)	0.98 (0.95, 1.01)
2010	0.86 (0.82, 0.89)	0.95 (0.90, 0.99)	0.95 (0.90, 0.99)
2009	0.86 (0.81, 0.90)	0.93 (0.88, 0.97)	0.93 (0.88, 0.97)
2008	0.86 (0.80, 0.93)	0.89 (0.83, 0.95)	0.89 (0.83, 0.95)
2007	0.78 (0.73, 0.84)	0.84 (0.80, 0.89)	0.84 (0.80, 0.89)
Male	0.85 (0.83, 0.88)	0.95 (0.92, 0.97)	0.95 (0.92, 0.97)
Rurality^a	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Occasional smoking	1.06 (1.01, 1.11)	1.00 (0.96, 1.04)	1.00 (0.96, 1.05)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.64 (1.59, 1.70)	1.46 (1.41, 1.50)	1.46 (1.41, 1.50)
10+	2.21 (2.10, 2.31)	1.84 (1.76, 1.92)	1.84 (1.76, 1.92)
Prior outpatient visit^b	3.11 (2.87, 3.36)	2.05 (1.89, 2.22)	2.04 (1.88, 2.21)
Prior ED visit^b	1.28 (1.24, 1.31)	1.04 (1.01, 1.06)	1.04 (1.01, 1.06)
Absence of prevalent comorbidities			
Diabetes	0.74 (0.72, 0.77)	0.86 (0.84, 0.89)	0.86 (0.84, 0.88)
Hypertension	0.75 (0.73, 0.78)	0.88 (0.86, 0.91)	-
COPD	0.77 (0.74, 0.79)	0.93 (0.90, 0.95)	-
Cancer	0.79 (0.75, 0.83)	0.92 (0.89, 0.96)	0.923 (0.89, 0.96)
Asthma	0.76 (0.73, 0.79)	0.93 (0.90, 0.95)	0.925 (0.90, 0.95)
Congestive heart failure	0.71 (0.68, 0.75)	0.93 (0.88, 0.97)	0.923 (0.88, 0.97)
Myocardial infarction	0.84 (0.79, 0.88)	0.99 (0.94, 1.03)	0.984 (0.94, 1.03)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			1.06 (1.01, 1.11)
Hypertension only			1.03 (0.98, 1.09)
COPD only			1.10 (1.03, 1.18)
Neither hypertension nor COPD			1.14 (1.09, 1.19)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S6. Multivariable regression analysis: Outpatient visits – Females

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.18 (1.14, 1.22)	1.08 (1.03, 1.12)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.97 (0.93, 1.01)	0.99 (0.95, 1.03)	0.99 (0.952, 1.03)
2010	0.88 (0.84, 0.93)	0.93 (0.88, 0.98)	0.93 (0.875, 0.98)
2009	0.89 (0.84, 0.95)	0.91 (0.86, 0.97)	0.91 (0.857, 0.97)
2008	0.88 (0.83, 0.94)	0.89 (0.84, 0.95)	0.89 (0.838, 0.95)
2007	0.78 (0.73, 0.82)	0.84 (0.79, 0.89)	0.84 (0.789, 0.89)
Rurality^a	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Occasional smoking	1.01 (1.00, 1.08)	0.99 (0.94, 1.04)	0.99 (0.94, 1.05)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.57 (1.50, 1.64)	1.44 (1.38, 1.50)	1.44 (1.38, 1.50)
10+	2.14 (2.02, 2.27)	1.84 (1.75, 1.94)	1.85 (1.75, 1.94)
Prior outpatient visit^b	2.90 (2.57, 3.28)	1.88 (1.66, 2.13)	1.87 (1.65, 2.11)
Prior ED visit^b	1.25 (1.21, 1.29)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
Absence of prevalent comorbidities			
Diabetes	0.75 (0.72, 0.79)	0.87 (0.84, 0.90)	0.87 (0.84, 0.90)
Hypertension	0.77 (0.75, 0.80)	0.89 (0.86, 0.92)	-
COPD	0.75 (0.73, 0.78)	0.91 (0.88, 0.94)	-
Cancer	0.83 (0.78, 0.88)	0.96 (0.91, 1.02)	0.96 (0.91, 1.02)
Asthma	0.77 (0.74, 0.80)	0.91 (0.89, 0.95)	0.91 (0.89, 0.94)
Congestive heart failure	0.74 (0.69, 0.80)	0.99 (0.93, 1.05)	0.99 (0.92, 1.05)
Myocardial infarction	0.79 (0.73, 0.85)	0.93 (0.87, 1.01)	0.93 (0.86, 1.00)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			1.03 (0.97, 1.09)
Hypertension only			0.99 (0.93, 1.06)
COPD only			1.04 (0.97, 1.12)
Neither hypertension nor COPD			1.13 (1.07, 1.19)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S7. Multivariable regression analysis: Outpatient visits – Males

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.29 (1.24, 1.34)	1.13 (1.07, 1.19)	-
Index Year			
2012	Ref.	Ref.	Ref.
2011	0.91 (0.87, 0.96)	0.98 (0.94, 1.03)	0.98 (0.94, 1.03)
2010	0.81 (0.75, 0.87)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
2009	0.79 (0.73, 0.86)	0.95 (0.88, 1.03)	0.95 (0.87, 1.03)
2008	0.77 (0.68, 0.87)	0.85 (0.76, 0.95)	0.85 (0.76, 0.95)
2007	0.80 (0.74, 0.87)	0.87 (0.79, 0.95)	0.87 (0.79, 0.95)
Rurality^a	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Occasional smoking	1.12 (1.04, 1.22)	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.66 (1.58, 1.74)	1.45 (1.38, 1.52)	1.45 (1.38, 1.51)
10+	2.16 (2.01, 2.32)	1.79 (1.67, 1.93)	1.79 (1.67, 1.92)
Prior outpatient visit^b	2.98 (2.69, 3.30)	2.11 (1.89, 2.33)	2.09 (1.88, 2.33)
Prior ED visit^b	1.30 (1.25, 1.36)	1.06 (1.01, 1.10)	1.06 (1.01, 1.10)
Absence of prevalent comorbidities			
Diabetes	0.72 (0.69, 0.75)	0.84 (0.81, 0.88)	0.84 (0.81, 0.87)
Hypertension	0.73 (0.69, 0.76)	0.87 (0.84, 0.91)	-
COPD	0.80 (0.76, 0.84)	0.96 (0.91, 1.00)	-
Cancer	0.75 (0.70, 0.80)	0.88 (0.83, 0.93)	0.88 (0.83, 0.93)
Asthma	0.79 (0.74, 0.85)	0.94 (0.88, 1.00)	0.94 (0.88, 1.00)
Congestive heart failure	0.69 (0.63, 0.75)	0.88 (0.82, 0.94)	0.88 (0.82, 0.95)
Myocardial infarction	0.83 (0.78, 0.88)	1.03 (0.98, 1.09)	1.03 (0.97, 1.09)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			1.10 (1.01, 1.19)
Hypertension only			1.08 (1.00, 1.16)
COPD only			1.21 (1.07, 1.38)
Neither hypertension nor COPD			1.15 (1.07, 1.24)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S8. Multivariable regression analysis: Emergency visits – Overall sample

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.20 (1.16, 1.25)	1.079 (1.027, 1.133)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.91 (0.87, 0.96)	0.95 (0.91, 1.00)	0.95 (0.91, 1.00)
2010	0.88 (0.81, 0.94)	0.94 (0.87, 1.01)	0.94 (0.87, 1.01)
2009	0.90 (0.84, 0.97)	0.96 (0.90, 1.04)	0.96 (0.90, 1.03)
2008	0.88 (0.80, 0.98)	0.90 (0.82, 0.99)	0.90 (0.82, 0.99)
2007	1.00 (0.92, 1.08)	1.01 (0.93, 1.10)	1.01 (0.93, 1.10)
Male	0.89 (0.85, 0.92)	1.00 (0.96, 1.04)	1.00 (0.96, 1.04)
Rurality^a	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
Occasional smoking	1.03 (0.94, 1.13)	0.98 (0.91, 1.07)	0.99 (0.91, 1.07)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.64 (1.54, 1.68)	1.32 (1.26, 1.37)	1.32 (1.26, 1.37)
10+	2.60 (2.44, 2.77)	1.87 (1.75, 1.99)	1.87 (1.75, 1.99)
Prior outpatient visit^b	1.63 (1.50, 1.77)	1.02 (0.94, 1.11)	1.02 (0.94, 1.11)
Prior ED visit^b	2.50 (2.39, 2.61)	1.89 (1.81, 1.97)	1.89 (1.81, 1.98)
Absence of prevalent comorbidities			
Diabetes	0.66 (0.62, 0.70)	0.79 (0.75, 0.83)	0.79 (0.75, 0.83)
Hypertension	0.72 (0.68, 0.75)	0.91 (0.87, 0.95)	-
COPD	0.61 (0.58, 0.64)	0.80 (0.76, 0.84)	-
Cancer	0.75 (0.68, 0.83)	0.94 (0.86, 1.03)	0.94 (0.86, 1.03)
Asthma	0.66 (0.62, 0.69)	0.83 (0.80, 0.87)	0.83 (0.80, 0.87)
Congestive heart failure	0.49 (0.44, 0.55)	0.76 (0.69, 0.84)	0.76 (0.69, 0.84)
Myocardial infarction	0.66 (0.60, 0.73)	0.90 (0.82, 0.99)	0.90 (0.82, 0.99)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			1.05 (0.95, 1.15)
Hypertension only			1.06 (0.96, 1.16)
COPD only			1.03 (0.93, 1.13)
Neither hypertension nor COPD			1.11 (1.05, 1.18)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S9. Multivariable regression analysis: Emergency visits – Females

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.17 (1.11, 1.23)	1.05 (0.98, 1.12)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.96 (0.90, 1.03)	0.98 (0.92, 1.04)	0.98 (0.93, 1.04)
2010	0.90 (0.81, 0.99)	0.88 (0.80, 0.97)	0.88 (0.80, 0.97)
2009	0.95 (0.87, 1.05)	0.95 (0.86, 1.04)	0.95 (0.86, 1.04)
2008	0.88 (0.78, 0.99)	0.88 (0.79, 0.99)	0.88 (0.79, 0.99)
2007	0.96 (0.87, 1.05)	0.97 (0.87, 1.07)	0.97 (0.87, 1.07)
Rurality^a	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
Occasional smoking	1.02 (0.90, 1.16)	1.00 (0.89, 1.11)	1.00 (0.89, 1.11)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.62 (1.53, 1.71)	1.33 (1.26, 1.41)	1.33 (1.26, 1.41)
10+	2.63 (2.45, 2.84)	1.90 (1.76, 2.05)	1.90 (1.76, 2.05)
Prior outpatient visit^b	1.53 (1.31, 1.78)	0.93 (0.80, 1.08)	0.93 (0.79, 1.08)
Prior ED visit^b	2.66 (2.52, 2.81)	1.97 (1.87, 2.08)	1.97 (1.87, 2.08)
Absence of prevalent comorbidities			
Diabetes	0.62 (0.57, 0.67)	0.75 (0.69, 0.81)	0.75 (0.69, 0.81)
Hypertension	0.72 (0.68, 0.77)	0.92 (0.86, 0.97)	-
COPD	0.59 (0.55, 0.63)	0.80 (0.76, 0.85)	-
Cancer	0.83 (0.73, 0.95)	1.05 (0.93, 1.19)	1.05 (0.92, 1.19)
Asthma	0.63 (0.59, 0.67)	0.80 (0.76, 0.85)	0.80 (0.76, 0.85)
Congestive heart failure	0.47 (0.40, 0.55)	0.80 (0.69, 0.92)	0.80 (0.69, 0.92)
Myocardial infarction	0.64 (0.53, 0.78)	0.88 (0.73, 1.05)	0.88 (0.73, 1.05)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			1.01 (0.89, 1.14)
Hypertension only			1.06 (0.93, 1.19)
COPD only			1.01 (0.88, 1.14)
Neither hypertension nor COPD			1.07 (0.99, 1.15)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S10. Multivariable regression analysis: Emergency visits – Males

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.29 (1.23, 1.35)	1.13 (1.05, 1.20)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.85 (0.80, 0.90)	0.91 (0.86, 0.97)	0.91 (0.86, 0.97)
2010	0.79 (0.71, 0.88)	0.95 (0.85, 1.06)	0.95 (0.86, 1.06)
2009	0.82 (0.75, 0.89)	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)
2008	0.95 (0.87, 1.05)	0.97 (0.87, 1.09)	0.97 (0.87, 1.08)
2007	0.80 (0.70, 0.91)	0.87 (0.76, 0.99)	0.87 (0.77, 0.99)
Rurality^a	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)	1.01 (1.01, 1.01)
Occasional smoking	1.04 (0.93, 1.18)	0.98 (0.89, 1.09)	0.98 (0.88, 1.08)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.53 (1.45, 1.62)	1.27 (1.20, 1.34)	1.27 (1.20, 1.34)
10+	2.18 (2.01, 2.37)	1.62 (1.49, 1.76)	1.63 (1.49, 1.77)
Prior outpatient visit^b	1.50 (1.37, 1.64)	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)
Prior ED visit^b	2.16 (2.05, 2.28)	1.78 (1.68, 1.88)	1.78 (1.68, 1.87)
Absence of prevalent comorbidities			
Diabetes	0.74 (0.69, 0.79)	0.85 (0.80, 0.91)	0.85 (0.79, 0.90)
Hypertension	0.75 (0.70, 0.80)	0.90 (0.85, 0.96)	-
COPD	0.71 (0.66, 0.76)	0.86 (0.81, 0.92)	-
Cancer	0.71 (0.63, 0.80)	0.85 (0.76, 0.94)	0.84 (0.76, 0.94)
Asthma	0.75 (0.70, 0.80)	0.89 (0.83, 0.95)	0.89 (0.83, 0.95)
Congestive heart failure	0.58 (0.50, 0.66)	0.78 (0.70, 0.87)	0.79 (0.71, 0.88)
Myocardial infarction	0.68 (0.62, 0.75)	0.90 (0.82, 1.00)	0.90 (0.82, 1.00)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			1.12 (0.98, 1.28)
Hypertension only			1.07 (0.95, 1.22)
COPD only			1.24 (1.06, 1.44)
Neither hypertension nor COPD			1.12 (1.04, 1.21)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S11. Multivariable regression analysis: Hospitalizations – Overall sample

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.21 (1.15, 1.28)	1.09 (1.02, 1.18)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.93 (0.86, 0.99)	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)
2010	0.88 (0.79, 0.97)	1.00 (0.89, 1.12)	1.00 (0.90, 1.12)
2009	0.89 (0.81, 0.98)	0.98 (0.88, 1.09)	0.98 (0.88, 1.09)
2008	1.04 (0.93, 1.15)	1.05 (0.93, 1.18)	1.05 (0.93, 1.18)
2007	0.77 (0.68, 0.87)	0.88 (0.78, 1.00)	0.89 (0.78, 1.01)
Male	0.89 (0.85, 0.95)	0.99 (0.94, 1.05)	0.99 (0.94, 1.05)
Rurality^a	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Occasional smoking	1.12 (0.99, 1.26)	1.08 (0.96, 1.21)	1.08 (0.96, 1.21)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.59 (1.50, 1.70)	1.30 (1.22, 1.39)	1.31 (1.22, 1.39)
10+	2.61 (2.40, 2.84)	1.82 (1.67, 1.98)	1.82 (1.67, 1.98)
Prior outpatient visit^b	2.06 (1.80, 2.36)	1.23 (1.07, 1.42)	1.23 (1.06, 1.42)
Prior ED visit^b	1.86 (1.75, 1.97)	1.40 (1.31, 1.49)	1.40 (1.31, 1.49)
Absence of prevalent comorbidities			
Diabetes	0.59 (0.55, 0.64)	0.73 (0.68, 0.78)	0.73 (0.68, 0.78)
Hypertension	0.63 (0.58, 0.67)	0.81 (0.75, 0.86)	-
COPD	0.64 (0.60, 0.68)	0.81 (0.77, 0.87)	-
Cancer	0.68 (0.61, 0.76)	0.82 (0.74, 0.91)	0.82 (0.74, 0.91)
Asthma	0.65 (0.60, 0.70)	0.85 (0.80, 0.91)	0.85 (0.80, 0.91)
Congestive heart failure	0.44 (0.39, 0.50)	0.70 (0.63, 0.78)	0.71 (0.63, 0.79)
Myocardial infarction	0.60 (0.54, 0.67)	0.81 (0.72, 0.90)	0.80 (0.72, 0.90)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			0.98 (0.88, 1.10)
Hypertension only			1.07 (0.95, 1.21)
COPD only			1.26 (1.08, 1.47)
Neither hypertension nor COPD			1.12 (1.02, 1.24)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S12. Multivariable regression analysis: Hospitalizations – Females

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.16 (1.08, 1.24)	1.09 (1.00, 1.19)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.95 (0.87, 1.04)	0.98 (0.90, 1.07)	0.98 (0.91, 1.07)
2010	0.92 (0.81, 1.04)	0.99 (0.87, 1.14)	0.99 (0.87, 1.14)
2009	0.96 (0.86, 1.07)	1.00 (0.88, 1.14)	1.00 (0.88, 1.13)
2008	0.97 (0.85, 1.10)	1.00 (0.88, 1.15)	1.01 (0.88, 1.15)
2007	0.92 (0.81, 1.04)	1.03 (0.90, 1.18)	1.03 (0.90, 1.18)
Rurality^a	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Occasional smoking	1.04 (0.91, 1.19)	1.04 (0.91, 1.19)	1.05 (0.92, 1.20)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.55 (1.43, 1.67)	1.29 (1.18, 1.40)	1.29 (1.18, 1.40)
10+	2.40 (2.19, 2.62)	1.71 (1.56, 1.89)	1.72 (1.56, 1.89)
Prior outpatient visit^b	1.96 (1.58, 2.43)	1.18 (0.94, 1.47)	1.16 (0.93, 1.45)
Prior ED visit^b	1.88 (1.74, 2.02)	1.44 (1.33, 1.56)	1.45 (1.34, 1.56)
Absence of prevalent comorbidities			
Diabetes	0.64 (0.59, 0.70)	0.74 (0.68, 0.81)	0.75 (0.68, 0.82)
Hypertension	0.69 (0.64, 0.76)	0.85 (0.78, 0.93)	-
COPD	0.59 (0.55, 0.64)	0.74 (0.69, 0.81)	-
Cancer	0.75 (0.65, 0.86)	0.89 (0.77, 1.04)	0.89 (0.76, 1.04)
Asthma	0.71 (0.66, 0.77)	0.90 (0.84, 0.97)	0.90 (0.83, 0.96)
Congestive heart failure	0.49 (0.42, 0.56)	0.75 (0.65, 0.86)	0.75 (0.65, 0.87)
Myocardial infarction	0.55 (0.47, 0.65)	0.72 (0.61, 0.87)	0.72 (0.60, 0.86)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			0.99 (0.85, 1.16)
Hypertension only			1.07 (0.91, 1.26)
COPD only			1.07 (0.91, 1.26)
Neither hypertension nor COPD			1.17 (1.04, 1.31)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.

Table S13. Multivariable regression analysis: Hospitalizations – Males

	Crude model HR (95% CI)	Adjusted model HR (95% CI)	Adjusted model with interactions HR (95% CI)
Treatment cohort	1.27 (1.17, 1.39)	1.10 (0.98, 1.24)	-
Index year			
2012	Ref.	Ref.	Ref.
2011	0.87 (0.78, 0.97)	0.93 (0.83, 1.05)	0.93 (0.83, 1.05)
2010	0.84 (0.72, 0.98)	1.04 (0.87, 1.24)	1.04 (0.87, 1.24)
2009	0.76 (0.65, 0.89)	0.93 (0.78, 1.11)	0.93 (0.78, 1.11)
2008	1.02 (0.87, 1.20)	1.05 (0.87, 1.27)	1.05 (0.87, 1.26)
2007	0.71 (0.57, 0.89)	0.83 (0.67, 1.03)	0.83 (0.68, 1.03)
Rurality^a	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Occasional smoking	1.13 (0.95, 1.35)	1.06 (0.90, 1.25)	1.06 (0.90, 1.25)
No. ADG comorbidities			
0-5	Ref.	Ref.	Ref.
6-9	1.53 (1.39, 1.67)	1.25 (1.13, 1.37)	1.24 (1.13, 1.37)
10+	2.69 (2.34, 3.09)	1.91 (1.66, 2.21)	1.91 (1.65, 2.20)
Prior outpatient visit^b	1.93 (1.62, 2.30)	1.23 (1.02, 1.48)	1.21 (1.00, 1.46)
Prior ED visit^b	1.73 (1.58, 1.90)	1.32 (1.20, 1.45)	1.32 (1.20, 1.45)
Absence of prevalent comorbidities			
Diabetes	0.61 (0.55, 0.68)	0.74 (0.67, 0.82)	0.74 (0.667, 0.815)
Hypertension	0.62 (0.57, 0.68)	0.80 (0.73, 0.88)	-
COPD	0.69 (0.62, 0.76)	0.85 (0.77, 0.93)	-
Cancer	0.63 (0.55, 0.73)	0.75 (0.65, 0.86)	0.75 (0.65, 0.86)
Asthma	0.67 (0.59, 0.76)	0.87 (0.76, 0.99)	0.87 (0.76, 0.98)
Congestive heart failure	0.47 (0.40, 0.55)	0.71 (0.61, 0.82)	0.71 (0.61, 0.82)
Myocardial infarction	0.66 (0.57, 0.76)	0.91 (0.79, 1.04)	0.90 (0.79, 1.03)
Interactions: treatment relative to control, within each comorbidity group			
Hypertension and COPD			0.97 (0.81, 1.16)
Hypertension only			1.06 (0.89, 1.26)
COPD only			1.23 (0.97, 1.56)
Neither hypertension nor COPD			1.18 (1.00, 1.39)

Note. Abbreviations: ADG = Aggregated Diagnostic Groups; COPD = chronic obstructive pulmonary disease; ED = emergency department; HR = hazard ratio.

^a Rurality Index of Ontario score (Kralj, 2009)

^b During 2 years up to index date.