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# Long-Term Macrolide Therapy for Chronic Obstructive Pulmonary Disease: A Population-Based Study

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| Complete List of Authors: | Yan, Marie; University of Toronto, Department of Medicine; The University of British Columbia, Department of Medicine<br>Saxena, Farah; Institute for Clinical Evaluative Sciences,<br>calzavara, andrew; Institute for Clinical Evaluative Sciences<br>Brown, Kevin; Public Health Ontario, Infection Prevention and Control; Institute for Clinical Evaluative Sciences; University of Toronto Dalla Lana School of Public Health<br>Garber, Gary; Public Health Ontario, Infection Prevention and Control; Ottawa Hospital Research Institute; University of Toronto, Department of Medicine<br>Gershon, Andrea; Institute for Clinical Evaluative Sciences; Sunnybrook Health Sciences Centre; University of Toronto, Department of Medicine<br>Johnstone, Jennie; Public Health Ontario, Infection Prevention and Control; University of Toronto Dalla Lana School of Public Health; Sinai Health System<br>Kumar, Matthew; Institute for Clinical Evaluative Sciences, DAS<br>Langford, Bradley; Public Health Ontario, Infection Prevention and Control<br>Schwartz, Kevin; Public Health Ontario; Institute for Clinical Evaluative Sciences; University of Toronto Dalla Lana School of Public Health; Unity Health Toronto<br>Daneman, Nick; Sunnybrook Health Sciences Centre, University of Toronto, Medicine; Institute for Clinical Evaluative Sciences; University of Toronto, Department of Medicine; Public Health Ontario |
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# Long-Term Macrolide Therapy for Chronic Obstructive Pulmonary Disease: A Population-Based Study

Marie Yan, MD[1,2], Farah E. Saxena, MSc[3], Andrew Calzavara, MSc[3], Kevin A. Brown, PhD[3,4,5], Gary Garber, MD[1,5,6], Andrea S. Gershon, MD MSc[1,3,7], Jennie Johnstone, MD PhD[4,5,8], Matthew Kumar, MSc[3], Bradley J. Langford, PharmD[5], Kevin L. Schwartz, MD MSc[3,4,5,9], and Nick Daneman, MD MSc[1,3,5,7]

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[2]Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[3]ICES, Toronto, Ontario, Canada

[4]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[5]Public Health Ontario, Toronto, Ontario, Canada

[6]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[7]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

[8]Sinai Health System, Toronto, Ontario, Canada

[9]Unity Health Toronto, Toronto, Ontario, Canada

Corresponding Author:

Dr. Nick Daneman

Sunnybrook Health Sciences Centre

2075 Bayview Avenue

Toronto, Ontario M4N 3M5

Canada

Email: nick.daneman@sunnybrook.ca

Author Contributions:

N.D., M.Y., F.E.S., A.C., K.A.B., G.G., A.S.G., J.J., B.J.L., and K.L.S. contributed to the study conception and design; M.Y., F.E.S., A.C., and N.D. contributed to coding and data acquisition; A.C. performed the statistical analysis; N.D., M.Y., and A.C. interpreted the results; M.Y. and F.E.S. drafted the manuscript and all authors contributed to the final draft.

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ABSTRACT

Background: Macrolides are recommended as an adjunctive treatment for patients with moderate to severe chronic obstructive pulmonary disease (COPD) who experience recurrent exacerbations. However, the prevalence and impact of this practice at the population level is not known. The objective of this study is to examine temporal trends in the provision of long-term macrolide therapy and associated clinical outcomes.

Methods: We performed an interrupted time series analysis using population-level health administrative data. The study cohort consisted of all Ontario residents with COPD, aged 65 years or older between April 1, 2004 and March 31, 2018.

Results: The rate of chronic macrolide use increased from 0.8/1000 persons in 2004 to 13.8/1000 persons in 2018 (in the severe COPD group, the rate increased from 1.3 to 32.3/1000 persons). The interrupted time series analysis showed that before 2011, the prevalence of macrolide prophylaxis increased at a rate of 0.44/1000 persons per year (95% confidence interval [CI] 0.39–0.50); after 2011, the rate of increase grew by 1.18/1000 persons (95% CI 1.07–1.29) to 1.63/1000 persons per year (95% CI 1.56–1.69). The seasonal pattern of COPD-related healthcare visits remained stable over the study period and there was no appreciable reduction in hospitalizations/emergency department visits.

Interpretation: In the past decade, there has been a significant rise in the use of long-term macrolide therapy for patients with COPD. However, the overall rate remains low, and thus there

has not been a detectable impact on the trend of COPD-related healthcare encounters in this population.

Abstract Word Count: 248 words

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory conditions worldwide.[1–3] One of the priorities of COPD management is preventing acute exacerbations, which are associated with increased mortality, accelerated disease progression, and reduced quality of life. In addition, COPD exacerbations contribute significantly to the economic burden associated with the disease.[4,5]

Although inhaled therapies are the mainstay of COPD treatment, many patients continue to experience exacerbations despite intensive inhaler regimens, and adjunctive therapies are required. In 2011, a seminal randomized controlled trial (RCT) by Albert et al. was published in the *New England Journal of Medicine*, reporting a decrease in the frequency of exacerbations when oral azithromycin (versus placebo) was added to usual care (MACRO trial).[6] The benefits of macrolide prophylaxis for prevention of exacerbations have subsequently been corroborated by other studies and systematic reviews.[7–10] The mechanism is thought to be related to macrolides' anti-inflammatory and immunomodulatory properties, in addition to their antibacterial action.[6,11,12]

Current guidelines suggest that chronic macrolide use should be considered for patients with moderate to severe COPD and recurrent exacerbations.[13,14] However, the prevalence of patients who receive prophylaxis is not known, and the impact of this practice on exacerbation rates and potential adverse events in the real-world setting has also not been studied. In this population-level study, we examined the trends in the provision of macrolide prophylaxis for COPD patients over time to determine whether publication of the landmark RCT was associated with increased

use of this intervention across the spectrum of COPD severity, and whether this was associated with changes in clinical outcomes.

## METHODS

### Data Sources

This study was performed at ICES (formerly known as the Institute for Clinical Evaluative Sciences) using health administrative data from the province of Ontario, Canada.[15–17] Details about the specific databases used can be found in the Appendix. All datasets were linked at the individual level using unique encoded identifiers and analyzed at ICES. Residents with COPD were identified using the ICES-derived COPD database, which has a sensitivity of 85% and specificity of 78% for identifying COPD patients (in our study the specificity should be increased since all included patients were required to be on at least one long-acting inhaler).[18] ICES-derived chronic disease cohorts that have been previously developed and validated using administrative databases were used to identify baseline comorbid conditions, such as asthma and congestive heart failure.[19,20]

### Patient Selection Criteria

Our study cohort consisted of Ontario residents with COPD, aged 65 years or older between April 1, 2004 and March 31, 2018. To be eligible for the study, each patient must be receiving at least one long-acting inhaler available through Ontario Drug Benefit, such as a long-acting muscarinic antagonist (LAMA), long-acting beta agonist (LABA), inhaled corticosteroid (ICS), or a combination thereof. The study period was divided into quarter-years (three-month

intervals). A patient could be included in multiple quarters, as long as they met eligibility criteria on or before the first day of the quarter. We excluded patients with a history of bronchiectasis and/or nontuberculous mycobacterial infection, since these are also indications for prolonged macrolide treatment. These patients were identified using the International Classification of Diseases Tenth Revision (ICD-10) and Ontario Health Insurance Plan diagnosis codes, as well as previous prescriptions for rifampin and/or ethambutol.

Baseline Characteristics

Baseline variables of interest included demographics, comorbidities, medication use, and healthcare utilization. We compared the baseline characteristics of eligible COPD patients before and after the MACRO study was published in August 2011 (designated as pre-Q3-2011 and post-Q3-2011)[6]; for the purposes of these comparisons, we randomly selected one eligible quarter per person in each time period.

Outcomes

Our primary outcome was the overall prevalence of chronic macrolide therapy amongst all patients with COPD in Ontario. This was calculated as the number (per 1000) of COPD patients who were receiving chronic macrolide prophylaxis overlapping the quarter, which was defined as having an active prescription for azithromycin, clarithromycin, or erythromycin for ≥90 consecutive days. To account for possible delays in dispensing refills, we allowed any number of gaps between prescriptions, provided that each gap was no longer than 14 days.

For secondary outcomes, we measured the potential benefits of macrolide prophylaxis via the incidence of COPD-related hospitalizations, ED visits, and outpatient exacerbations requiring high-dose steroids (receipt of an oral corticosteroid within seven days of an outpatient visit for COPD) in each quarter. We captured the potential harms of macrolide prophylaxis via the incidence of hospitalization or ED visits due to any one of the following: arrhythmias potentially related to macrolide-induced QT prolongation including cardiac death, hearing impairment, general adverse medication events and drug allergy, antibiotic-resistant organisms, *Clostridioides difficile* colitis and non-infectious diarrhea, or candidiasis (ICD-10 codes listed in Appendix Table S1). For all outcomes, the denominator of at-risk individuals included all COPD patients meeting inclusion/exclusion criteria at the start of the quarter.

We examined for potential indication creep by stratifying by COPD severity and comparing the proportion of mild, moderate, and severe COPD patients who received macrolide prophylaxis. COPD severity was defined in two ways: 1) therapy-based severity and 2) exacerbation-based severity. We defined therapy-based severity by the number of classes of long-acting inhaler treatments in the preceding two years: one inhaler class (mild), two inhaler classes (moderate), or three inhalers classes and/or supplemental oxygen (severe). Exacerbation-based severity was defined using COPD-related hospital encounters in the preceding two years: an inpatient hospitalization (severe), an ED visit (moderate), or neither (mild). After assigning patients to responsible physicians (based on who prescribed their chronic inhaler therapy), we examined physician variability in the percentage of their COPD patients for whom they prescribed macrolides in the most recent study year (fiscal year 2017).

## Statistical Analysis

We examined temporal trends in the incidence of macrolide prophylaxis over time (per 1000 persons) between April 1, 2004 and March 31, 2018 (14 years, 56 quarters). The unit of analysis was the quarter. To test the specificity of our findings, we also examined temporal trends in other common antimicrobial agents that have not been endorsed for chronic prophylaxis in this population, namely cephalexin and nitrofurantoin. We performed an interrupted time series analysis to assess for changes in the incidence of macrolide prophylaxis, using a linear model with two parameters in addition to the intercept: the pre-period slope and the post-period slope change.[21] Statistical analyses were performed using SAS version 9.4m5 (2017, SAS Institute Inc., Cary, NC).

## Ethics Approval

The use of data in this project was authorized under section 45 of Ontario's *Personal Health Information Protection Act*, which does not require review by a Research Ethics Board.

# RESULTS

## Baseline Characteristics

There were 919,008 Ontarians aged 65 or older with COPD between April 1, 2004 and March 31, 2018. We excluded 472,480 individuals who were not receiving a long-acting inhaler and 12,402 with a history of bronchiectasis and/or mycobacterial infection, resulting in 434,126 eligible subjects for our study (Appendix Figure S1). There were 254,457 patients eligible pre-

Q3-2011 and 312,370 patients eligible post-Q3-2011. COPD patient characteristics were similar in the pre-Q3-2011 and post-Q3-2011 periods (Table 1).

Prevalence of Macrolide Prophylaxis

The prevalence of macrolide prophylaxis increased during the study period from 0.8 per 1000 persons in 2004-Q2 to a high of 13.8 per 1000 persons by the end of the follow-up period. In contrast, the prevalence of cephalexin and nitrofurantoin chronic prophylaxis were generally stable throughout the study period (Figure 1). When stratified by therapy-based COPD severity, patients in the severe group exhibited a steep increase in the prevalence of macrolide prophylaxis over time (from 1.3 to 32.3 per 1000). Those with mild and moderate severity exhibited less pronounced increases in prevalence over the study period (Figure 2A). When stratified by exacerbation-based severity, both the moderate and severe groups exhibited similarly large increases in prevalence over time (Figure 2B). The interrupted time series model showed that macrolide prophylaxis increased by 0.44 (95% CI 0.39 – 0.50) per 1000 persons each year before the RCT publication in August 2011, and thereafter increased by 1.18 per 1000 (95% CI 1.07 – 1.29) to a rate of 1.63 (95% CI 1.56 – 1.69) per 1000 persons per year (Figure 3).

Over 80% of macrolide prophylaxis regimens used azithromycin. The most common regimen was equivalent to a daily dose of <150 mg of azithromycin (35.7% of regimens), followed by 250–499 mg of azithromycin (30.8%), and 150–249 mg of azithromycin (13.7%). Physicians who prescribed chronic macrolides had a median of 4.5% of their COPD patients on prophylaxis, with wide variability across prescribers (interquartile range (IQR): 2.1% - 10.0%). Median use

and variability across prescribers were higher among patients with severe COPD (by therapy-based criterion, median 8.3% (IQR: 1.5% - 18.7%).

Temporal Trends in Clinical Outcomes

There was a strong seasonality in COPD-related outcomes, but no observable change in frequency or slope after Q3-2011 (Figure 4). Among the most severe stratum of COPD patients by therapy-based definition, for which macrolide prophylaxis was more common, there was also no detectable change in outcomes after Q3-2011 (Figure 5). Similar results were seen for those with severe COPD defined by exacerbations (data not shown).



## INTERPRETATION

In this population-level study involving COPD patients over age 65 in Ontario, Canada, we found that there has been a significant and steady rise in the use of macrolide prophylaxis in the past decade. This effect is primarily attributed to the landmark paper published in August 2011 demonstrating the efficacy of macrolides in reducing exacerbations and the subsequent inclusion of this practice into major clinical guidelines.[6] To our knowledge, this is the first study to demonstrate the prevalence of macrolide prophylaxis at a population level. Previously, one study using the United Kingdom primary care database between 2000 and 2009 had reported that only 0.61% of COPD patients received antibiotic prophylaxis (most frequently with non-macrolide antibiotics), however, this study was conducted prior to the 2011 RCT publication, and before the practice was widely incorporated into clinical guidelines.[23]

Most of the trials involving macrolide prophylaxis focused on patients with moderate to severe COPD, and this is reflected in all the major clinical guidelines. Specifically, the latest joint statement from the American Thoracic Society and the European Respiratory Society in 2017 suggests macrolides for patients with "moderate to very severe airflow obstruction and exacerbations despite optimal inhaled therapy".[14] Similar recommendations have been published by the Canadian Thoracic Society and American College of Chest Physicians.[13,24] To examine for indication creep, we stratified the patients by severity based on their long-acting inhaler medications and exacerbation rates in the preceding two years. Our results showed that, in general, physicians are prescribing in accordance with these guidelines. Patients who received macrolides are overwhelmingly those who continue to have exacerbations despite being on triple inhaled agents, especially if they have a recent history of COPD-related hospitalizations or ED visits. When patient severity was stratified by exacerbation rates, there was also a notable upward trend in the use of macrolide prophylaxis in the mild group. Although this may reflect indication creep, these patients may have also had outpatient exacerbations that were not captured in the study.

There was heterogeneity in the antibiotic regimens that patients received. The most common one was equivalent to a daily dose of <150 mg of azithromycin. This likely corresponds to the regimen of azithromycin 250 mg thrice weekly. Of note, this is a smaller dose compared to the 250 mg daily regimen tested in the MACRO trial. This may be a deliberate choice by clinicians, possibly due to concerns regarding side effects and/or patient inconvenience. Certain commentators have argued that given the long half-life of azithromycin, daily dosing may in fact be too aggressive.[25,26] Respirologists may also have more familiarity with thrice weekly

regimens since this approach is also routinely applied to patients with cystic fibrosis and other causes of bronchiectasis.[27,28]

In terms of patient outcomes, the seasonal pattern of COPD-related healthcare visits remained stable over the years and there was no appreciable reduction in COPD hospitalizations or ED visits associated with the growth in macrolide use. We believe that this is primarily because the overall use of prophylaxis remained low at the end of the study period (maximum 13.8/1000 COPD patients, 32.3/1000 severe COPD patients). Therefore, any benefits at the individual level would not necessarily translate to measurable changes at the population level. Furthermore, patient adherence was inferred from drug dispensing data, but true adherence is not known. In addition, the MACRO trial's analysis of healthcare utilization only showed a significant reduction in unscheduled office visits (an outcome that we were unable to measure in this study due to database limitations), not hospitalizations or ED use.[6]

There were also no apparent changes in the overall pattern of possible COPD-related adverse events over time. In the MACRO trial, there were no differences in the rate of serious adverse events between the two arms of the study, but hearing decrements on audiometry testing were more common in the azithromycin group. Our composite outcome also included other risks associated with macrolides such as cardiac arrhythmias, allergic reactions, and diarrhea or *C. difficile* colitis. However, there are limitations with how these events were captured in this study. Because administrative databases were used, it is impossible to determine the proportion of events that should be attributed to macrolide use. Additionally, some of the minor or more subtle adverse effects (such as hearing loss) may not be recognized by patients or may not lead to

healthcare encounters that would be captured in this study. Furthermore, the absence of population-wide microbiology data during this study interval meant that we were unable to examine for one of the most important potential patient- and societal-level harm of widespread macrolide use, namely the selection of increased macrolide resistance in key human pathogens, such as *Streptococcus pneumoniae, Streptococcus pyogenes, and Staphylococcus aureus*.

## Limitations

There are other notable study limitations in addition to those mentioned previously. The COPD cohort was identified using an ICES-derived definition. Although it has been previously validated, its sensitivity and specificity are imperfect.[18] Because we used health administrative data, we also did not have individual spirometry data to help classify the patients by severity (other relevant variables such as smoking status were also not available). However, our method of stratifying by baseline inhaler medications and exacerbation rates appear to be valid given the clear delineation in trends in treatment and outcomes between the different groups. Although we found that patient selection for prophylaxis generally conformed to clinical guidelines, we do not have specific data to determine whether patients were also appropriately screened for contraindications such as prolonged QT intervals and baseline hearing impairment.

## Conclusion

There has been a significant rise in the use of macrolides as prophylaxis for moderate to severe COPD patients with recurrent exacerbations. The overall rate remains low, and so there has not been a detectable impact on the trend of COPD-related healthcare encounters at a population level. As this practice becomes increasingly common, it will be important to monitor its potential

benefits on COPD exacerbations but also its potential impact on adverse events and antimicrobial resistance patterns.

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REFERENCES

1. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017 Sep;5(9):691–706.
2. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016 Jan;21(1):14–23.
3. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, Gasevic D, Sridhar D, Campbell H, Chan KY, Sheikh A, Rudan I, Global Health Epidemiology Reference Group (GHERG). Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health. 2015 Dec;5(2):020415.
4. Gold Reports [Internet]. Global Initiative for Chronic Obstructive Lung Disease - GOLD. [cited 2019 Oct 6]. Available from: https://goldcopd.org/gold-reports/
5. Pavord ID, Jones PW, Burgel P-R, Rabe KF. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2016 Feb 19;11(Spec Iss):21–30.
6. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JAD, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, Make B, Marchetti N, Martinez FJ, Madinger NE, McEvoy C, Niewoehner DE, Porsasz J, Price CS, Reilly J, Scanlon PD, Sciurba FC, Scharf SM, Washko GR, Woodruff PG, Anthonisen NR. Azithromycin for Prevention of Exacerbations of COPD. N Engl J Med. 2011 Aug 25;365(8):689–98.
7. Herath SC, Normansell R, Maisey S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018 30;10:CD009764.

8. Yao GY, Ma YL, Zhang MQ, Gao ZC. Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: a meta-analysis. Respiration. 2013;86(3):254–60.

9. Naderi N, Assayag D, Mostafavi-Pour-Manshadi SMY, Kaddaha Z, Joubert A, Ouellet I, Drouin I, Li PZ, Bourbeau J. Long-term azithromycin therapy to reduce acute exacerbations in patients with severe chronic obstructive pulmonary disease. Respir Med. 2018;138:129–36.

10. Wang Y, Zijp TR, Bahar MA, Kocks JWH, Wilffert B, Hak E. Effects of prophylactic antibiotics on patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2018 01;73(12):3231–43.

11. Friedlander AL, Albert RK. Chronic macrolide therapy in inflammatory airways diseases. Chest. 2010 Nov;138(5):1202–12.

12. Martinez FJ, Curtis JL, Albert R. Role of macrolide therapy in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2008 Sep;3(3):331–50.

13. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Balter M, Beauchesne M-F, D'Urzo A, Goldstein R, Kaplan A, Maltais F, Sin DD, Marciniuk DD. Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence. Can J Respir Crit Care Sleep Med. 2019 Oct 18;0(0):1–23.

14. Wedzicha JA, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Hurst JR, Miravitlles M, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;50(3).

15. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol. 2003;10(2):67–71.

16. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, Laupacis A. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Sciences; 2006.

17. Canadian Institute for Health Information, Canadian Health Information Management Association. CIHI data quality study of Ontario emergency department visits for 2004-2005: executive summary. [Internet]. Ottawa: Canadian Institute for Health Information; 2007 [cited 2019 Oct 6]. Available from: http://secure.cihi.ca/cihiweb/products/vol1_nacrs_executive_summary_nov2_2007.pdf

18. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. COPD. 2009 Oct;6(5):388–94.

19. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J. 2009 Dec;16(6):183–8.

20. Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. Chronic Dis Inj Can. 2013 Jun;33(3):160–6.

21. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017 01;46(1):348–55.

22. Seemungal TAR, Wilkinson TMA, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1139–47.

23. James GDR, Petersen I, Nazareth I, Wedzicha JA, Donaldson GC. Use of long-term antibiotic treatment in COPD patients in the UK: a retrospective cohort study. Prim Care Respir J. 2013 Sep;22(3):271–7.

24. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, Celli BR, Dechman G, Dransfield MT, Fiel SB, Foreman MG, Hanania NA, Ireland BK, Marchetti N, Marciniuk DD, Mularski RA, Ornelas J, Road JD, Stickland MK. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015 Apr;147(4):894–942.

25. Wenzel RP, Fowler AA, Edmond MB. Antibiotic Prevention of Acute Exacerbations of COPD. N Engl J Med. 2012 Jul 26;367(4):340–7.

26. Peters J, Anzueto A. Azithromycin once daily for 1 year reduced acute COPD exacerbations. Ann Intern Med. 2012 Jan 17;156(2):JC1-10.

27. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, Soyza AD, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep 1;50(3):1700629.

28. Mogayzel PJ, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B. Cystic Fibrosis Pulmonary Guidelines. Am J Respir Crit Care Med. 2013 Mar 27;187(7):680–9.

TABLES

**Table 1. Baseline characteristics of patients pre- and post-Q3-2011.**

| Characteristics | Pre-Q3-2011 N=254,457* | Post-Q3-2011 N=312,370* |
|---|---|---|
| **Demographics** | | |
| Sex | | |
| Female | 132,279 (52.0%) | 162,602 (52.1%) |
| Male | 122,178 (48.0%) | 149,768 (47.9%) |
| Age at index | | |
| Mean ± SD | 76.42 ± 7.64 | 76.37 ± 8.13 |
| Median (IQR) | 76 (70-82) | 75 (69-82) |
| Age at COPD diagnosis | | |
| Mean ± SD | 68.73 ± 9.34 | 66.53 ± 10.73 |
| Median (IQR) | 68 (62-75) | 66 (59-74) |
| Income quintile | | |
| Missing | 1,232 (0.5%) | 967 (0.3%) |
| 1 (lowest) | 61,399 (24.1%) | 78,962 (25.3%) |
| 2 | 55,665 (21.9%) | 69,872 (22.4%) |
| 3 | 49,324 (19.4%) | 61,227 (19.6%) |
| 4 | 45,992 (18.1%) | 53,434 (17.1%) |
| 5 (highest) | 40,845 (16.1%) | 47,908 (15.3%) |
| Rural† | | |
| Missing | 287 (0.1%) | 374 (0.1%) |

| | | |
|---|---|---|
| No | 211,047 (82.9%) | 261,532 (83.7%) |
| Yes | 43,123 (16.9%) | 50,464 (16.2%) |
| **Comorbidities** | | |
| Asthma | 96,907 (38.1%) | 107,543 (34.4%) |
| Congestive heart failure | 70,177 (27.6%) | 78,542 (25.1%) |
| Ischemic heart disease (preceding 2 years) | 35,404 (13.9%) | 34,650 (11.1%) |
| Pneumonia (preceding 2 years) | 69,587 (27.3%) | 78,700 (25.2%) |
| **Healthcare utilization** | | |
| Hospitalizations per year‡ | | |
| Mean ± SD | 0.42 ± 0.69 | 0.37 ± 0.67 |
| ED visits per year‡ | | |
| Mean ± SD | 0.77 ± 1.54 | 0.83 ± 1.56 |
| **Medication use** | | |
| Corticosteroid days per year‡ | | |
| Mean ± SD | 12.92 ± 51.62 | 11.12 ± 47.22 |
| High-dose corticosteroid days per year‡ | | |
| Mean ± SD | 1.01 ± 4.95 | 1.26 ± 5.15 |
| Any oral steroid in previous 2 years | 70,570 (27.7%) | 96,733 (31.0%) |
| Number of long-acting inhaled agents at baseline | | |
| 1 | 140,977 (55.4%) | 140,905 (45.1%) |
| 2 | 76,832 (30.2%) | 111,904 (35.8%) |
| 3 | 36,648 (14.4%) | 59,561 (19.1%) |
| Inhaled therapy types | | |

| | | |
|---|---|---|
| LAMA only | 73,406 (28.8%) | 90,693 (29.0%) |
| ICS only | 64,056 (25.2%) | 48,270 (15.5%) |
| LABA only | 3,515 (1.4%) | 1,942 (0.6%) |
| LABA + ICS | 66,114 (26.0%) | 94,058 (30.1%) |
| LAMA + LABA | 2,157 (0.8%) | 11,697 (3.7%) |
| LAMA + ICS | 8,561 (3.4%) | 6,149 (2.0%) |
| LAMA + LABA + ICS | 36,648 (14.4%) | 59,561 (19.1%) |
| Supplemental oxygen | 17,841 (7.0%) | 27,679 (8.9%) |

SD = standard deviation; IQR = interquartile range; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta agonist.

*There were 132,701 individuals eligible in both eras.

†Rurality had 0.1% missing for each era.

‡Based on the preceding two years.

FIGURE LEGENDS

**Figure 1.** Increase in the prevalence of chronic macrolide therapy among COPD patients over time, as compared to trends in chronic prophylaxis with other common antimicrobial agents.

**Figure 2.** Prevalence of long-term macrolide therapy among COPD patients over time, stratified by a) therapy-based severity and b) exacerbation-based severity.

**Figure 3.** Interrupted time series analysis demonstrating increase in long-term macrolide therapy associated with publication of seminal randomized controlled trial demonstrating efficacy of azithromycin for prevention of exacerbations in 2011.[6] RCT = randomized controlled trial.

**Figure 4.** Overall temporal trends in COPD-related clinical outcomes. ED = emergency department.

**Figure 5.** Temporal trends in COPD-related clinical outcomes among patients with severe COPD (severity defined by intensity of inhaled therapy). ED = emergency department.

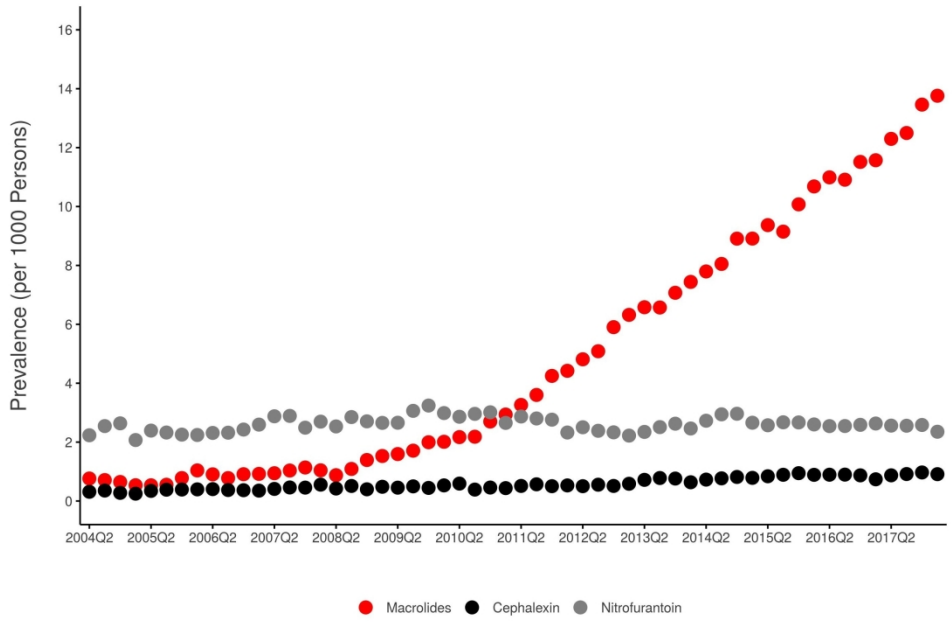



Figure 1. Increase in the prevalence of chronic macrolide therapy among COPD patients over time, as compared to trends in chronic prophylaxis with other common antimicrobial agents.

781x518mm (96 x 96 DPI)

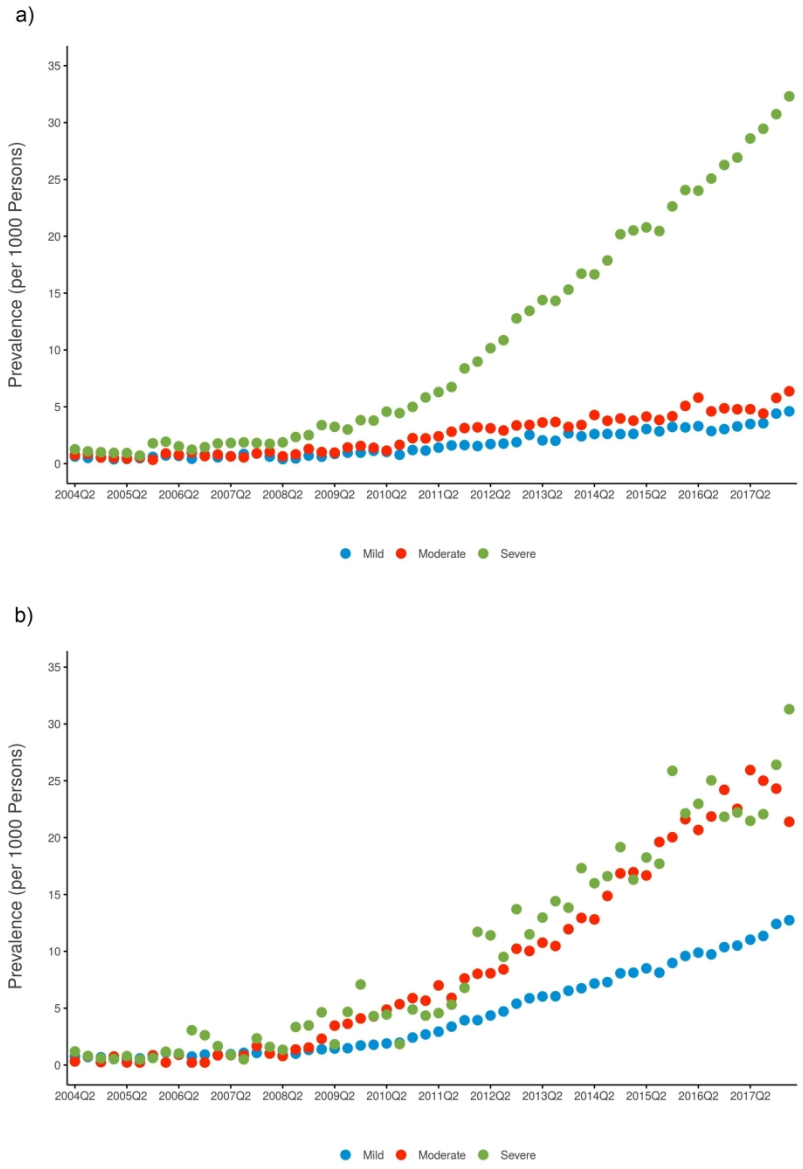



Figure 2. Prevalence of long-term macrolide therapy among COPD patients over time, stratified by a) therapy-based severity and b) exacerbation-based severity.

251x355mm (300 x 300 DPI)

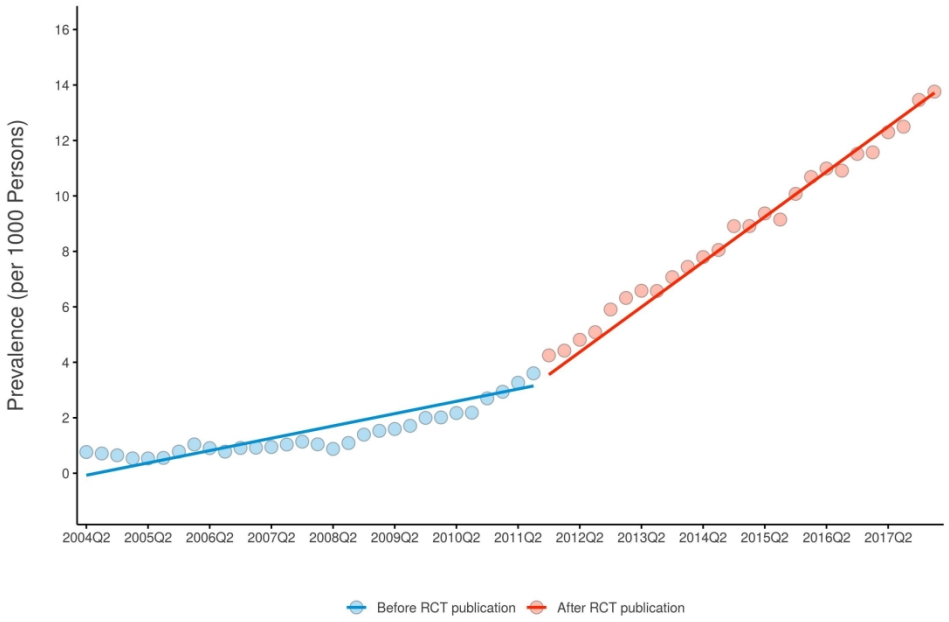



Figure 3. Interrupted time series analysis demonstrating increase in long-term macrolide therapy associated with publication of seminal randomized controlled trial demonstrating efficacy of azithromycin for prevention of exacerbations in 2011.6 RCT = randomized controlled trial.

781x519mm (96 x 96 DPI)

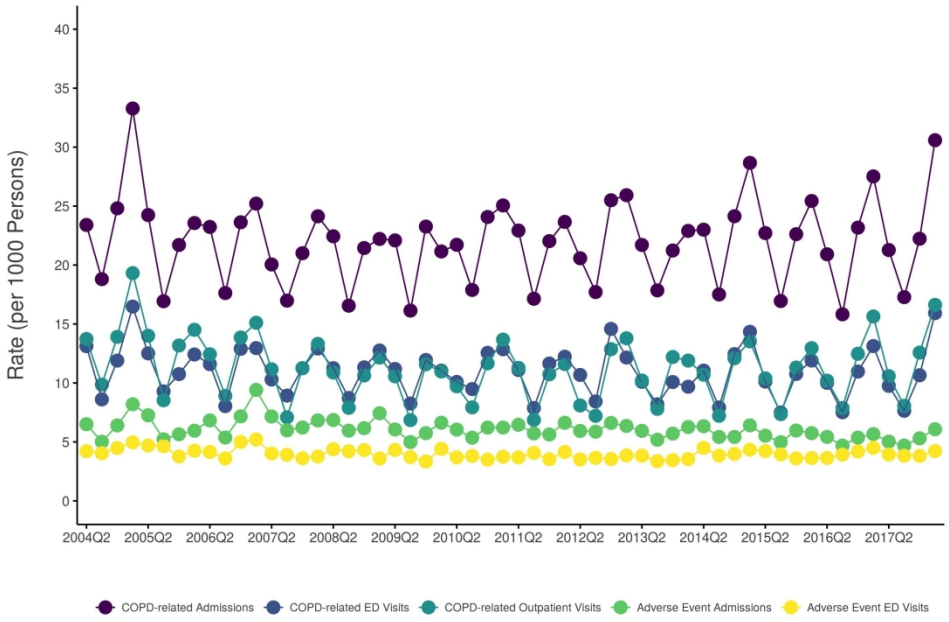



Figure 4. Overall temporal trends in COPD-related clinical outcomes. ED = emergency department.

780x519mm (96 x 96 DPI)

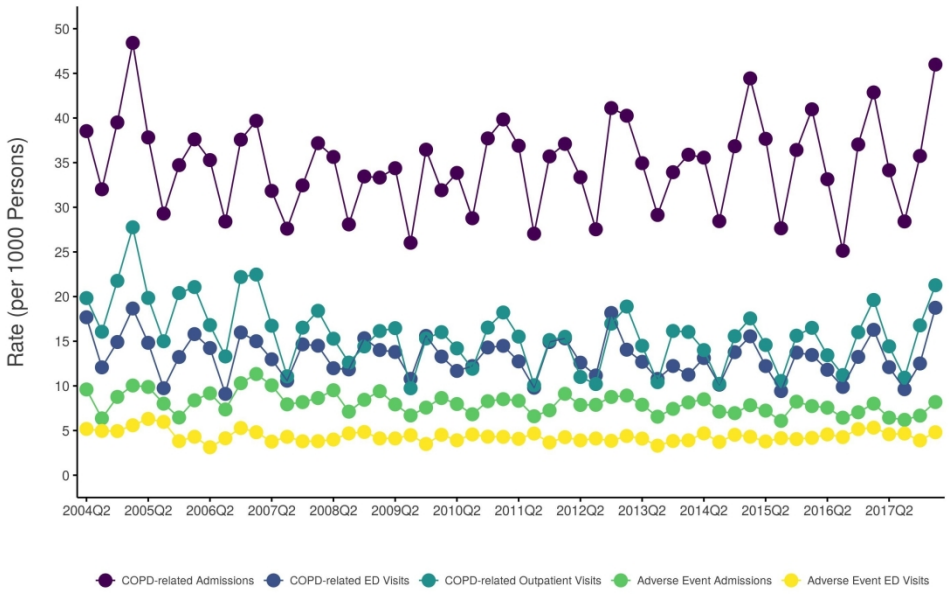



Figure 5. Temporal trends in COPD-related clinical outcomes among patients with severe COPD (severity defined by intensity of inhaled therapy). ED = emergency department.

780x484mm (96 x 96 DPI)

# Appendix

## Long-Term Macrolide Therapy for Chronic Obstructive Pulmonary Disease: A Population-Based Study

Marie Yan, Farah E. Saxena, Andrew Calzavara, Kevin A. Brown, Gary Garber, Andrea S. Gershon, Jennie Johnstone, Matthew Kumar, Bradley J. Langford, Kevin L. Schwartz, and Nick Daneman

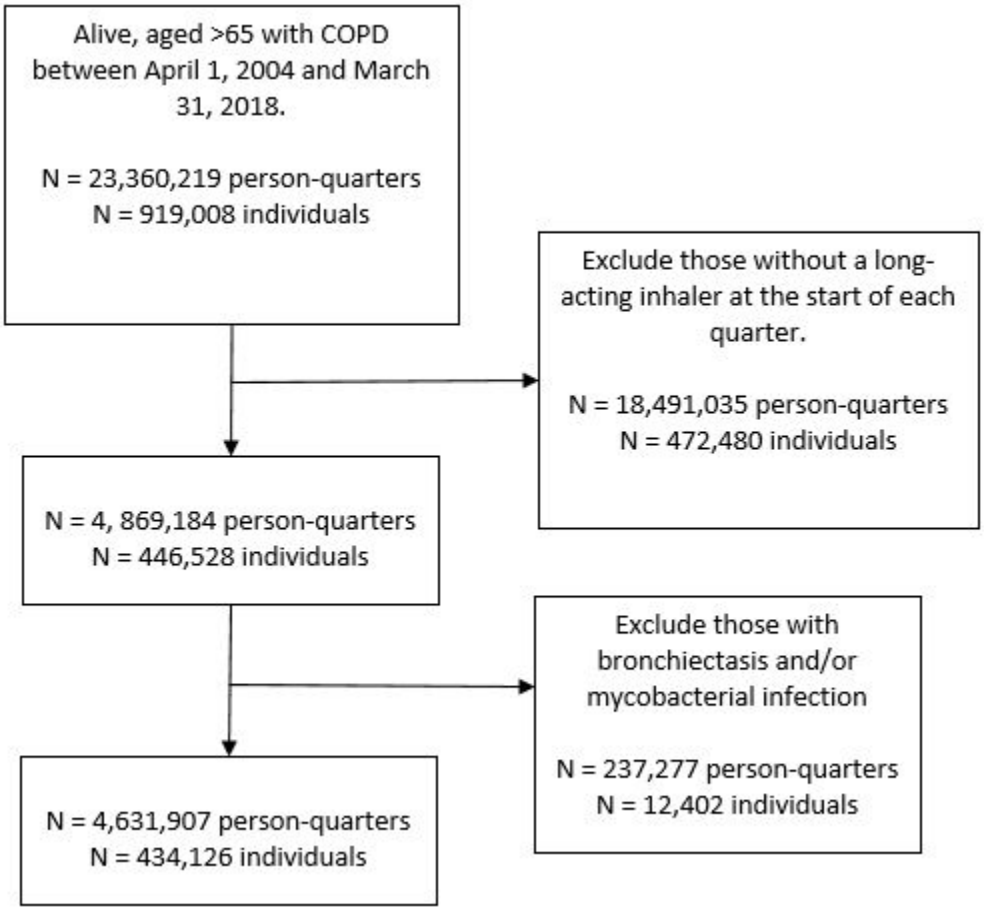
Data Sources

The Ontario Health Insurance Plan is publicly funded and covers all medically necessary services for residents of the province. The Ontario Drug Benefit program covers prescription medications (including respiratory inhalers) for patients aged 65 and over, and this database has an accuracy exceeding 99% for drugs dispensed by Ontario pharmacies.[1] Four other administrative databases were used for information on demographics, supplemental oxygen use, hospitalizations and emergency department visits. The Registered Persons Database includes patient demographics, such as age, sex, neighbourhood, income quintile and rurality. Information on supplemental oxygen use was obtained from the provincial Assistive Devices Program. The Discharge Abstract Database contains individual-level data for acute, rehabilitation, chronic and day surgery institutions in Ontario.[2] The National Ambulatory Care Reporting System includes patient visits to hospital and community-based ambulatory care (i.e., day surgery, outpatient clinics, and emergency department visits).[3]

**Table S1.** International Classification of Diseases Tenth Revision (ICD-10) codes used for each exclusion criterion, comorbidity, or potential adverse event examined in the study.

| Condition | ICD-10 Codes |
|---|---|
| Infection due to other mycobacteria | A31 |
| Bronchiectasis | J47 |
| Ischemic heart disease | I20–I25 |
| Pneumonia | J10.0, J11.0, J12–J18 |
| Arrhythmias potentially related to macrolide-induced QT prolongation including cardiac death | I46, I49.0, I49.8, I49.9 |
| Hearing impairment | H90.3, H90.4, H90.5, H90.6, H90.7, H90.8, H91.0, H91.8, H91.9 |
| General adverse medication events and drug allergy | Y40.3, T88.6, T88.7 |
| Antibiotic-resistant organisms | U88, U89 |
| *Clostridioides difficile* colitis and non-infectious diarrhea | A04.7, K52.9 |
| Candidiasis | B37 |

**Figure S1.** Study flow chart.



REFERENCES

1. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol. 2003;10(2):67–71.
2. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, Laupacis A. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Sciences; 2006.
3. Canadian Institute for Health Information, Canadian Health Information Management Association. CIHI data quality study of Ontario emergency department visits for 2004-2005: executive summary. [Internet]. Ottawa: Canadian Institute for Health Information; 2007 [cited 2019 Oct 6]. Available from: http://secure.cihi.ca/cihiweb/products/vol1_nacrs_executive_summary_nov2_2007.pdf

STROBE Statement—checklist of items that should be included in reports of observational studies

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1, 3 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 6, 7 |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7, 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 9 |
| Study size | 10 | Explain how the study size was arrived at | N/A |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 9 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 9 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | N/A |
| | | (*e*) Describe any sensitivity analyses | N/A |

Continued on next page

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Appendix |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | Appendix |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | N/A |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time<br>*Case-control study*—Report numbers in each exposure category, or summary measures of exposure<br>*Cross-sectional study*—Report numbers of outcome events or summary measures | Figure 1 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10 |
| | | (*b*) Report category boundaries when continuous variables were categorized | N/A |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 10 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 14 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11–14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | N/A |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 2 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.