Title: Long-term macrolide therapy for chronic obstructive pulmonary disease: a population-based study	
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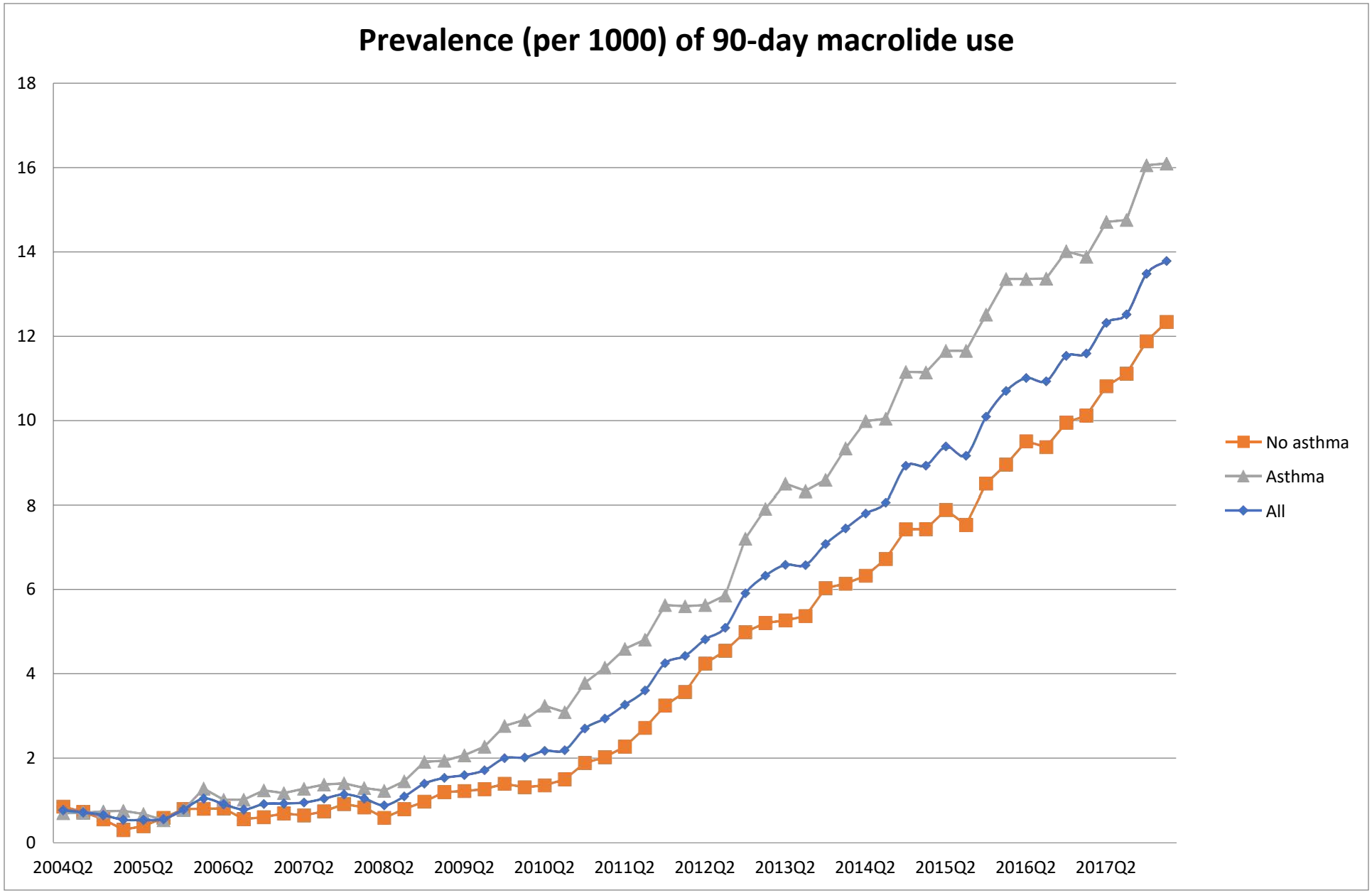
Reviewer 1: Wilson Pace	
Institution: Family Medicine, University of Colorado	
Comments	**Author response**
First, it is not clear how dual diagnosis individuals were handled. There is very little known about individuals with both an asthma and a COPD diagnosis. The percent of individuals with a COPD diagnosis as well as an asthma diagnosis (either a single dual diagnosis or as two separate ICD-10 codes) appears to vary around the world. In the US dual diagnoses can be found in some health systems on up to 40% of people with a COPD diagnosis. In European countries this may be as low as 10%. The handling of these individuals should be clarified and instead of just removing all of the dual diagnosis individuals (as is so common) a sensitivity analysis with three groups (with asthma, without asthma and combined) would be preferable from this reviewer's perspective.	Around 34-38% of the cohort (Table 1) also had a diagnosis of asthma. The caveat with using health administrative data is that it is not clear whether these patients truly had co-existing asthma or whether some were misclassified, given the clinical similarities between asthma and COPD and the frequent overlapping use of the terms in medical records. Patients with dual diagnoses were not treated differently in this study. In the sensitivity analysis requested by reviewer #1, there was no difference in the overall trend of macrolide use between the groups with and without asthma (please see figure below on page 9 of this document, data not included in manuscript due to reasons described above).
Second, it is not clear why outcomes were only examined using full population-based analytics. The likelihood that individuals placed on macrolides are like even other individuals with severe COPD is low. Thus, it would seem that matching the populations on macrolides to a group not on macrolides as closely as possible would be a logical step. While typically one thinks of using propensity scoring to understand if an outcome remains significant after controlling for non-random assignment, there are some instances where using the technique can tease out effects that are hidden at the full population level. This may be one of those places given the low overall use of macrolides. Alternatively, the	We did not perform propensity matching because our paper is not intended to replicate or question the results of the MACRO trial, which has already demonstrated the effectiveness of macrolides compared to control in preventing COPD exacerbations. Our primary interest was in understanding the real-world uptake of macrolide use, given its potential implications on antimicrobial resistance. We included outcome data for reader interest, but the overall low rate precluded detection of any outcome changes at the population level. We have rephrased the paper to highlight this point and underscore that the

authors could perform a reverse power analysis to help the reader understand the magnitude of change in exacerbation rates that they could pick up given underlying rates and the size of the various populations being analyzed. As it currently stands it is hard to place the negative outcomes into perspective.	outcome data does not discredit the results of the MACRO trial.
Reviewer 2: Mohsen Sadatsafavi	
Institution: Centre for Clinical Epidemiology and Evaluation	
Reviewer comments	**Author response**
1. The authors have not fully described how patients with COPD were identified in the data. They mention that "ICES. Residents with COPD were identified using the ICES-derived COPD database". In order to improve the reproducibility of this research, please provide the full definition (at least in the Supplementary Material).	The ICES-derived COPD database has been previously validated, and details can be found in the accompanying reference by Gershon et al. published in 2009.
2. This reviewer is concerned about the message this manuscript sends around the analysis of trends in exacerbations before/after 2011. Did we really expect to see a trend in exacerbation with this level of therapy? What if the use of macrolides has actually bent an upward curve? In general, what other policy-level changes could have happened before/after 2011? The authors' desire to examine trends in outcomes is understandable. However, this reviewer suggests that they interpret the findings in its context: COPD exacerbation trends are the results of interplay among many different factors, and as such not observing a decline after 2011 is not surprising (especially low rate of preventive therapy). The authors refer (in the Discussion) to the MACRO study also not being able to detect a	We agree with the reviewer's concern. Our paper is not intended to replicate or question the results of the MACRO trial, which has already demonstrated the effectiveness of macrolides. Our primary interest was in understanding the real-world uptake of macrolide use, given its potential implications on antimicrobial resistance. We included outcome data for reader interest, but it may be misinterpreted. We have rephrased the paper to highlight this point and emphasize that the outcome data do not discredit the results of the MACRO trial. We are not aware of any government level health policy changes pre/post- 2011 that may have affected the outcome data.

signal in ED and hospital visit. However, MACRO was seriously underpowered for these outcomes. Currently, the manuscript sends the massage that macrolides might have failed to work in the real world. This can unnecessarily discourage patients and care providers.	
3. Abstract: in the Methods section, please mention that the interrupted time series was pre-specified to compare before and after 2011. Right now it can be interpreted that this time point emerged from the analysis (as in a change-point regression).	This has been changed accordingly.

4. Page 7 of 37 (using the generated page numbers on top-left): "each patient must be receiving at least one long-acting inhaler available through Ontario Drug Benefit, such as a long-acting muscarinic antagonist (LAMA)". At what point this criterion was examined? Was it examined once during follow-up? Such that included patients had used these medications at some point during the follow-up? Or, as the sentence in the manuscript immediately following the quoted sentence implies, this criterion was examined for each quarter-year? If the latter, this reviewer is not sure how the appropriateness of macrolide therapy (as discussed in the manuscript) could be interpreted given that only quarters associate with inhaled medication use are included. Please clarify.	Eligibility criteria including use of long-acting inhalers were re-examined for each quarter-year, i.e. the study cohort was recreated for each quarter-year. This was part of our eligibility criterion because we wanted to increase the specificity of our definition of COPD. It seems highly unlikely that a patient would be given macrolide prophylaxis for COPD if they were not put on any maintenance inhalers first, and we suspect that for patients in this situation, the macrolides would probably be prescribed for another indication.	
5. Page 8 of 37, lines 28-30: "for the purposes of these comparisons, we randomly selected one eligible quarter per person in each time period". Quarter and time period are mentioned in the same sentence, which makes this sentence difficult to interpret.	This has been changed: "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 this comparison, we randomly selected one eligible quarter per person from each period."	Page 7, line 131 onwards
6. Page 9 of 37, first three lines: is it not that some exacerbations are treated by antibiotics? Would it not add to the accuracy of exacerbation definition if antibiotic use is also defined as part of criteria?	We did not include antibiotics in the definition since not all COPD exacerbations necessarily require treatment with antibiotics.	
7. Severity of COPD has a rather specific definition (e.g., GOLD COPD grades). The definitions the authors have used, while relevant for the analysis, do not equate the familiar concept of COPD severity. How about simply referring to this analysis as subgroup analysis stratified by medication and exacerbation 'gradients'?	We edited the methods section to clarify that due to the lack of spirometry data, mild/moderate/severe COPD was defined using surrogates (i.e. baseline inhaler therapy intensity and exacerbation rate). We otherwise kept the terminology as mild/moderate/severe COPD to maintain clarity for the readers. "We did not have individual spirometry data, therefore COPD severity was defined using two surrogates: 1) baseline inhaler therapy and 2) exacerbation rate." This is also discussed in the limitations section.	Page 8, line 155 onwards

8. Page 11 of 37, lines 47-50: Can the authors also report which percentage of physicians prescribed macrolides?	Out of the 24,009 physicians who prescribed long-acting inhalers to study subjects in 2017, 1,565 (6.5%) of those prescribed long-term macrolides to at least one patient. This was not included in the manuscript due to word count constraints, but we can add if the Editor prefers.	
9. Page 13 of 37, lines 22-26: "Patients who received macrolides are overwhelmingly those who continue to have exacerbations despite being on triple inhaled agents". While there is overall evidence on such associations, this sentence is not particularly backed up by results. Can the authors report on this proportion? According to CTS guidelines, azithromycin is only indicated for patients who are on triple therapy and still exacerbate (≥2 moderate or ≥1 severe in the past 12 months). As such, these are the only truly eligible group. "Patients who received macrolides are overwhelmingly those…" is legitimate if the vast majority of patients on macrolides satisfies this definition.	We have made the following changes: "Patients who received macrolides are overwhelmingly those who were already on triple inhaled agents and presumably continued to have exacerbations despite this."	Page 13, line 252 onwards
10. Page 14 of 37, line 35: COPD-related adverse events -> macrolide-related adverse events?	This has been changed accordingly.	Page 14, line 281
11. Page 14 of 37, line 50: impossible -> difficult?	This has been changed accordingly.	Page 14, line 287


Prevalence (per 1000) of 90-day macrolide use
18
16
14
12
10
8
6
4
2
0
2004Q2
2005Q2
2006Q2
2007Q2
2008Q2
2009Q2
2010Q2
2011Q2
2012Q2
2013Q2
2014Q2
2015Q2
2016Q2
2017Q2
No asthma
Asthma
All