Reviewer's report

Title: Diagnosis of asthma/COPD related to drug prescribing: a register based cross-sectional study in Swedish primary health care

Version: 1 Date: 4 October 2013

Reviewer: Shamil Haroon

Reviewer's report:

Major Compulsory revisions

1. Sharpen up the title: e.g. "Medication prescribing for asthma and COPD: a register-based cross-sectional study in Swedish primary care."

2. As a diagnostic tool salbutamol or other SABA or SAMA may be used to perform post-bronchodilator spirometry. I don't know whether this needs to be prescribed before it can be used for this purpose in Sweden but this needs to be clarified somewhere in the report, probably in either the methods or discussion. If this does need to be prescribed then this needs to be accounted for in the analysis.

3. Introduction: There has been very little mention of prescribing for COPD. Why is all the focus on asthma when the study seems to be looking at COPD as well? Please also comment more fully on prescribing for COPD in the introduction.

4. Include a table with the ATC-codes for the included medications. This could be included as a supplementary table.

5. Explain why anticholinergics were not considered in this study.

6. The section describing the study population is inadequate and inappropriately describes data extraction for specific drug labels. Instead describe the target population, and state the inclusion and exclusion criteria.

7. Clearly state the primary and secondary outcomes of the study in the methods section.

8. Method- random sample for detailed analysis: Describe the sampling method used to derive the random sample.

9. Clarify the purpose for group A, group B and the random sample in the methods section. Explain why these three groups were necessary for the study design.

10. Please provide a more detailed and specific analysis plan in the methods section, including the statistical methods. The pre-specified hypothesis tests should be clearly stated.

11. The methods and results should include staging of the severity of disease for both asthma and COPD. Without knowing the disease spectrum of the study population, it is extremely difficult to make inferences about the appropriateness of prescribing.
12. Describe the general characteristics (e.g. age, sex) of the study population with comparisons of the three groups at the beginning of the results section.

13. The discussion would benefit from more structured subheadings to help navigate the reader. In fact the whole manuscript would benefit by using the STROBE guidelines for the reporting of observational studies. I strongly recommend the authors look at these guidelines and revise their manuscript so it meets these criteria.

Minor Essential Revisions

1. Reword the first sentence of the abstract background: e.g. "Adherence to clinical practice guidelines is recommended for the diagnosis and treatment of patients to achieve optimum care."

2. The second sentence of the abstract background states that there is a gap between physician-diagnosed asthma and prescribed medication indicated for asthma. You should also comment on COPD.

3. Rather than write asthma/COPD, write "asthma or COPD" or "asthma and COPD".

4. In the last sentence of the abstract background, change "asthma/COPD medication" to "appropriate medication".

5. In the background methods, change the term "observational" to "cross-sectional".

6. The abstract methods should comment on the primary outcomes and briefly mention the analysis plan.

7. In the abstract results comment on the number and proportion of subjects who had asthma, COPD and both diagnoses.

8. In the first sentence of the abstract results clarify or define the population being referred to- is it the general primary care population or patients with asthma or COPD?

9. In the second sentence of the abstract results: e.g. "In total 46% of patients who were prescribed medication for asthma or COPD lacked a diagnosis of either condition."

9. In the third sentence of the abstract results change "prescribed to off-label indications" to "prescribed for off-label indications".

10. Reword the first line of the abstract conclusion: e.g. "Our study shows that there was a large discrepancy between the prevalence of diagnosed COPD and asthma and the prescription of medication indicated for these conditions. These findings suggest that the prevalence of prescriptions of medications indicated for asthma and COPD should not be used to estimate the prevalence of these conditions in primary care.

11. In the third sentence of the abstract conclusions you comment on asthma. You should also comment on COPD.
12. Reword the last two sentences in the abstract conclusion: e.g. "Currently the prescribing of medications for asthma and COPD does not adhere to national clinical guidelines. We recommend that the prescribing of these medications and the medical management of both asthma and COPD is regularly audited to improve the prescribing practices in Skarabourg."

13. Introduction-paragraph 1- sentence 1: reword "are respiratory diseases causing" to "represent".

14. Introduction-paragraph 1- sentence 3: reword "with an estimate of approximately 8 percent for asthma in Sweden" to "with an estimated prevalence of 8% in Sweden".

15. Introduction-paragraph 1- sentence 4: You mention that 4-6% of the adult population has COPD. Is this in Sweden or globally? Please clarify.

16. Introduction-paragraph 1- sentence 5: Reword this sentence: e.g. "There are a number of national international guidelines for the diagnosis and management of asthma and COPD."

17. Introduction-paragraph 1- sentence 5: e.g. However the diagnosis and management of these conditions often stray from these guidelines leading to both under-diagnosis, misdiagnosis and inappropriate prescribing practices.

18. Introduction-paragraph 2- sentence 1: reword "diagnosed asthma" to "a formal diagnosis of asthma being made."

19. Introduction-paragraph 2- sentence 1: Delete "With the current insights."

20. Introduction-paragraph 2- sentence 2: I'm unclear what this means. Consider rephrasing to "Thus the discrepancy between diagnosed asthma and prescribed asthma medication can potentially be reduced in these age groups."

21. Introduction-paragraph 2- sentence 4: Was this also in the Netherlands?

22. Introduction-paragraph 3- sentence 4: Expand on how off-label prescribing may be appropriate in the context of asthma and COPD.

23. Introduction- paragraph 4- last sentence: I don't think this sentence makes sense. I would probably delete the entire sentence.

24: Aim of the study: Reword: e.g. "The aim of this study was to examine the relationship between the prescribing of medications indicated for asthma and COPD and the recorded diagnosis of these conditions."

25. Method- setting- sentence 1: change "system" to "primary healthcare service".

26. Method- setting- sentence 2: Delete "the" between "1998" and "information". Delete "the" between "including" and "diagnostic". Add an apostrophe after "physicians". Replace "are" between "notes" and "assembled" to "have been". Keep "described elsewhere and previously used in register-based studies" in parentheses.

27. Method- study population- sentence 1: insert "the" between "from" and "SPCD". Insert "and" between "extracted" and "designated".
28. Method- study population- sentence 2: reword to "Medications were identified by their respective ATC-codes". Delete from "were short-acting" to "R03AK06)"

29. Method- study population: reword the sentence on ICD-codes e.g. "ICD codes J45 and J44 were used to identify patients with asthma and COPD, respectively."

30. Method- random sample for detailed analysis- paragraph 1. Describe the sampling method used to derive the random sample.

31. Method- random sample for detailed analysis- paragraph 1- sentence 2: delete "A number" and "detailed".

32. Method- random sample for detailed analysis- paragraph 1- sentence 3: Delete "A total of" and replace with "insufficient".

33. Method- random sample for detailed analysis- paragraph 1- sentence 4: reword, e.g. "The records of these patients were reviewed in detail."

34. Method- random sample for detailed analysis- paragraph 1- sentence 5: insert "the" between "included" and "indication" and replace "given" with "recorded".

35. Method- random sample for detailed analysis- paragraph 1- last sentence: This is unclear. Please explain why it was done. Are you stating that you were checking for the representativeness of the random sample in terms of key demographic and clinical factors?

36. Method- random sample for detailed analysis- paragraph 2- make a bullet point list.

37. Method- statistical methods- sentence 2: reword, e.g. "The data were presented as absolute numbers and percentages and the statistical significance of differences between groups were assessed using chi-squared tests with a significance threshold of p<0.05".

38. Results- paragraph 3- sentence 1: change "diagnosis" to "diagnoses" and change "Figure" to "figure".

39. Results- paragraph 3- sentence 3: insert "patients" between "youngest" and "and".

40. Results- paragraph 3- sentence 4: How was this average calculated? Was it a weighted average?

41. Results- paragraph 3- sentence 4: delete "gap" and replace with "discrepancy" and insert "prescribing" between "medication" and "and".

42. Results- paragraph 3- sentence 5: reword, e.g. "As expected asthma was the predominant diagnosis in younger patients and in patients older than 30 years COPD rose in prevalence with age".

43. Results- paragraph 3: Also comment on the trend in the mismatch between prevalence of asthma and COPD medication prescriptions and prevalence of disease with age. Perhaps you should quantify this.

44. Results- random sample- paragraph 1- sentence 2: insert "the" between in"
and "SPCD".

45. Results- random sample- paragraph 2- sentence 3: Delete "Consequently". Change "were lacking diagnosis" to "therefore lacked a diagnosis".

46. Results- random sample- paragraph 2- sentence 4: change "Out of these individuals" to "However, among these individuals"

47. Results- random sample- paragraph 2- sentence 5: Please define what constitutes a provisional diagnosis. This should have been described in the methods.

48. Results- random sample- paragraph 2- sentence 6: "30%" appears to be incorrect (85/235=36.2%). Similarly 54% appears to be incorrect (150/235=63.8%). I think either the wording of the sentence or the denominator you have used in the calculation has been mixed up.

49. Results- random sample- paragraph 2- sentence 7: Rephrase, e.g. "Although there appeared to be differences in prescribing by sex, a chi-squared test to assess differences in prescribing between men and women was not statistically significant (p=0.061).

50. Results- random sample- paragraph 2- sentence 8: replace "diagnose" with "investigation" and replace "or acute bronchitis" with "and acute bronchitis."

51. Results- random sample- paragraph 3- sentence 1: insert "a" between "with" and "recorded".

52. Results- random sample- paragraph 3- sentence 1: Please clarify whether these were the same medications or different medications or does this refer to the number of course of medication?

53. Results- random sample- paragraph 3- sentence 3: insert "medication" after "off-label" and delete "action".

54. Results- random sample- paragraph 3- sentence 3:State how this p-value (p<0.001) was derived.

55. Results- random sample- paragraph 3- sentence 3: "also SABA as only medication"- I don't understand this- please clarify. Earlier in the sentence you state that a single prescription of SABA was the most common. What is the difference between this and "SABA as the only medication".

56. Results- final sentence: That doesn't sound very surprising. What's more interesting is the difference in the prescribing rate between those with diagnoses and those without. I would therefore try to quantify this.

57. You should also comment on the relatively low level of spirometry testing for both COPD and asthma.

58. Discussion- paragraph 1- sentence 1: "recorded diagnosis...data." Rephrase, e.g. "...recorded prevalence of asthma and COPD and the prescribing of related medication, among a large broadly representative group of patients, and based on individual patient records."

59. Discussion- paragraph 1- sentence 2: You stated that subjects with disease were under-medicated. This isn't necessarily true. You did not grade the severity
of disease so it is difficult to ascertain how much and what types of medication may have been indicated for the study population.

60. Discussion- paragraph 2- sentence 1: delete "a complex representation" to "the complex overlap". Rephrase "medication of asthma/COPD" to "medication prescribing for asthma and COPD."

61. Discussion- paragraph 2- sentence 2: Replace this sentence with "The figure illustrates the large discrepancy between the prevalence of asthma and COPD and the prescribing of medication indicated for these conditions."

62. Discussion- paragraph 2- sentence 3: delete "the" between "of" and "individuals". Replace "indicate" with "likely indicates".

62. Discussion- paragraph 2- sentence 4: I'm unclear what this means. Please clarify.

63. Discussion- paragraph 3- sentence 1: delete "indicate" and replace with "probably indicates".

64. Discussion- paragraph 3- sentence 2: replace "under diagnosing of individuals actually having" with "under-diagnosis of". Also delete "for asthma and COPD" at the end of the sentence.

65. Discussion- paragraph 3- sentence 3: delete this sentence and add to the end of sentence 2 "as compared to the national prevalence of 8% and 4%, respectively."

66. Discussion- paragraph 4- sentence 3: replace "and among...among the oldest" to "and a relatively lower volume of prescribing in the elderly population, which runs counter to the findings of another Swedish study." Also I'm not sure this is clear from the results- could you please clarify this.

67. Discussion- paragraph 4- sentence 5: Please explain how this would account for this discrepancy. Also please clarify the last part of this sentence "and other caregivers for the youngest" (this is unclear).

68. Discussion- paragraph 5: this is a rather large paragraph. Please divide it into several smaller paragraphs.

69. Discussion- paragraph 5- sentence 1: The definition of "off-label" used in this study should also be included in the methods section.

70. Discussion- paragraph 5- sentence 2: Please explain who you defined a provisional diagnosis of asthma or COPD (as compared to a confirmed diagnosis).

71. Discussion- paragraph 5- sentence 3: Delete "per definition".

72. Discussion- paragraph 5- sentence 4: Delete this sentence "This...made."

73. Discussion- paragraph 5- sentence 6: replace "records" with "history".

74. Discussion- paragraph 5- sentence 6: Was that 20% of medications that were initially considered to have been prescribed off-label or was it of all medications prescribed? Please clarify.

75. Discussion- paragraph 5- sentence 7: Replace "this" with "our".
76. Discussion- paragraph 5- sentence 9: Insert "off-label prescribing in" between "concerning" and "children".

77. Discussion- paragraph 5- sentence 12: Replace "procedure" with "practice" and replace "indicating lack" with "suggesting a lack"

78. Discussion- paragraph 5- sentence 13: Replace "waist" with "waste".

79. Discussion- paragraph 5- sentence 13: You may need to expand on this- I wasn't aware prescribing of SABAs for example was commonly associated with significant side effects in either adults or children. Are you referring to specific medications? If so, which ones?

80. Discussion- paragraph 5- sentence 14: delete "a diagnostic tool" and replace with "part of a diagnostic assessment".

81. Discussion- paragraph 5- sentence 15: rephrase "the measurements...were investigated objectively" to e.g. "a trial of medication may have been used for diagnosis rather than peak expiratory flow measurement or spirometry since these objectives measures were lacking in a large number of patients."

82. Discussion- paragraph 5- sentence 16: This end of this sentence is a bit nebulous. Please be more specific.

83. Discussion- paragraph 6- sentence 1: delete "of the patients".

84. Discussion- paragraph 5- sentence 1: Explain over what time period these medications were prescribed.

85: Discussion- paragraph 5- sentence 1: "indicating that patients...treatment"- I don't agree with this. This depends on the severity and control of disease which your study has not addressed.

86. Discussion- paragraph 5- sentence 2: This sentence is very confusing. You state that 79% of the patients with asthma received medication at least once and then go on to say that 37% did not receive any medication. How can this be so?

87. Discussion- paragraph 5- sentence 3: You mention adherence. How does your study capture information on adherence? I didn't see this in the results so I can't see how your results suggest medication adherence is low.

88. Discussion- paragraph 5- sentence 4: replace "seem somewhat" with "appears".

89. Discussion- paragraph 5- sentence 5: replace "they contribute" to "contributed". Delete "asthma/COPD".

90. Discussion- paragraph 5- sentence 6: delete "one year" and replace with "a year's". Replace "data indicate" with "findings suggest".

91. Discussion- paragraph 5- sentence 6: Over-medication in which group? Patients with COPD? Patients without a diagnosis of COPD. Please be more specific.

92. Discussion- paragraph 5- sentence 10: rephrase, e.g. "This is a clear shortfall in the diagnosis of COPD and a lack of clinical resource and training may be responsible." Do you have any references on level of spirometry training and
availability of spirometry in Swedish primary care? If so I would include a comment on this.

93. Discussion- paragraph 5- sentence-10: rephrase, e.g. "Against this background of deficiencies in objective diagnostic measures, a trial of medication to help diagnose asthma and COPD appears to be widespread practice."

94. Discussion- paragraph 6- sentence- 6: delete this sentence.

95. Discussion- paragraph 6- sentence- 7: replace "levels of asthma...prevalence" with "prevalence of asthma and COPD cannot be reliably estimated from the prevalence of prescribing of medication indicated for either condition".

96. Discussion- strengths and limitations- paragraph 1- sentence 1: How complete was the database? Did cover 100% of the study population? If not you may wish to state "The database we used had good coverage of the population of Skaraborg (and state the percentage coverage if this is known)". Also insert "the" between "for" and "population".

97. Discussion- strengths and limitations- paragraph 1- sentence 3: insert "of patient records" after "examination".

98. Discussion- strengths and limitations- paragraph 1- sentence 4: rephrase, e.g. "However the characteristics of our random sample were similar to the whole population of Skaraborg (table 1) and therefore likely to be representative of the region."

99. Discussion- strengths and limitations- paragraph 1- sentence 5: delete "performed" and insert "of patient records after "field".

100. Discussion- strengths and limitations- paragraph 2- sentence 1: insert "or appropriate coded" after "documented".

101. Discussion- strengths and limitations- paragraph 2- sentence 2: replace "analysis" with "examination".

102. Discussion- strengths and limitations- paragraph 2- sentence 3: replace "are" with "were".

103. Discussion- strengths and limitations- paragraph 2- sentence 4: rephrase, e.g. "Also we did not have data on pharmacy dispensing or medication compliance."

104. Discussion- strengths and limitations- paragraph 2- sentence 6: The medication use was limited to asthma/COPD medication. Why is this a limitation? Isn't this what the study is about?

105. Discussion- strengths and limitations- paragraph 2- sentence 8: rephrase, e.g. "Our evaluation of off-label medication use is limited by indication. We did not examine off-label prescribing by age, dosage, duration, or route of administration."

106. Discussion- strengths and limitations- paragraph 2- sentence 9: Delete this sentence.

107. Conclusion- sentence 1: delete "the" before "prescriptions".
108. Conclusion- sentence 4: Our findings suggest more effort must be made to improve the prescribing of medication indicated for asthma and COPD so they align with current guidelines. Regular audit of medication prescribing may help to achieve this.

109. Author contribution: insert "the" before "paper" and "manuscript".

110. Table 1 and 2 should include severity of asthma and COPD. This is really quite important to explain type and volume of medication prescribing, particularly in the random sample.

111. Table 1. Rephrase note, e.g. "Groups A and B are not mutually exclusive as some patients with COPD also have a diagnosis of asthma."

112. Be more specific in the table header: Demographic characteristics of subjects in the random sample (stratified by recorded asthma or COPD diagnosis, provisional diagnoses, trial by medication and off-label prescribing).

Discretionary Revisions

1. There is a study by Dr Rupert Jones and colleagues which is soon to be published (the abstract was recently presented at the last ERS Congress) that shows very poor prescribing practices in relation to COPD in UK primary care. It would be worth having a look for this and you may wish to reference the abstract, which you can find on the ERS website.

2. A useful follow-on study would be to do an economic evaluation of the excess costs incurred in Sweden from inappropriate prescribing of medication for asthma and COPD.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests