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Title	Cost-related nonadherence to prescribed medicines among older Canadians in 2014: a cross-sectional analysis of a telephone survey
Authors	Augustine Lee BA, Steve Morgan PhD
Reviewer 1	Dr. John S. Sampalis BSc BA MSc PhD
Institution	JSS Medical Research, St-Laurent, Que.
General comments (author response in bold)	This is excellent work. Congratulations for quantifying what we are all suspecting. I have the following comments and suggestions: 1.Your outcome measure, being dichotomous, defined as any prescription in the last 12 months that was not filled due to financial reasons (CRNA) may not actually capture the outcome correctly. This is because by most definitions, patients that have a Medication Possession Ratio (MPR) > 80%; meaning in general that they take more than 80% of their prescriptions, are considered to be adherent to treatment. Hence by your definition, you may be including patients that have missed only one monthly dose in the non-adherent group, and this may be OK. What I believe happens though is that patients miss more than one monthly dose and this would make the consequences even more severe from an outcomes perspective. It would be interesting, if you have the data, to report the distribution of number of monthly missed doses per year. This would give us a better description of the problem. **Response: We agree that available survey data on CRNA are an imperfect gauge or the problem. But they are the best gauge we currently have to measure the relative performance of different systems in their ability to encourage access to needed medicines. Perhaps for future work among the linked health data centres in Canada, a study could be developed to more carefully measure the degree of adherence to therapies across provinces, following an index event such as AMI. That would be a fantastic study to see.** 2. With patients taking more than one medication it will also be important to know if they are non-adherent to all of them or just some of them. **Response: This too is a limitation of current survey work on CRNA. There is a Canadian team working on asking CCHS questions that will follow up on CRNA responses with a query about which treatments they did not take as prescribed.** 3. Another dimension that is missing in your analysis is more qualitative and somewhat related to the above comment. Missing a dose of a medication for hyperlipidemia may have different impact that missing a dose of medication for diabetes or congestive heart failure or even an anti-psychotic. One hypothesis may be that patients prioritize the important medications and use their resources to pay for the more critical ones. Perhaps the profile of medications for which the respondents missed doses would be helpful. This in combination with the number of medications used will complete the profile of patients and their drug utilization. If we has this information, we can better appreciate the impact of the problem. **Response: This too is important work that requires more than survey information, indeed more than administrative data. One of us (Morgan) is involved in a qualitative study to understand whether and how patients prioritize medications when facing affordability challenges. That work is not likely to be published until late 2017.** 4. A sensitivity analysis in which the "don't know" answers were removed or considered in the opposite direction, i.e. having had CRNA would convince us that there is no bias in the results. **Response: This is a valid point. In our preliminary data analyses, we did exclude “don’t know” responses. The results were very similar and we therefore opted to include the more conservative view of the nature of the problem of CRNA on the assumption that “do not know” is more likely to mean “no” than something akin to a “yes.”** 5.Given that this was a multi-national survey, it would be interesting to see how Canada compares to other countries with different health care systems. At least then we may be able to suggest that the Canadian Universal Health Care System offers some benefits. Perhaps this analysis in detail can be another paper, but a brief mention in the discussion would be interesting. **Response: We have a forthcoming paper that assesses CRNA across countries. If published in time, we will cite it in this paper’s discussion section.** 6. Why use Ontario as a reference category. This makes interpretation of the results

	confusing. The real question is whether living in one region is associated with an increased rate of CRNA when compared to the rest of the country. I would suggest changing the model specifications to "indicator" so that the logistic regression parameter estimates and derived OR represent the comparison of the region to the rest of Canada. **Response: We appreciate the suggestion for an alternative approach. Given that the Ontario reference group is considered a standard approach as other studies of CRNA in Canada, we have opted to keep the regressions as reported so that results can be more readily compared to previous studies.** 7. Logistic regression models have low positive predictive accuracy when we have low prevalence of the outcome. In this analysis the prevalence of the outcome is 8.3%. This means, that even if the LR model classifies all observations as negative (not having the outcome) it will be 92% accurate but will have low positive predictive value. You should assess the model fit and consider revising the level for positive classification or repeating the analysis with one or preferably more smaller random sample of non CRNA respondents, as example 3:1 or 5:1 of controls to cases. **Response: We don't disagree that statistical models of low frequency events have limited predictive power. We conducted model specification tests and our pseudo R2 values are not out of line with comparable work (.11). Thus, we feel it is appropriate to use these models, which are consistent with all other studies of CRNA that we have come across.**
Reviewer 2	Dr. Irfan Amir Dhalla
Institution	University of Toronto, Department of Medicine, Toronto, Ont.
General comments (author response in bold)	This is a well written paper on an important topic, and makes a nice contribution to what we already know on this topic. I have no major comments. Here are a few minor suggestions for the authors to consider as they revise the manuscript: ABSTRACT 1. I'd suggest making clear in the background sentence that only older adults were included. **Response: Have edited the abstract accordingly.** RESULTS 1. Where the authors note that 4690 patients had completed data, I would suggest including the denominator again. **Response: We have edited the text accordingly.** 2. Small typo - 665 should be 65 **Response: We have edited the text accordingly.** DISCUSSION 1. I'd recommend using adherence, adhere, etc., and not compliance, comply, etc. **Response: Thanks for catching that. We have edited the text and appreciate that the use of specific terms is important in this field.** 2. In the second paragraph, one key reason is likely that drug coverage is better in the 65+ population in Canada. The authors note this in the third paragraph but I think it should be in the second paragraph as well (or instead). **Response: We have edited the text accordingly.** 3. The sentence starting with "We do not believe that regional and socioeconomic..." is correct but perhaps slightly awkwardly worded, since some readers will assume "national differences" mean those between regions or provinces, when the authors really mean differences between one group of Canadians and another. **Response: We have edited the text to clarify our intended meaning.** TABLE 1 1. I am struck by how large the difference in CRNA between the 55-65 (should it be 64?) and 65+ populations is. Perhaps this could be emphasized more in the text. **Response: We have added further discussion of this finding.** GENERAL 1. Might it be possible to use the model estimate the expected CRNA for a low-income 60 year old woman in fair or poor health who does not have private insurance? This might make for an interesting few sentences in the discussion. **Response: Thank you. We have added a line in the discussion section that**

	places results in context using the predicted probability for a sample vignette.
Reviewer 3	Dr. Jae Kennedy
Institution	Washington State University, Health Policy and Administration
General comments (author response in bold)	A solid, but slightly unfocused analysis of CWF data. 1. I'd suggest including unadjusted odds ratios in table 2, and more clearly explaining and justifying the stratification by age group. **Response: We have provided the unadjusted odds ratios in an appendix, as it was difficult to fit into a single table with stratification. We chose to stratify by age group owing to the differences in availability and/or extent of public drug coverage at age 65 in several Canadian provinces.**