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Title	Prescription medication nonadherence associated with food insecurity: a population-based cross-sectional study
Authors	Fei Men PhD, Craig Gundersen PhD, Marcelo L. Urquia PhD, Valerie Tarasuk PhD
Reviewer 1	Dr. Joel Lexchin
Institution	School of Health Policy and Management, York University, Toronto, Ont.
General comments (author response in bold)	This study looks at the relationship between food insecurity and cost related nonadherence to prescription medications. 1. The authors should mention that people who cannot afford prescription drugs are just as likely to forgo essential as nonessential medications. **We added a brief discussion of this point in the "limitations" (page [p] 10; line [l] 228-232).** 2. Line 135: I'm not sure how the authors arrived at the figure of 753 nonadherents. 7231 subjects x nonadherence rate of 9.2% = 665. **The number "753" was unweighted from the actual sample whereas "9.2%" was weighted percentage. We added bootstrap confidence interval after all weighted percentages in the revised text to avoid confusion (p 6; l 142).** 3. Lines 148-149: I'm confused about the meaning of the phrase "reporting of three or more conditions among those with any condition." **The phrase refers to those who reported having three or more chronic conditions while limiting the sample to those with any condition. We removed this outcome along with several others from the revised text.** 4. Line 219: Whether insurance coverage eliminates nonadherence would depend on whether there were still copays, deductibles, etc. and what their size is as the authors note below. **We rephrased the sentence in the second paragraph of "interpretation" section to stress the importance of out-of-pocket expenses on nonadherence (p 9; l 208-211).** 5. Lines 233-234: Patients may also avoid seeing doctors because they know that they would not be able to afford to purchase a prescription. **We emphasized this possibility in the revised "limitations" (p 9-10; l 220-225).**
Reviewer 2	Dr. Michael Robert Law
Institution	Centre for Health Services and Policy Research, The University of British Columbia, Vancouver, BC
General comments (author response in bold)	This paper presents an analysis of association between food insecurity and cost-related nonadherence in Canada. The analysis uses the Canadian Community Health Survey conducted by Statistics Canada in 2015-16. I have several comments about the analysis outlined below. Abstract: 1. The methods section should outline how many respondents were used **We added number of respondents to the methods section (page [p] 1; line [l] 11).**

Introduction

2. The claim that "Law and colleagues found one-fifth of Canadians had no insurance for prescription drugs" is not correct. The question on the CCHS which this refers to asks whether someone has insurance that covers all or a part of the cost of their prescription drugs. Therefore, people that have catastrophic coverage (e.g. Ontario's Trillium program, BC's Fair Pharmacare) might report 'no' when in fact they do have drug insurance. The number of truly uninsured individuals in Canada is in fact very low, but the terms of that insurance may not offer financial protection.

We removed the sentence from the introduction and made clear elsewhere in the text that the insurance status was self-reported and that lack of enrollment and high out-of-pocket costs could still result in nonadherence for those with insurance coverage (e.g. p 8; l 186-190).

Methods

3. It's unclear to me why the authors chose to focus only on the working-age population. I believe it would be very interesting to see if the associations they found also appear in youth and older adults.

We added seniors 65 years and older to our sample. The results largely remained the same (p 7; l 155-158). We did not include the youth in the main analysis because they were not assigned bootstrap weights by Statistics Canada. However, we included the youth in an exploratory test with simple (versus bootstrap) weights applied and found similar results as the ones from adult sample (prevalence ratio [PR] 1.86, 95% confidence interval [CI] 1.31-2.64 for marginal food insecurity; 3.87, 95% CI 2.97-5.03 for moderate food insecurity; and 5.13, 95% CI 3.90-6.73 for severe food insecurity).

4. The methods state that Yukon was not included in the food security module, but it does not appear in the triage figure (Fig 1). This should be taken out.

Yukon did not show up in the triage figure because all territories were excluded from the rapid response module. We clarified this point in the revised "setting" section (p 4; l 79-82) and Fig 1 (p 19).

5. While the paper initially presents itself as an exploration of the link with food insecurity, the authors present a series of models on other factors. These should be included in the introduction section with respect to their motivation.

We excluded all outcomes from the original Table 2 to focus on cost-related nonadherence. We clarified our motivation for the secondary analyses in the "outcomes" section (p 4; l 92-93).

6. The methods state that the authors used "robust standard errors", but do not indicate whether they used the appropriate sample weights and bootstrapping methods required to correctly analyze this survey. If they have not used these methods, they should do so in any future version.

We used 1000-replication bootstrap weights from CCHS in our revised analyses (p 6; l 133). For the sensitivity analysis using multiple imputation on covariates with missing values and that including the youth 12-17 years old in the sample, we used simple weights due to incompatibility with and

absence of bootstrap weights, respectively. Prevalence ratios (PR) for marginal, moderate, and severe food insecurity were 1.84 (95% confidence interval [CI] 1.28-2.66), 3.75 (95% CI 2.84-4.96), and 4.99 (95% CI 3.79-6.58), respectively (p<0.002 for all), in the sensitivity test applying multiple imputation. The comparable figures for the other sensitivity test including youth were 1.86 (95% CI 1.31-2.64, 3.87 (95% CI 2.97-5.03), and 5.13 (95% CI 3.90-6.73) for marginal, moderate, and severe food insecurity, respectively (p<0.0006 for all). These results were qualitatively similar to the ones from the main analyses shown on Table 2 from the manuscript (p 17).

7. It's not clear how predicted probabilities were calculated. I assume at the sample mean of other covariates, but that should be laid out.
We calculated the sample mean of individual probabilities as opposed to probabilities at means. This information was added to the "statistical analysis" section (p 6; l 125).

Results

8. As above, the statement regarding "79.6% had prescription insurance" is incorrect as public insurance is notably under-reported in Canada (see Grootendorst, Newman, and Levine. 2003).
We removed the sentence and made clear in "limitations" and elsewhere that the insurance coverage was self-reported and likely underreported (p 10; l 236).

9. Any reported proportions in the first paragraph should also include 95% confidence intervals, particularly those with smaller sample sizes.
We added 95% confidence intervals to all weighted proportions in "results" (p 6-7; l 142-153) and Table 1 (p 15-16).

10. Overall, I found the results hard to follow. There are a ton of different analyses without a lot of interpretation to lead the reader through the story. I think the authors should seriously consider simplifying their presentation.
We removed the original Table 2 and its associated analyses to focus on nonadherence. We kept three secondary outcomes from Table 3 (former Table 4) to explore the relationship between food insecurity and nonadherence-related health repercussions.

Conclusions

11. While CRNA could be on the pathway to poorer health, as the authors suggest, it could also be that both factors derive from a common cause (income insecurity). This possibility should be acknowledged in the paper.
We acknowledged this possibility in the revised "limitations" (p 10; l 225-227).

12. The authors are correct to point out the large number of people who are currently insured who experience CRNA. The policy implication here is that the cost to patients should be reduced regardless of the insurance plan in question.
We added this implication to the revised "interpretation" (p 9; l 215-217).

	13. I'm not convinced that panel data would eliminate the issues of causality for this analysis, as it would require significant changes in income that likely don't occur. A natural experiment caused by a change in prescription drug costs would be one option (but a rare one). **We removed the suggestion on "panel data" from the "limitations" (p 9-10).** 14. It's unclear to me how one would study food insecurity from clinical records. **We removed the suggestion on "clinical records" from the "limitations". Indeed, food insecurity is measured using self-reported survey data. Our revised "limitations" focused on the potential biases from self-reported variables other than food insecurity (p 10; l 235-239).** 15. The authors suggest in the final paragraph that these issues ought to address both issues, but don't talk about whether there are programs or policies that might do this. An exploration of this topic would be interesting, particularly as they are making a claim that they are linked in their analysis. **We added a brief discussion of the policies that increase income and reduce out-of-pocket prescription spending to the "interpretation" section (p 9; l 199-217). Due to limited space and scope, we are leaving discussion of specific policy alternatives to future work.**
Reviewer 3	Dr. Steve Morgan
Institution	Centre for Health Services and Policy Research, The University of British Columbia, Vancouver, BC
General comments (author response in bold)	I read this paper with interest because it concerns the CRNA literature that I have contributed to and the food security literature that I was interested in learning more about. 1. The authors present a sub-analysis of the 2016 Canadian Community Health Survey in an effort to quantify the association between CRNA and food insecurity. They find strong associations that are worthy of publication; however, the manuscript could be improved with the addition of a theoretical or conceptual framework to guide analysis and some possible changes to the empirical modelling. **We discussed our conceptual framework in the second paragraph of the text. We also made changes to the empirical modeling as suggested (page [p] 2-3; line [l] 48-63).** 2. I think the most important change that could be made to this paper would be the addition of a theoretical framework to help the reader understand factors that influence CRNA, factors that influence food security, the degree of overlap in those factors of influence, and, possibly, any direct associations between food insecurity and CRNA. **We added Goldsmith et al. (2017) and Piette et al. (2006) in our conceptual framework to explain determinants of CRNA (p 2; l 49-53). There is a substantial overlap between the CRNA determinants and food insecurity determinants, though the association between food insecurity and CRNA is more likely to stem from low resource versus a direct causal link (p 10; l 226-227).** 3. I am familiar with conceptual models that might be applied to understand factors that influence CRNA. These would include behavioral models of health services

utilization more generally (e.g., Andersen and Aday's concepts of predisposing, enabling, needs-related factors), as well as models that are specific to the CRNA phenomenon (e.g., the work by Piette and colleagues). Although I'm not familiar with the food security literature, I'm sure there are models that would help to identify and categorize factors that might make household susceptible to food insecurity.

Similar to CRNA, food insecurity is also mainly determined by financial constraints, represented by income, homeownership, and insurance in our model. CRNA and food insecurity share a lot of demographic determinants as well (e.g. sex, age, Aboriginal status, household type, province of residence). Although unable to account for all types of determinants in our models, we have incorporated the major confounders to the extent possible.

4. Identifying and categorizing factors that could influence CRNA and food insecurity can assist with model development as well as interpretation of findings. Regarding the former, for example, I admire the comprehensive nature of the model that is specified in this study; however, I do worry that the model may be over specified and that there may be some multicollinearity as a result.
Removing education and income source from the model does substantially lower variance inflation factor (VIF) without affecting the model fit. Therefore we removed the two variables as suggested (p 5; l 108-116).

5. The fully adjusted models in this paper include the source of income, level of income, level of income squared, education, and presence of extended health insurance. In previous work by my research team, including unpublished work done in preparation of models that we have published, we have found factors such as income, education, and employment (which might be akin to source of income in this study) to be reasonably predictive of the presence of drug insurance. I think the authors could address the potential risk of resulting multicollinearity by presenting the results of a more parsimonious model that included fewer variables intended to capture the gist of entire categories of influence (e.g., boil down the enabling factors to just income quintiles and presence of insurance).
We removed education and income source from our model and transformed the continuous income measure into income quartiles (p 5; l 108-116). Given the space limitation and our focus on food insecurity, we did not experiment with alternative sets of covariates.

6. Particularly given that there are studies from the United States that look at CRNA and food insecurity, as well as studies from Canada that look at food insecurity and chronic disease management, a conceptual framework would also make the contributions of this paper clearer and the policy implications more compelling. This need not be a detailed conceptual manuscript; something as simple as a table describing independent variables and the likely pathway through which they influence the outcomes of CRNA and food insecurity would suffice.
We explained the potential pathway through which CRNA and food insecurity may be linked through financial constraints and other socioeconomic determinants in the revised text (p 2-3; l 48-57).

7. Regarding the modeling in the paper, the method section uses the term "secondary outcomes" to described would appear to be explanatory/independent variables.

We removed the "frequency of nonadherence" and "cost of last forgone prescription" from the analyses, which appeared to be causes of CRNA. Instead, we focused our secondary outcomes on the perceived consequences of CRNA, including "nonadherence to drugs for chronic illnesses", "worse health", and "greater health care usage" (p 4; l 92-101).

8. Regarding some of the indicator variables, it would be helpful to the reader if we could understand why certain cut offs were used. Why, for example, was three or more chronic conditions from the selected list of conditions used as the cut off for that indicator variable? Wish this the modal / median value for the variable? Or was this threshold chosen on the basis of a particular theory or previous studies? The same question could be asked for the indicator variable concerning the number of different drugs prescribed for a patient.
We removed all the outcome variables of the original Table 2 from our analyses, including the two variables referenced above.

9. Minor note: the sentence describing the choice of 0.05 as a level for statistical significance needs to be modified simply to make it clear that that was deemed by the authors as statistically significant.
We removed the sentence from the text (p 6) and presented the actual p-value in the text when it was between 0.05 and 0.1 (e.g. p 7; l 156).

10. The results concerning the prevalence of CRNA are similar to previous studies, especially those using the same cycle of the CCHS, albeit with a different sample selection. The discussion section should simply clear make this clearer, possibly noting that some differences in findings would be expected by way of the focus on the working-age population and the exclusion of the province of Ontario.
We clarified this point in the "interpretation" section (p 8; l 182-184).

11. The study includes several results that show a high degree of correlation between food insecurity and CRNA. This is perhaps not surprising. But the findings that strike me as most interesting are those that are fully adjusted for sociodemographic confounders, including income and insurance. The authors discussed this briefly on page 9, where are they site previous studies that talk about the accumulation of multiple financial hardships. I think the pathways here deserve to be more carefully explored.
We added a brief discussion in the revised "interpretation" on the association between food insecurity and nonadherence after adjusting for insurance and other confounders (p 8; l 184-190).

12. Although the authors did find an association between food insecurity and the perceived implications of CRNA, I think that finding needs to be treated with caution. The direction of causality is just not yet clear.
We added this caution to the revised "limitations" section (p 10; l 225-227).

13. I am not sure if the work by Laurie Goldsmith (SSM 2017) would be of use here, and I confess I am a co-author of some of that work, but I think there is evidence that families are creative and adaptive under financial pressures associated with medicine costs. This is not to say that they don't experience CRNA, but rather that they balance decisions concerning which medicines to adhere to with decisions concerning other essential elements of a household

	budget - - such as food. **We added Goldsmith and colleagues' (2017) work as a building block for our conceptual model and acknowledged the possibility of trade-offs between food and medication in the introduction (p 2; l 49-53).** 14. Again, conceptual framework underpinning the work might help clarify the potential meeting in policy significance of the findings. **Consistent with our conceptual framework, we propose reducing financial constraints by raising disposable income and lowering out-of-pocket drug expenses in the revised "interpretations" section (p 9; l 199-217).** 15. My takeaway from this study is that people who live in households with accumulating financial strains from essential household expenditures are at risk of making unfortunately sacrifices in terms of medicines and food. Policy solutions for food insecurity are certainly receiving a great deal of attention but not as much policy traction as one might hope - - one example of the lack of traction for such policies would be the (arguably deliberate and malicious) termination of the guaranteed income trial in Ontario. In contrast, policy solutions to the medicines problem are currently under serious consideration in Canada – universal, comprehensive, prescription drug coverage. This is potentially a good thing for the health system. This study seems to add that this could even have broader social policy implications if alleviating the financial strains of medicine needs would free up budgets in households with accumulating financial strains for other essentials, including food. **We mentioned national pharmacare program in the "interpretation" section as potentially helpful for reducing out-of-pocket drug expenses (p 9; l 207). We did not go into detail discussion of any policy alternative due to space and scope constraints.** 16. As a minor note, on page 10 the authors cite a US-based study (Choudhry et al. 2011) of the effects of reducing copayments on patient adherence to post-AMI drug treatments. It is important to note that this study focused on a population of relatively well paid, working Americans. As a consequence that particular study would not necessarily be a rationale for income testing copayment exemptions under a universal drug plan. In fact, that studies findings would suggest that people of even moderate income benefit from copayment exemptions – to the extent that adherence to treatment is a desirable outcome. **We rephrased the relevant sentence to make Choudhry et al. (2011) a supporting evidence for lowering out-of-pocket expenses for the general public (p 9; l 213-215).** 17. In the limitation section, the authors might wish to cite the work by Sara Allin concerning the role of prescription drug insurance in determining whether or not Canadians might seek medical care (Health Economics 2009). That would add to the argument that the CRNA measures in the CCHS potentially understate the extent of access barriers caused by the lack of affordability of prescription drugs in Canada. **We added Allin and Hurley's paper to the "limitations" section as an evidence of potential underestimation of our results (p 10; l 224).**
Reviewer 4	David Dai
Institution	St. Michael's Hospital, Toronto, Ont.

General comments (author response in bold)	The manuscript was well-written, and the statistical analyses were appropriately conducted. The research question was clearly-stated, however it was easy to get lost in the many sub-questions and secondary analyses being addressed throughout the manuscript. This is not necessarily a fault on the authors - it is exceptional that they considered the research question from multiple lenses. The manuscript overall would benefit from a trimming of analyses and/or reorganizing of the results, with added emphasis on the primary results and clear demarcation from the secondary results. **We removed all but three secondary outcomes to focus on the primary results (page [p] 4; line [l] 92-101).**
	A few specific suggestions:
	1) Authors stated subjects with missing data on food insecurity was excluded from analysis (line 59). Was there missing data on other variables in the data? A sensitivity analysis between the complete case analysis (what is done here) to an analysis employing multiple imputation may be worthwhile to assess the impact of missing data bias.
	There were 750 adults with missing data on drug insurance, household type, housing tenure, or Aboriginal identity (p 6; l 130-132). As a sensitivity test, we experimented imputing those missing values with chained multiple imputation using household income, sex, age, food insecurity status, and province of residence as predictors. Sample household weights were applied. Prevalence ratios (PR) for marginal, moderate, and severe food insecurity were 1.84 (95% confidence interval [CI] 1.28-2.66), 3.75 (95% CI 2.84-4.96), and 4.99 (95% CI 3.79-6.58), respectively (p<0.002 for all). These results were by and large unchanged from the pre-imputation ones (p 7; l 161-164). **We did not impute household food insecurity status because of its large amount of missing values and the extreme lack of predictability using observable characteristics. This decision is also in line with the norm in food security research.**
	2) Several subgroup analyses and interactions were explored. I would be interested to see how these effects differ by sex and age, particularly given the between sex ratio and food insecurity. **We experimented with by-sex and by-age-quartile analyses. There was no interaction between sex and food insecurity (p>0.1 for all). As with age interactions, the association between moderate food insecurity and cost-related nonadherence of the first age quartile was half as much as that of the second age quartile (PR 0.51, 95% CI 0.30-0.86, p=0.011); no other interactions were significant between age and food insecurity (p>0.05 for all). On top of the absence of significant results, we are more concerned that interacting sex or age with food insecurity would render interpretation of results difficult since respondents from CCHS 2016 rapid response module were allowed to answer questions regarding medication use on behalf of other household members. With unclear information on whether the respondent was the one receiving prescriptions, we are essentially dealing with a household versus person-level variable on cost-related nonadherence, which in turn prevents meaningful interpretation of individual characteristics. Thus, we have not included sex or age interactions in this**

paper.

3) Due to the number of comparisons being made, the results look cluttered visually (eg. Table 2). It is also not immediately clear upon looking at this table what the analysis shows; all p-values for trend are very small, however in some samples the trend is clearly attenuated (eg. Prescription sample with 3+ prescriptions as outcome, Non-welfare sample with drug insurance as outcome). **We removed Table 2 and its associated analysis from our paper to focus on cost-related nonadherence.**

4) More description is needed on how the p-values for trend were derived in all of the analyses, especially given the seemingly lack of difference in statistical significance in the various analyses in Table 2 despite obvious differences in strength of trend.
We derived "p-values for trend" by treating food insecurity as a continuous variable in an alternative set of regressions. However, we felt they might not add important information in this case and therefore withdrew them from the revised text.

5) It was considerate of the authors to include quadratic terms for age and income to account for potential non-linearity. However, quadratic terms are very unstable in the extreme ends of the data; additionally, they impose a fixed functional form in the relationship between the variables that may not be reasonable. As such, they are often not the best way to address non-linearity. Restricted cubic splines are a much more flexible way of accounting for non-linearity and would be my recommended approach
We experimented with restricted cubic splines for age and income but found the coefficients non-significant and hard to interpret. Instead, we replaced the original "continuous + quadratic" combinations by quartiles of age and income to account for nonlinearity (p 15), which is easier to interpret and relatively stable in the extremes of data.