Author's response to reviews

Title: Association between unemployment rates and prescription drug utilization in the United States, 2007-2010

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Author's response to reviews: see over
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Dear Sir or Madam,

On behalf of my co-authors, I would like to submit a revised version of the enclosed manuscript, entitled “Association between unemployment rates and prescription drug utilization in the United States, 2007-2010”, to be considered for publication in BMC Health Services Research. Thank you for your helpful review, and the opportunity to use it to improve the overall clarity and rigor of our report. As requested, with this revision we have provided a point-by-point response to the concerns raised by the Editor and both Reviewers, as detailed below.

Thank you for your consideration.

Sincerely,

Daniel Kozman

Editor’s Comments

1. Given the ecological nature of the study, I share the reviewers’ concerns about establishing causation and the need for caution in interpretation of results. The conclusion should reflect this. However, it is more difficult to make a case for prescription drug use leading to changes in unemployment rates than vice versa, so I don’t think the authors need to labour this point.

   We appreciate with this point and have modified our Discussion (page 13, paragraph 1, sentence 3) to more cautiously frame our results.

2. I agree with Reviewer 2 that the formulation of the hypothesis (“We hypothesized that increasing unemployment would be associated with increasing use of some therapies such as oral contraceptives and decreasing use of other therapies such as PDE inhibitors and statins that are used for “lifestyle” or asymptomatic chronic conditions) requires more justification. As it stands, the authors risk charges of reverse engineering the paper.

   We appreciate these comments. These hypotheses were developed a priori and we now explicitly state this using the term “a priori”. We have also provided additional justification as well as references in the Background section to support them (page 4, paragraph 3, sentences 3-5; references #18-20).
3. Tables: Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website.

_We believe our Table 1 is an important summary of key literature, although we are unclear from these instructions as to whether this type of text is more suitably presented in an alternative format. We would be happy to work with the Publisher’s to identify the optimal means of presenting this information._
Reviewer #1

1. The authors opt for a random effects model that in some sense partitions the variance from the model above into within- and across- state effects. However, I am not clear whether counterfactual reasoning (for testing your hypothesis) would use the across-state effect. I would welcome a clearer justification for their specific random effects model, and an explicit discussion of what confounders this random effects model does not rule out (e.g., autocorrelated errors, monthly [not seasonal] factors shared across all states that cause both predictably high unemployment rates [e.g., January layoffs after the holidays] and drug sales, etc.).

We appreciate these queries and suggestions. First, the reviewer questions whether our hypothesis testing requires analysis of an across-state effect. Due to concerns about unmeasured confounding, we believe that the within-state analyses offer stronger evidence of the association between unemployment and medication use than across-state analyses. Nevertheless, we believe the across-state analyses also provide valuable information about this association and indeed the results of these analyses generally conform with one another. Second, the Reviewer requests more clear justification for our random-effects model, as well as an explicit discussion of what confounders this type of model does not address. We have modified the Methods to provide this information (page 6, paragraph 3, sentences 4-6).

2. "In addition to the absence of any strong effect of the recession on prescription utilization" -- this quote contrasts the large inverse association between atypical and across-state unemployment rates, so I assume that the main findings involve within-state results. Again, the exposition of the across state (i.e., exploration?) and within-state (hypothesis test?) analyses could be clearer, if you wanted to retain the random-effects model.

The Reviewer raises an important point, namely, how we summarize the main findings in light of some discordance in the results depending upon the therapeutic class examined and whether or not within- vs. across-state results are considered. Overall, we believe that our results are fairly summarized in our Conclusion to the Abstract and manuscript. With that said, the suggestion to better explicate the role of within- vs. across-state analysis is helpful, and we have modified the Methods (page 6, paragraph 3, sentences 4-5) to do so.

3. More discussion on why you had specific a priori hypotheses of associations in some drug classes but not others, why the 16% effect of atypical antipsychotics with 1% change in unemployment rate might occur, whether changes in oral contraceptive use indicate potential changes in fertility behavior, or whether drug use even gauges true time-varying incidence of health conditions. I would welcome a more precise discussion of at least a subset of the findings. What specific testable propositions for future inquiry arise from your research?

Please see response to Editor Comment #2.

4. Typo- "and we the elderly accounted for only approximately one-quarter of the entire market of therapies examined."
We have corrected this (page 12, paragraph 2, sentence 5).

5. Please reference the source of BLS data (website or other)

We have added this reference (reference #21).

6. Inconsistent description of time frame, I count only 34 months--"retail prescription drug use over a five-year period."

We appreciate this comment and have corrected this (page 4, paragraph 3, sentence 1). Our data spans 35 months.

7. With discussion of IRR, this is a multiplicative, not additive, scale, so 1/.75 = 1.33, not 1.25, correct?

The IRR is a multiplier, meaning that if a rate is 100 and a 1 unit increase in a variable is associated with an IRR of 0.75, this would predict that this rate would become 100 x 0.75 = 75, or 25% lower.

8. How can 95% CIs in Table 2 be so precise with only 1,700 state-month observations?

We agree that this is unusually precise, and we believe this is due to the fact that utilization and other state level variables do not vary significantly on a monthly basis. This follows from the fact that state-level population characteristics and trends in behavior are highly aggregated, smoothing out much noise in the underlying data that would typically lead to less precise estimation. Additionally, each state-month observation of unemployment was stratified by gender and age group, leading to potentially 6 cases for each state-month. As Reviewer #2 points out, we would ideally have unemployment rates for each combination of gender and age group, but must simply assume that unemployment affects all equally due to limitations of data availability from the Bureau of Labor Statistics Local Area Unemployment Survey.

9. Appendix Table missing a parenthesis

We were unable to locate this error but will review any typeset proofs carefully.

10. Also, standard errors would be welcomed, N= observations, degrees of freedom? Diagnostics would be helpful

We appreciate this suggestion and have modified the alternate table in the Appendix to include standard errors for each cell and report degrees of freedom and Akaike Information Criterion (AIC) for each model, in addition to the Bayesian Information Criterion (BIC) already reported. See response to Reviewer #1 Comment #8 for explanation of degrees of freedom. We could also add a note explaining these inter-model
differences at the Editors’ discretion. We continue to provide an estimate of goodness of fit – Bayesian Information Criterion (BIC) in Table 2 (page 19).
Reviewer #2

1. While this study is quite novel, the importance of the study is unclear. As an ecological analysis, causation cannot be inferred and it’s not clear what we are learning from these counterintuitive findings. Ideally, an analysis that differentiated trends in pharmaceutical utilization (which have been increasing over the past decades) from trends that resulted from the economic recession would be best. For instance, could a difference-in-differences analysis be conducted that compared pharmaceutical utilization in states with the smallest changes in unemployment over the course of the recession with states with the largest changes in unemployment over the course of the recession?

Our overall goal was to examine whether the recent economic recession, the worst economic downturn since the Great Depression, was associated with reductions in prescription utilization. Although our study was an ecological one, we use a stronger analytic design than many other strategies for examining this research question, since we exploit temporal and geographic variation and use methods that allow us to parse out the association due to higher or lower average unemployment versus the association due to relative changes in unemployment. The difference-in-differences analysis suggested would provide a roughly similar parsing of the effect if state average unemployment was included in the model, but not an actual estimate of how utilization varies according to this average. Nevertheless, we agree that any inference at causality would be just that, and have framed our results cautiously. Please see response to Editor Comment #1.

2. I also think the Introduction needs greater clarity. What is the precise hypothesis being tested (i.e., why is it expected that oral contraceptives would be used at higher rates but “lifestyle” drugs at lower rates – with more time on one’s hands, I would expect utilization of “lifestyle” drugs to increase)? The bulk of the Introduction is framed around the issue that patients are price sensitive and so they can be expected to lower utilization. But a lot of the evidence (in paragraph 3) is not directly relevant. Furthermore, it is unclear how much copays and the like changed for patients. Even if they lose their job, they may retain the health insurance coverage via COBRA or through their severance package (for a period of year, for instance). Given that the analysis is quite “macro”, I would favor an Introduction that focuses on the big picture as well but better clarifies the hypotheses that inspired the research.

We appreciate these comments. One of the aspects of this inquiry that makes it interesting is that there are a variety of pathways whereby the recession might impact medication use. We attempt to address many of these in the Background, although based on the Reviewer’s suggestion, we have now edited the Background for clarity and breadth, including discussion of insurance coverage and individuals’ price sensitivity (page 3, paragraph 1) and justification of our a priori hypotheses (page 4, paragraph 3, sentences 3-5).

3. Given that nearly all of the over 65 population is retired, eligible for Medicare coverage and eligible for Social Security payments, they are highly unlikely to be affected by the recession and the accompanying high levels of unemployment. I would suggest excluding this population from your main analyses and not just reporting the under 65 analyses as sensitivity analysis.

We appreciate these comments, although there is some evidence that the impact of the recession did not spare the elderly. For example, as published by the Kaiser Family Foundation (Medicare Chart Book,
Fourth Edition, 2010 accessed at http://facts.kff.org/chart.aspx?cb=58&sctn=164&p=1, 10.8% of Medicare beneficiaries above the age of 65 did not have prescription drug coverage in 2008. Of those beneficiaries who did have drug coverage, 26% reached the coverage gap, and 20% of those who reached the gap either stopped taking a medication in that drug class (15%), reduced their medication use (1%), or switched to a different medication in that drug class (5%). We believe including this population ensures that our estimates are conservative. Nevertheless, we do report results of analyses focusing solely on individuals less than 65 years of age. We have emphasized this further, as well as the fact that our results did not change substantively in these more restricted investigations (page 11, paragraph 1, sentence 1).

4. I was surprised that there was no discussion of insurance/COBRA in the first paragraph of the Introduction.

We appreciate this comment and now discuss the role of insurance/COBRA in the first paragraph of the Background (page 3, paragraph 1, sentence 7).

5. How does rising unemployment lead to increased rates of chronic disease (htn, hyperlipid, CAD)? Is it because patients now have the time to make an appointment with a physician? One study of the impact of the recession on colonoscopy rates: http://www.ncbi.nlm.nih.gov/pubmed/22155558.

We appreciate this query and reference. As we discuss in the Background, there are a variety of ways that unemployment may be associated with increased rates of chronic disease. We have modified our Background discussion to include the interesting reference that the reviewer provides (page 3, paragraph 1, sentence 8; reference #9).

6. Are all patients under 21 excluded? I would argue that they should be, since they are disproportionately eligible for public health insurance programs and parents will make different decisions about medication use for their children than they would for themselves. Furthermore, nearly all of the pharmaceutical classes studied are relevant only to adults.

The reviewer makes a good point. Individuals under 21 years of age constituted a small proportion of utilization for many of the drug classes we examined. However, our sensitivity analysis testing for differential levels of utilization by the young (under 20 years) and old (65+ years) compared to adults (20-64 years) demonstrated that younger patients did exhibit significant if often smaller rates of utilization for oral contraceptives, opiates, atypical antipsychotics and anti-depressants. In addition, we believe that most parents will make financial sacrifices to ensure that their children receive recommended treatments, and thus that our inclusion of children and adolescents should suppress evidence of any hypothesized declines in utilization due to increased unemployment, making our analyses somewhat more conservative than they would otherwise be. Thus, we propose to continue to include these subjects, although we defer to the Editor's discretion.

7. Does the Bureau of Labor Statistics provide unemployment data by age? It would be more interesting to focus the analysis on age categories (21-35, 36-50, 51-64 or whatever) as younger adults were more likely to lose their “stable” jobs during the economic recession.
While we agree that unemployment data by age group would be preferable, the Local Area Unemployment Survey does not, as far as we know, release this data by month at the state level, which was our unit of analysis.

8. Does the IMS data include $4 prescriptions? It should be clear if these are included, particularly since patients with less disposable income are likely to turn to cheaper sources for prescriptions during times of economic hardship like a recession.

We appreciate this comment. The data does include payment for these $4 prescriptions, and this has now been explicitly stated in the Methods (page 6, paragraph 1, sentence 1) and Discussion (page 12, paragraph 2, sentence 4) sections.

9. The finding of variation in prescription use across states is less interesting as presumably state populations have varying rates of disease for which these medications are prescribed. While this information needs to be reported in the Results, I’m not sure a paragraph in the Discussion on this finding is needed.

We appreciate this point and although we believe this variation may be of interest to many readers, we have now shortened and combined the content this paragraph with that of the first paragraph of the Discussion (page 11).

10. One strength of this study that deserves mention is that the focus was on sales, not adherence. When trying to understand whether the recession had an impact on pharmaceutical utilization, sales is key (as people are making the decision to purchase the prescription), as opposed to prescribing by physicians (since patients may not actually purchase the prescription) or adherence to the prescription (which is complicated by many other factors).

We appreciate these supportive comments.