PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-related nonadherence to prescribed medicines among older adults: a cross-sectional analysis of a survey in eleven developed countries
AUTHORS	Morgan, Steve; Lee, Augustine

VERSION 1 - REVIEW

REVIEWER	James X. Zhang, PhD, MS The University of Chicago, USA
REVIEW RETURNED	04-Oct-2016

GENERAL COMMENTS	This paper addresses an important topic: cost-related nonadherence to prescribed medicines (CRNA) among older adults, hypothesizing that cost-related access barriers will be higher in countries without universal coverage for pharmaceuticals than in countries providing universal coverage of prescription drugs at little or no direct cost to patients. The authors found that across most countries, the prevalence of CRNA was higher among lower income residents and lower among residents over age 65. The methods employed are reasonable, and the paper is well written. The authors appropriately acknowledged that response rates in the survey data varied from 16% to 60% across countries, potentially introducing bias in the samples. Such low response rates may have skewed some results to a large degree, and hence a listing of the response rates along with the overall CRNA rates will benefit the readers in interpreting the resulting with caution. The authors have also performed the adjusted analysis using logistic regression techniques to control for a number of potential confounders. Since the direction and magnitude of such potential confounders varies significantly from one country to the other, a statistic of discriminatory power of the model may be warranted (i.e., area under ROC curve, a c-statistic) to illuminate unexplained residuals of CRNA behaviors across nations. Beyond the effects of income and age (likely a composite variable of insurance coverage and disease burden), the CRNA rates are largely attributable to the out-of-pocket payments (OOPs) for medications. The authors indicated the effect of OOPs a number of times, and hence some quantification of the effect of OOPs may be illuminating (for example, grouping countries by levels of OOPs and insurance benefit design). Lastly, the use of brand-name drugs, in lieu of generic drugs, might be a significant driving force for out-of-pocket payments in some of the countries such as the United States. Based on the paper, it is not

	clear if the higher CRNA in some countries are due to higher OOPs, higher rates of brand-name drug prescription, or both. Both are possible and some discussion along this line will inform understanding of where policy gaps are.

REVIEWER	Sara Allin Assistant Professor, University of Toronto Senior Researcher, Canadian Institute for Health information, Canada
REVIEW RETURNED	10-Oct-2016

GENERAL COMMENTS	This is an interesting descriptive study of the recent international survey conducted by the Commonwealth Fund to examine variations in cost-related non-adherence to medications. I have the following comments for the authors to consider: 1. Provide some further discussion on the policy importance of cost-related non-adherence in the introduction. o is there any correlation with other indicators of accessibility (e.g., diabetics receiving insulin; etc.) o is it the only measure of accessibility that is comparable across countries? o do any of the countries included here use it for monitoring health system performance? o some evidence of health impacts could be brought up to the introduction. 2. Table 1 is very helpful and informative. Where did the information come from? Where sources are available, please provide references. E.g., was it the Barnieh reference? MISSOC tables? And what is the reference period for this data? More details would be extremely helpful. Also it helps to convert all local currencies into GBP (one in Norway isn't converted) and note the date of the exchange rate in a note under the table. 3. Could the authors offer any speculation for the inverse income effect that was found in the UK and France? Is this consistent with other studies? Or are the estimates unstable because of small sample sizes? 4. Limitations could also include some discussion about the inability for the survey question to distinguish between necessary and potentially unnecessary (or even potentially harmful) medications. Minor comments The introductory paragraph could benefit from some additional references, and examples. - briefly, what are some "potentially important differences in the extent of coverage offered"? do they relate to the breadth of coverage (what drugs are included) or the depth of coverage (how much patient contributions are relied on) - the statement "among these differences is the fact that neither the US or Canada has thus far achieved universal coverage of essential medicines" isn't really related to the previous sentence which was referring to differences among countries who had achieved universal coverage. Why was the United Kingdom chosen as the reference group for the analysis? The conclusions section could also point out that this study confirms earlier estimates/shows similar patterns to earlier estimates based on surveys of the general population, and sicker people.

REVIEWER	van Mierlo, Trevor Evolution Health Systems
REVIEW RETURNED	17-Oct-2016

GENERAL COMMENTS	This paper assesses effects of costs on access to medicines. Leveraging telephone survey data from eleven high-income countries, outcomes were derived from self-reported cost-related nonadherence (CRNA). CRNA was defined as not filling a prescription or skipping doses within a 12-month period due to out-of-pocket costs. Across most jurisdictions, CRNA was higher among those with lower incomes, and lower among older adults. Differences in national prevalence of CRNA appear to follow lines of availability of coverage and patient charges within drug plans. The study is well executed, with clear methods and straightforward statistical techniques. The paper is well written and will be appreciated by several audiences. Results appear consistent with other studies analyzing the relationship between cost and medication non-adherence. Once published, this paper will add to the literature as it specifically examines CRNA across a specific population in several countries. An important issue is that results strongly suggest that within the populations studied, medication non-adherence could be significantly impacted by reducing, or eliminating, cost. While cost is certainly a contributing factor the authors fail to address other issues that are topical in the non-adherence literature. In order to improve the paper and contextualize it within current research, there are three issues that the authors should address: 1. Medication and treatment non-adherence is complex, and there is a very rich history of empirical examination of this issue, which the authors need to briefly acknowledge at the onset of the paper. For example, at the patient level, non-adherence is generally defined as intentional or non-intentional. A cursory scan of the literature will assist the authors with these important definitions. In this study, the authors are presumably addressing a type of intentional non-adherence (CRNA). 2. There is also a body of work, much of it US-based, on addressing the relationship between cost and medication non-adherence. Interventions, such as coupons or co-pays, have been implemented and examined with questionable success. In order to contextualize findings, that authors should acknowledge this work. 3. While cost is certainly an issue, some emerging research indicates that behavioral factors may outweigh costs. While cost is certainly a contributing factor, especially amongst those who have lower incomes, medication non-adherence remains an issue for fully covered populations. For full disclosure, this reviewer has examined this issue: van Mierlo T, Fournier R, Ingham M. Targeting Medication Non-Adherence Behavior in Selected Autoimmune Diseases: A Systematic Approach to Digital Health Program Development. PLoS ONE 10(6): e0129364. The authors should be congratulated for a well-designed study. Results should have an impact on policy. However the main issue is that researchers or policy-makers with experience in the area may

	dismiss the article as behavioral factors were not included in the model, and not discussed.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
The authors appropriately acknowledged that response rates in the survey data varied from 16% to 60% across countries, potentially introducing bias in the samples. Such low response rates may have skewed some results to a large degree, and hence a listing of the response rates along with the overall CRNA rates will benefit the readers in interpreting the resulting with caution. The authors have also performed the adjusted analysis using logistic regression techniques to control for a number of potential confounders. Since the direction and magnitude of such potential confounders varies significantly from one country to the other, a statistic of discriminatory power of the model may be warranted (i.e., area under ROC curve, a c-statistic) to illuminate unexplained residuals of CRNA behaviors across nations.
R: To assist with interpretation of explanatory power, we have included pseudo R-squared values to the regression tables. We believe these are the most familiar statistics for average readers.

Beyond the effects of income and age (likely a composite variable of insurance coverage and disease burden), the CRNA rates are largely attributable to the out-of-pocket payments (OOPs) for medications. The authors indicated the effect of OOPs a number of times, and hence some quantification of the effect of OOPs may be illuminating (for example, grouping countries by levels of OOPs and insurance benefit design).
R: We have run separate regressions for countries grouped by levels of OOPs in their systems. We tried a number of groupings, including grouping the UK with the Netherlands (also very low OOPs). Provided that the USA, Canada, and Australia are not grouped with other countries, grouping other systems did not produce different results: the same countries (USA, Canada, and Australia) are significantly different than the reference group whereas all other groupings remain undifferentiated.

Lastly, the use of brand-name drugs, in lieu of generic drugs, might be a significant driving force for out-of-pocket payments in some of the countries such as the United States. Based on the paper, it is not clear if the higher CRNA in some countries are due to higher OOPs, higher rates of brand-name drug prescription, or both. Both are possible and some discussion along this line will inform understanding of where policy gaps are.
R: We have added a discussion of the potential for tiered formularies and reference based reimbursement to affect OOPs in some countries.

Reviewer: 2
This is an interesting descriptive study of the recent international survey conducted by the Commonwealth Fund to examine variations in cost-related non-adherence to medications. I have the following comments for the authors to consider: 1. Provide some further discussion on the policy importance of cost-related non-adherence in the introduction.
R: We have expanded the introduction section with further information about the importance and causes of CRNA.

2. Table 1 is very helpful and informative. Where did the information come from? Where sources are available, please provide references. E.g., was it the Barnieh reference? MISSOC tables? And what is the reference period for this data? More details would be extremely helpful. Also it helps to convert all local currencies into GBP (one in Norway isn't converted) and note the date of the exchange rate in a note under the table.

R: The table has been edited and sources provided in a footnote. All coverage details were obtained from and validated by managers of public and statutory health systems in each country.

3. Could the authors offer any speculation for the inverse income effect that was found in the UK and France? Is this consistent with other studies? Or are the estimates unstable because of small sample sizes?
R: Differences in both systems may stem from reduced patient charges for low income individuals.

4. Limitations could also include some discussion about the inability for the survey question to distinguish between necessary and potentially unnecessary (or even potentially harmful) medications.
R: We have made edits to include this limitation.

Reviewer: 3
In order to improve the paper and contextualize it within current research, there are three issues that the authors should address:

1. Medication and treatment non-adherence is complex, and there is a very rich history of empirical examination of this issue, which the authors need to briefly acknowledge at the onset of the paper. For example, at the patient level, non-adherence is generally defined as intentional or non-intentional. A cursory scan of the literature will assist the authors with these important definitions. In this study, the authors are presumably addressing a type of intentional non-adherence (CRNA).
R: We have added further details about CRNA to the introduction and discussion section.

2. There is also a body of work, much of it US-based, on addressing the relationship between cost and medication non-adherence. Interventions, such as coupons or co-pays, have been implemented and examined with questionable success. In order to contextualize findings, that authors should acknowledge this work.
R: We have added a line to explain that some policies (such as couponing) in the USA are intended to encourage adherence with medications.

3. While cost is certainly an issue, some emerging research indicates that behavioral factors may outweigh costs. While cost is certainly a contributing factor, especially amongst those who have lower incomes, medication non-adherence remains an issue for fully covered populations. For full disclosure, this reviewer has examined this issue: van Mierlo T, Fournier R, Ingham M. Targeting Medication Non-Adherence Behavior in Selected Autoimmune Diseases: A Systematic Approach to Digital Health Program Development. PLoS ONE 10(6): e0129364.
R: We have added further details about CRNA to the introduction and discussion section.

VERSION 2 – REVIEW

REVIEWER	James Zhang The University of Chicago, USA
REVIEW RETURNED	18-Nov-2016

GENERAL COMMENTS	This is a stronger manuscript. The authors reported pseudo R-squared as a goodness-of-fit measure. Since there are multiple Pseudo R-squareds which vary greatly in values within the same model, it will be helpful to indicate which Pseudo R-squared the authors are reporting. Nevertheless, the Pseudo R-squareds reported were in the range of 0.08-0.15, indicative of large unexplained variability. A brief discussion of this limitation will

	illuminate the gaps in knowledge and policies.

REVIEWER	Sara Allin University of Toronto, Canada
REVIEW RETURNED	04-Nov-2016

GENERAL COMMENTS	The revised paper is much improved and adequately addresses my previous comments. The low response rate is an important limitation that may impact how results are interpreted; it would help if the authors simply added the country representing the lowest (16%) and that with the highest response rate (60%) directly in the text, on page 12.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Since there are multiple Pseudo R-squareds which vary greatly in values within the same model, it will be helpful to indicate which Pseudo R-squared the authors are reporting.
Response: we have specified the type pseudo R-squared statistics reported.

Nevertheless, the Pseudo R-squareds reported were in the range of 0.08-0.15, indicative of large unexplained variability. A brief discussion of this limitation will illuminate the gaps in knowledge and policies.
Response: we added this discussion to the limitations section of the paer.

Reviewer: 2
The low response rate is an important limitation that may impact how results are interpreted; it would help if the authors simply added the country representing the lowest (16%) and that with the highest response rate (60%) directly in the text, on page 12.

Response: we have expanded our discussion of the low response rate and specific countries that are the outliers in rates of response.