Author's response to reviews

Title: Non-adherence to drug therapy and drug acquisition costs in a national population - an individual-based register study

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Author's response to reviews: see over
Manuscript “Non-adherence to drug therapy and drug acquisition costs in a national population - an individual-based register study” submitted to BMC Health Service research.

To the editor of BMC Health Service Research

Thanks for your valuable comments on our paper. Below each comment are numbered and commented:

**Associate Editor's Comments:**

1) "The manuscript addresses an interesting and important issue. However, one of the reviewers made some strong points about the lack of evidence behind key parameters in the model, namely, rates of secondary adherence. I agree with the reviewer that more effort should be made to identify evidence to inform these parameters. At a minimum, a thorough (not necessarily systematic) review of the literature should be described to convince the reader that you have tried to find relevant data."

1. Authors’ comments

In the revised manuscript added the following paragraphs in the Discussion section:

**Discussion**

There exists an “enormous amount of quantitative research” concerning medical adherence but there is no golden standard for measurement [1] and studies of medical adherence vary widely in terminology, definitions and methods [2, 3]. Both primary and secondary non-adherence are problems for health care across all therapeutic areas, but the majority of the adherence research has been referred to secondary non-adherence and to chronic therapies [4, 5]. In 2003, World Health Organisation published “Adherence to long term therapies: evidence for action”, which included specific reviews of non-adherence in therapies for asthma, cancer, depression, diabetes, epilepsy, hypertension, tuberculosis [6]. Subsequently, comparing studies of secondary adherence estimates for hypertension, hyperthyroid, type 2 diabetes, seizure disorders, hypercholesterolemia, osteoporosis, and gout [7] and secondary adherence estimate for prostaglandin analogs, statins, bisphosphonates, oral antidiabetics, angiotensin II receptor blockers and overactive bladder medications have being presented [5]. There are also a large number of specific studies and reviews of adherence for specific medical condition e.g. diabetes, hypertensions and dyslipidaemia [8], osteoporosis [9], anticancer treatment [10], HIV [11], and mental disorder [12] etc. The reported results vary widely depending on the disease, study setting and measurements.

As direct measurements of medication consumption is usually not feasible, refill adherence has been applied as an estimate of adherence in population-based studies [13]. However, when medication adherence is estimated from e.g. pharmacy claims database, the estimates are substantially inflated as non-adherence and early non-persistent patients are largely not included in the estimations [14]. Various studies have reported primary adherence rates of nearly 50% in psoriasis [15], 31.4% in diabetes [16], 24.3% in hypertension [17], and 19.9% antidepressants [18]. In addition, pharmacy claims database are not feasible for estimating the secondary adherence
(medication taken as prescribed) of “short-term” or “acute” therapies, e.g. all 11 measurements of refill adherence reported by Hess et al are relevant only to secondary adherence for chronic / continuing therapies [19].

Reviewer: Geva Vashitz

2) The study aim to estimate the drug acquisition cost related to non-adherence to drug therapy in Sweden. It reflects the immense costs related to non-adherence. This is an important issue for health services policy. The large sample gives the results a strong impact.

Some comments that can improve the manuscript:
The Abstract: The background section should be tightened. There is some confusion between ‘non-adherence’ and ‘adherence’ – perhaps it is better to use one term.

2. Authors’ comments

We have shorted the background section and we more consistently use the term “non-adherence”.

3) Could you please explain in which strata is the adherence measured (across all patients?), and clarify the terms “total adherence” and “age adherence rates”.

3. Authors’ comments

In order to estimate the drug acquisition cost related to non-adherence to drug therapy in an entire national population we used the actual individual-based data of all dispensed outpatient prescriptions to all patients in the entire Swedish population.

Adherence is commonly divided into of primary adherence (prescription being filled by patient) and secondary adherence (medication used as prescribed). With “total adherence” we refer to the sum of primary and secondary adherence, (i.e. adherence). “Age adherence rates” refer to the different rates of secondary adherence for patients in different age that previous studies have presented.

In order to clarify we do not use the term “total adherence” in the revised manuscript, and in Abstract, we have reformulated the second sentence in the paragraph under the heading “Methods”:

“In the model, the total drug acquisition cost was successively adjusted for the assumed different the rates of primary non-adherence (prescriptions not being filled by the patient) and secondary non-adherence (medication not being taken as prescribed) according to the patients age, therapy, and the number of dispensed drug per patients.”

4) The introduction is well written. The literature is relevant and adequate.
Method: Although I understand the use of the word “individual” to describe a person, it is sometimes ambiguous. Perhaps “patient” or “person” would be clearer.

4. Authors’ comments

In the revised manuscript we more consistently use the term “patient”, instead of “individual”.

5) There some paragraphs of 1-2 lines that should be merged into bigger paragraphs.

5. Authors’ comments

In the revised manuscript we have merged some small paragraphs into bigger.

6) Adherence definition: I wonder is the authors could compare their adherence measures to other measures such as MPR and PDC. This is not mandatory; however it will make the results difficult to be compared to other studies.

6 Authors’ comments

The terminology, definition and methods to determine adherence differ greatly in published literature [2, 20] and multiple measures of adherence are found in research literature. Hess and colleagues [19] found multiple terms used to describe adherence and they reported 11 different measurements to calculate refill adherence from administrative data such as pharmacy claims databases: Continuous Measure of Medication Acquisition (CMA); Continuous Multiple Interval Measure of Oversupply (CMOS); Medication Possession Ratio (MPR); Medication Refill Adherence (MRA); Continuous Measure of Medication Gaps (CMG); Continuous, Single Interval Measure of Medication Acquisition (CSA); Proportion of Days Covered (PDC); Refill Compliance Rate (RCR); Medication Possession Ratio, modified (MPRm); Dates Between Fills Adherence Rate (DBR); and Compliance Rate (CR). All measurements are related to secondary adherence and to chronic therapies, only.

According to Hess et al, five of these measures produce equivalent results for measuring prescription refill adherence (secondary adherence). According to David Nau, Pharmacy Quality Alliance (PQA) is the most common measures MPR and PDC, but Hess et al recommended MRA as the preferred measure of adherence using administrative data.

In our study of drug acquisition cost related to non-adherence we made assumptions on primary and secondary adherence rates based on e.g. Briesacher et al [7] estimated secondary adherence with MPR and Yeaw et al [5] used PDC as measurement. In three reviews: [8-10] many different type as measurements are include, e.g. urinary metabolites, self reported, physician interview, microelectronic monitoring system (MEMS) and prescription refill records.

In the revised manuscript we have added the following paragraph in the Methods section:
“Adherence measurement options include drug claims data, interviews, surveys, pill counts and drug assays. The majority of adherence research has addressed secondary adherence of chronic therapies [4]. There exists a large number of varying measurements to estimate secondary adherence of long-term therapies from administrative data including e.g. MRA, MPR, and PDC [19]. “

7) Can you please describe how the “I” (ingested adherence) was recorded – was it self-reported?

7. Authors’ comments

The medical adherence rate is the rate between prescribed drugs and ingested drugs. There are several types of measurements options according to estimate adherence rate e.g. drug claims data, interviews, surveys, pill count, drug assays. Our estimates on cost related to non-adherence are based on assumption grounded on many previous studies, e.g. a review in which studies with self reported adherence are included [10].

8) Figure 1 should be explained: to which drugs does it relate? Does the DDD is calculated across all drugs?

8. Authors’ comments

Figure 1 refers to the principal relation between DDD per individual/patient, and the number of dispensed drugs per individual/patient for prescribed, dispensed and ingested drugs.

To simplify the article (se also reviewer comments no 16) we in the revised manuscript omitted figure 1 and 2.

9) There is a mixture between method and results section; some results are described in the method section.

9. Authors’ comments

In the method section we assign for the assumptions we apply in our model on primary non-adherence and secondary non-adherence for patients in different age, with different therapies and with different number of dispensed drugs.

10) The language is rather fluent and the article is easy to read. However there are some style and grammar mistakes that can be checked by an English-native speaker.

10. Authors’ comments
An English-native speaker has checked the revised manuscript.

11) Table 2: ATC codes should be transparent to the reader. I suggest shortening the table to present summary measures. It is currently too detailed.

11. Authors’ comments

The information in table 2 is summarized in the result section under the heading “Drug acquisition cost with regard to drug therapy”. In the revised manuscript we have removed Table 2 from the manuscript to “electronic supplements”.

12) Could you please describe the “individuals” line in Figure 3?

12. Authors’ comments

“Individuals” refer to the actual number of individuals/patients in the entire population of Sweden with 1 to 30 different dispensed drugs.

In order to clarify we have in the revised manuscript rewrite the figure legend:

“Figure 1. Number of patients, public financed drug cost and patient co-payment in Sweden 2006. Number of patients, total amount of public financed drug cost and patient co-payment for patient with 1 to 30 different dispensed drugs in Sweden 2006.”

Reviewer: Michael A Fischer

13) Major Compulsory Revisions

General comment: My main concern with this paper is with the overall concept. As noted in the specific comments below, the basic assertion of this paper is that medications purchased but never taken represent a source of potentially needless spending. This assertion is hard to argue with. However, the percentage of medications never taken is basically assumed by the authors, which makes the results of the paper seem arbitrary. At a minimum, the authors should provide much more robust justification for why they assume the rates of secondary adherence that they use in this analysis, as well as a stronger argument for why this analysis represents a contribution beyond the intuitive concept summarized above.

13. Authors’ comments

In the present study we estimate the drug acquisition cost related to non-adherence in an entire national population. In literature, medication non-adherence is supposed to be determinant on several factors (see background page 4). Our manuscript present, to our knowledge, the first analyze that weigh up results from previous study concerning primary adherence, and different secondary adherence rates due to patients’ age, type of drug therapy, and number of drugs.
In order to clarify we in the revised manuscript in the Method section added more references to previous studies concerning rates of primary and secondary adherence to which we based our assumption.

14) Abstract: A terminology issue, here and throughout: “drug acquisition cost related to non-adherence” does not precisely capture the phenomenon the authors describe. Nor does the term “redundant” that they use later. A more precise definition would be helpful.

14. Authors’ comments

The aim of the present study was to estimate the drug acquisition cost related to non-adherence to drug therapy in an entire national population. The total acquisition drug cost is the sum of the entire drug cost of all dispensed drug during a 12 –month study period, which also equals the drug cost related to primary adherence (prescription being filled by patient). Based on several previous studies of estimates of secondary non-adherence we calculate the drug acquisition cost related to drugs that are not used as prescribed (secondary non-adherence).

In order to clarify we have rewritten the paragraph under the heading “A model to estimate the share of drug cost related to non-adherence” in the method section.

We have also replaced the term “redundant” cost” with “unnecessary” cost or “waste” medical spending.

15) Page 4, bottom: The terms primary and secondary adherence are not always defined this way. In other papers, authors use primary adherence to refer to the filling of a prescription after it is first written and secondary adherence to refer to continued filling of medications after that. The authors should clarify if they are proposing new definitions of these terms or if these definitions have been used previously in the literature.

15. Authors’ comments

The terminology, definitions and methods to determine adherence differ greatly in the published literature. In the present study we use the most common definition of primary and secondary adherence. (Primary adherence is defined as the drugs that patient fills from a prescription and secondary adherence to the drug patient ingest as prescribed.) Although, there exist variation of this definition of secondary adherence e.g. “patient takes medication as prescribed” [21], ”correct use of medication” [22], “used as prescribed” [23], “used as recommended” [24], “taking medication as prescribed” [25].

It is also correct that some studies use refills of prescription (refill adherence) as a measure to estimate secondary adherence. Steiner et al argue that “Refill adherence can be a useful source of adherence information in population-based studies when directs measurements of medication
consumption is not feasible” [13]. Hess et al displayed 11 different measurements of secondary adherence, all based on refill adherence [19].

In order to clarify that we use definitions that have been used in numerous of previous studies we in the revised manuscript have put in references to previous studies that use the terms primary and secondary adherence.

“Medical adherence is commonly divided into primary adherence (prescription being filled by patient) [16, 21, 23] and secondary adherence (medication used as prescribed) [21, 23, 24].”

16) Page 9: The specification of the model seems to me to be an overcomplication of a relatively simple concept. The concept shown in the equation can be stated as “the percentage of dispensed medications that are not taken by patients represents wasteful medical spending.” One may choose a different term than “wasteful,” but the concept is the same and is almost a tautology. This is the central issue with this paper- does it really show us anything beyond a multiplication exercise?

16. Authors’ comments

We agree with the reviewer, “the percentage of dispensed medications that are not taken by patients represents wasteful medical spending”. Our attempt was to use results from previous studies concerning primary and secondary adherence and try to assess how much of total drug expenditure, measured in currency and in percent, that can be seen as needless medical spending due to non-adherence.

Health care’s economic resources are limited and in our opinion it is both interesting and important to present an estimate, based on several previous studies, that states that around 40% of total drug expenditure is related to drugs not taken as prescribed. (See also the paragraph under headings “The relevance of the total drug acquisition cost due to non-adherence” and “implication for health care” on page 19 in the revised manuscript.)

17) Page 10: Given the critique above, the sections on page 10 are the crux of the entire paper. The authors need to provide a more robust justification, with citations from the literature, to support the three adherence rates that they choose to apply to different types of therapy. Otherwise the entire set of calculations seems unduly arbitrary.

17. Authors’ comments

Based on previous studies we in the present study make assumption in order to illustrate the different rate of secondary adherence for patient in different age, with different medication therapy, and with different number of dispensed drugs.
In literature, the overwhelmingly number of studies of adherence refer to studies of secondary adherence of chronic drug therapy, measured as refill adherence by e.g. MPR or PDC etc over a 12- or 24-month period. Results from previous studies concerning non-adherence rate for short-term therapies are often qualitative and not quantitative, but since chronic/continuing drug therapy represent approximate 75% of all dispensed DDD and 60% of the cost of all dispensed drugs, it showed up that different assumption of the secondary adherence rate for “short-term” drug therapies only had a marginal effect on total drug cost related to non-adherence. (See also the paragraph under the heading “The validity of the estimate of the total drug acquisition costs due to non-adherence” in Discussion in our manuscript).

In order to simplify, we in the revised manuscript reduce the number of categories of drug therapies from three to two. The previous categories “when needed” and “temporary” are replaced with the category “short-term” drug therapy, defined as the ATC –groups in which the average DDD/patient was below 200 DDD. In the revised manuscript Method section we also put in more references in support for the made assumptions in the model.

18) Page 14, second-last paragraph: I am not certain in this case how varying the primary non-adherence rate (based on the definitions of primary and secondary used by the authors) should change the estimates at all, since the calculations are based entirely on secondary adherence.

18. Authors’ comments

In the present study the calculations are based on both the rate of primary and secondary adherence. In literature, as well as in the present study, primary adherence refers to the amount of prescribed drugs that patient actual fill from prescription. The rate of primary adherence thereby “determines” the total drug acquisition cost. (A country with low rate of primary non-adherence combined with a normal rate of secondary adherence, e.g. Sweden, have a large proportion of cost related to non-adherence relative a country with a high rate of non-adherence combined with a normal rate of secondary adherence, e.g. USA.)

19) Page 17, top: The final sections of this first paragraph are very problematic. The assumptions that the authors make about medication-taking behavior drive the entire study. If these are all rough assumptions, the reader is left much less certain about the importance of this analysis,

19. Authors’ comments

In the present study we refer to the well-established relation between non-adherence to drug therapy and the number of drugs given to a patient. In the revised manuscript we have added three more references in support for our assumptions about different rate of secondary adherence for individuals with different number of dispensed drugs [25-27].

20) Page 20, limitations: The authors must discuss at length here the fact that this analysis is driven entirely by some strong assumptions (outlined in the comments
above) and that several of those assumptions do not have clear support in the literature.

20. Authors’ comments

In our opinion our assumptions do have clear support from previous studies. In the revised manuscript we have rewrite the paragraph under the heading “Strengths and limitations” in order to underline that our assumption, based on several previous studies, all can be challenged because they are put together into one single calculation and that results from previous study concerning short-term medical treatment often are less precise than studies of chronic therapies, based on refill adherence measurements.

“The study is based on individual data on pharmacy claims without any sample, recall or interview bias for all patients with dispensed drugs in an entire national population. The study combined actual pharmacy claims data with general assumptions based on previous studies of different non-adherence rates for patients in different age groups, drug therapies, and with a varying number of dispensed drugs. A limitation is that the assumptions made in the present study are based on previous studies which often only focus on adherence to one specific long-term medical therapy. Results from previous studies concerning non-adherence rate for short-term therapies, patients’ age, and number of dispensed drugs per patient are often only qualitative. Consequently, certain of the assumptions about varying non-adherence rates in the present study are relatively rough. Furthermore, the register includes all dispensed prescriptions drugs but has no information regarding other types of drugs e.g. OTC-drugs and CAM. Nor has the register any information about the volume and the distribution of prescribed drugs which are not filled, nor as regards the rate of filled drug not taken as prescribed.”

Minor Essential Revisions

21) Page 17, last line: “denominators” should be “determinants” or a similar word

Discretionary Revisions

21. Authors’ comments

We have replaced “denominators” with “determinants”

22) Page 6, first paragraph: This paragraph can be cut.

22. Authors’ comments

In the revised manuscript this paragraph have been omitted

23) Page 18, second-last paragraph: The point made about the relationship between secondary and primary adherence is reasonable, but unless that relationship is
included in the models used in this paper, it is not clear what this point contributes.

23. Authors’ comments

Our study is based on individual-based data from Sweden. In an international perspective Sweden (and the Netherlands) sticks out with a relatively low rate of primary non-adherence, probably due to a comprehensive drug reimbursement system.

In order to make it easier for the reader to interpret the results to other countries with less comprehensive drug reimbursement system we wrote the paragraph
References:


