Author's response to reviews

Title: Are prescribing doctors sensitive to the price that their patients have to pay in the Spanish National Health System?

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised version of our manuscript “Are prescribing doctors sensitive to the price that their patients have to pay in the Spanish National Health System?” (previously entitled “Moral hazard and double agents. The agency relationship in drug prescription in the Spanish National Health System”) [MS: 1696918554441119]) submitted for your consideration for publication in BMC Health Services Research.

We have changed the title in response to some concerns expressed by the referees (see below). In response to other concerns and suggestions we have made the following changes:

Reviewer 1: Atonu Rabbani

#01. Reviewer 1. Overall Assessment. In the article, the authors have correctly identified an issue which is central to the whole narrative around comprehensive coverage of health care cost through a mechanism so that the unanticipated and idiosyncratic burden from adverse health shock is shared by a pool of people through pre-payments. Government is regarded essential in this mechanism and most high-income countries the cost associated with health care, e.g. prescription drugs, is facilitated through public expenditure. However, containing the increasing cost of prescription drugs (among others) is important and physicians and their prescription practices are understood to be very important. In that regards, the authors address an important issue and finding the right incentive to make sure the appropriate prescription is written at the lowest cost is very essential for the efficiency of the health care system for any country.

However, it is important to realize that the choice of appropriate drugs by a physician for a specific patient is a complex interplay among many factors and I feel this is not addressed sufficiently in the paper. The physician take into consideration the disease and its severity along with factors that are specific to the patients (e.g. other health conditions, possible contraindications and interaction with other drugs that the person is taking along with other covariates such as age, sex etc.) and these factors are not observed by the researchers given the prescription data they are using for the study. I feel this is an important limitation of the present study.

We agree with the reviewer that the “choice of appropriate drugs by a physician for a specific patient is a complex interplay among many factors”. Our study design, ecological in nature, cannot address this topic (the appropriate drug for a specific patient) because, as the reviewer says, we cannot take into account the disease and its severity, comorbidities, contraindications, interactions and so on. But our study is not focused on the “choice of the appropriate drugs for a specific patient” from any possible drugs, but on the choice of a specific active ingredient (or the same active ingredient at different prices in the case of generic drugs) within one definite and reasonably homogeneous therapeutic group.
As we stated in the previous version “the average price discrepancy for a pharmacological group between two healthcare areas is due to price differentials in the shopping cart of dispensed drugs”. As an example, in the case of the statins group, the shopping cart includes generic simvastatin (market share about 35%), brand-name atorvastatin (about 50%) and some other generic statins (Pravastatin, Fluvastatin and Lovastatin, about 15%) with a reduced market quota. Our study does not analyze the decision to treat (treat vs. not treat) or the selection of a therapeutic class (eg. statins vs. other antihyperlipidemic drugs), but the selection of a specific statin within the statins group. There is no evidence on the superiority of one specific statin over another and there are not any clinical reason (severity, comorbidity, contraindications, interactions, sex, age, ...) to systematically use the high price drug (atorvastatin) in pensioners and the low price drug (simvastatin) in non-pensioners. Patients with more severe conditions can use stronger doses of the same drug (for example, atorvastatin 40 or 80 mg, vs. atorvastatin 10 mg; simvastatine 40 vs. simvastatine 10) but as we use the DDD metric, this circumstance suppose a reduced (not higher) DDD price for patients with more severe conditions with stronger dose prescriptions.

This situation is very similar in the case of ACEIs & ARBs (there are no reasons for treating pensioners with ARBs and non-pensioners with the cheaper ACEIs), diuretics, nitrates, Ca++ channel blockers, flavonoids, SSRIs, MAOIs, lithium (note that we analyze the three anti-depressive groups separately), typical antipsychotics, atypical antipsychotics (also analyzed separately), anti-dementia drugs, hypnotics, anxiolytics or psychostimulants. Nowadays antiplatelet drugs can have the bias indicated by the reviewer, because clopidogrel is used more in elderly people than AAS (in fact, clopidogrel prescriptions have a preview authorization control requiring age 65 or older). We commented on this limitation in the discussion section of the previous version, indicating that in these groups “the price differential is a compositional effect not related with the agency relationship (i.e., the requirements for the prior authorization of clopidogrel consider age over 65 as a criterion and because all people over 65 are pensioners with no copayment, we have a compositional effect).”.

Nonetheless, because the three reviewers have expressed this concern we do not think we had explained this situation adequately, so we have included new paragraphs in the methods and the discussion section, in an attempt to clarify the question.

#02. Reviewer 1. Major Compulsory Revisions #1. The identification of implications of an agency relationship between a patient and a doctor comes from exploiting the variation in the cost for a class of drugs between two distinct groups of patients (pensioners and non-pensioners) and whether full co-payment (FC) or reduced co-payments is associated with certain class of drugs. This scheme makes it difficult to interpret the apparent differences in the payments per unit of prescription per class. The pensioners are very different than non-pensioners in terms of age, disease patterns and its severity. These unobserved (and uncontrolled for) attributes will surely bias the estimates and the differences in the cost of acquiring drugs will certainly be correlated with these factors. However, given the authors are using pharmacy level data and (as noted) do not have information on the individual patients (see pp.6-7), the associated difference can very well be misinterpreted. Authors should address this issue.

1 Rosuvastatin was not marketed in Spain that year.

2 The unitary price of each pill decreases with higher doses. In fact, the price of the packages with different dosages is relatively similar.
This concern has been responded to in the previous comment (see response #1). Nevertheless, we discuss those issues in the discussion section and the aim of the paper is just to test whether the average price of the drugs prescribed by the doctors for treating specific homogeneous medical conditions is the same for particular groups of patients paying different co-payments. Indeed, even if the answer is YES, the explanation of that fact could be related to the co-payment regime or not. We have changed the text in some places to avoid misinterpretation (see response #3, #5 and other).

#03. Reviewer 1. Major Compulsory Revisions #2. It seems that the authors are applying a simplistic model for physician behavior and I am not even sure how exactly the agency paradigm invoked on page 4 (paragraph 1) are derived from the economic theory from reference [1]. The physician’s prescription behavior can best be derived in a set up where patients’ well being, institutional background (incentive structure incorporating monitoring and contractual arrangement based on observable outcomes, probably referred to as “variable incentives” on page 4, paragraph 1, line 1) and market incentives (marketing campaign targeted toward physicians, see comment 6 below). Thus variations in cost of a prescription belonging to a drug class will be result of interactions of all these factors which might be associated with the amount of co-payments a person (or a group of persons) will receive. This would certainly bias the results. While I do not expect that all aspects of the reality can be controlled in the data that the authors are using, this needed to be discussed liberally in the introduction and/or discussion sections.

- We agree with the reviewer that factors other than agency relationship could explain the price behaviour described. We have eliminated some specific references to the agency relationship from the title and from the main text and abstract. Instead, we refer to GP sensitivity to prices paid by patients, including the reference in the introduction section.

- Our reference 1 is a gold standard reference on agency relationship from the Handbook of Health Economics. It is an excellent reference on the theory of agency aimed at readers that are not familiar with health economics.

- Nonetheless this is an important, essential issue: it could be inferred that differences in the prices of prescribed drugs between those patients that have to pay for them and those patients with full coverage are a consequence of the co-payment regime, or could it be due to other confounding factors (other incentives to doctors, marketing campaigns or “induced prescription” among others)? The key question is whether the drugs in each therapeutic group are homogeneous enough, that is, if the groups are comparable in the contextual and compositional variables, if they are basically homogeneous in everything except co-payment. As we argued previously (see response #1) the therapeutic groups selected –except for antiplatelet drugs- match that premise sufficiently.

#04. Reviewer 1. Minor Essential Revisions #3. It is not obvious if there are variations in co-payment level across regions for different drug classes. If there are such variations then authors should have some comments on why such variations exist across regions and control for the regional differences (through fixed effects, for example) in the econometric specifications.

- Although there could be regional effects due to contextual factors related to management or general incentives to prescribe generics or cheaper drugs, there are no variations in co-payment levels across regions. We have included a new paragraph to clarify this point.
**#05. Reviewer 1. Minor Essential Revisions #4.** The choice of drug classes should be justified. There are two drug classes in the paper. The psychotropic drugs are certainly are very discretionary in nature thus they may vary in terms of choice of drugs depending on other factors which may have nothing to do with “agency” motive of the physician. This will certainly bias the results.

- As described in the manuscript the selection of pharmacological groups was opportunistic, depending on the previous projects on variation in cardiovascular and psychotropic drug prescription. **No changes have been made regarding this comment.** Moreover, the reviewer’s argument seems to be related to the “choice of drugs” among all cardiovascular or psychotropic and our study refers to the choice of a specific drug (or the same drug with a different price) within a homogenous therapeutic group of drugs (for example: the choice of one specific statin from among the shopping cart of statins: only 5 medicines but more than 200 different packages at different price from more than 50 different manufacturers, including brand-name and generic drugs). See responses #1, #2 and #3.

**#06. Reviewer 1. Minor Essential Revisions #5.** Looking at the drug class level will certainly hide the fact the portfolio of drugs may be very different between pensioners and non-pensioners and also between classes associated different levels of co-payments. If possible, I would certainly like to see the cost differentials at the drug levels so that heterogeneity of use of drugs within a class is controlled for (beyond random effects at the class level).

- The portfolio of drugs for each specific therapeutic group was the same for pensioners and non-pensioners and was specified in Table 1. As mentioned previously, each therapeutic group includes different medicines –and the same medicine made by different manufacturers- from the same or a similar class of therapeutic group, but we have not disaggregated information about the DDD or sales of each specific package (national codes). **No changes have been made regarding this comment.**

**#07. Reviewer 1. Minor Essential Revisions #6.** Some of the institutional features of Spain are probably ignored in the paper. While it is generally understood that direct-to-consumer advertisement for drugs are not permitted in Spain, marketing strategies that target physicians may be permissible and that may change the prescription motive for a physicians. So if such strategies systemically address physicians treating pensioners, one can find the apparent difference in cost for these two groups (i.e. pensioners vs. non-pensioners).

- Differences in prices between those patients that pay and those that do not pay for the drug could be due, among other factors, to the marketing campaigns directed at doctors persuading them to prescribe expensive drugs, but these promotional activities are usually aimed at specific groups of patients (hyperlipidemic, hypertensive, schizophrenic, depressed, …) not to pensioner or non pensioner groups. Anyway, in the current version of the manuscript we do not attribute causal mechanisms to the fact that doctors discriminate prescribing prices depending on co-payments, we just check the evidence for that. **We have inserted a new sentence into the discussion section on this issue.**

**#08. Reviewer 1. Minor Essential Revisions #7.** Also, since the variations come from variation across different “autonomous regions” one should also address the possibility of the role that migration may play in the observed variations in cost. The “pensioners” may decide to live in the regions where the copayment policies are more liberal and accommodating to their needs. If the sicker pensioners systematically choose based on these regional policies then one can
find the apparent variations in the data which again may not have anything to do with the agency motive of doctors.

- The copayment policies are homogeneous in all Spanish regions. In any case, this phenomenon is not very plausible in Spain where geographical mobility is rare, and more so at older ages. In addition, fixed effects for regions are not significant in the models. **We have included a new paragraph to clarify this point.**

#09. Reviewer 1. Minor Essential Revisions #8. One implication of the finding seems to be switching from FC to RC will make doctors choosing drugs such that patients as well as the system pay less. If so, at least for classes of drugs included in the analysis authors should think about showing the aggregate savings based on some back-of-the-envelope calculation. This will certainly show how important these findings are for aggregate drug spending.

- Unfortunately we have not been able to disaggregate data to do this interesting analysis. **No changes have been made regarding this comment.**

#10. Reviewer 1. Minor Essential Revisions #9. While authors mentioned the variable incentives that the physicians receive (p.5), this idea was not followed up later in the analysis or discussion as this may play an important role whether they will act as an agent of the “system”.

- Although economic incentives for prescribing generic or cheaper drugs (vg. ACEIs vs. ARBs) are common in Spain, we have not found any studies evaluating the impact of these incentives in our context. **We have included a new paragraph about the possible effect of economic incentives in the discussion section.**

#11. Reviewer 1. Minor Essential Revisions #10. The statistical model (M1, see page 8 for the model specification and page 20, table 3 for the estimated values) suggest that the mean value for class-region observations with FC is higher compared to the RC. Firstly, it is not obvious what the baseline observation is and how to interpret that. Secondly, authors did not discuss if there were a systematic association between drug classes and copayment status which may lead to higher prescription cost. Thirdly, the level effects may persist even in models M2 and M3 (see page 8 for the models). But that indicator variable was included in the model. Authors should justify this.

- M1 is a model with only one categorical binary regressor and it is equivalent to an ANOVA with two groups. The interpretation is: the price of FC drugs on average is 9.74€ higher for pensioners than for non-pensioners. RP drugs are priced more or less equally for active patients and for pensioners. The difference in price between active patients and pensioners is estimated at -0.32€, which is not significant. An alternative way to show M1 would be to specify a constant and a dummy for one of the groups, the other being the reference group. That equivalent model with RC as the reference would be:

\[
DP_{ij} = -0.32 + 9.42FC_{ij} + U_{j0} + e_{ij}.
\]

We think it is clearer to show M1 as a group-comparison specification, which is without intercept and including both categories. **No changes have been made regarding this comment.**

Reviewer 2: Antonio Sarria-Santamera

#12. Reviewer 2. Major Compulsory Revisions #1. This paper aims to identify the presence
and intensity of the agency relationship between general practitioners and patients in Spain. For this purpose, the authors analyze patterns of prescriptions for cardiovascular diseases and mental illnesses in a series of areas in Spain.

The main problem of this work is the information analyzed, which do not include data about age, sex, or clinical condition of the patients. They have information regarding the administrative status of the patients receiving the prescription, which is linked to the level of copayment: pensioners (free of charge), and non-pensioners who could be paying full copayment (40%) or reduced copayment.

The main hypothesis of this work is that it would be expected that doctors would prescribe at the same average price for non-pensioners and pensioners, ceteris paribus, which in this case should mean that patients characteristics are comparable. However, this paper assumes that pensioners (which would be much older, therefore sicker) are comparable to non-pensioners (younger people). An explanation to the differences in medicines prescription they have identified is that doctors could treat patients differently based not only on the prices of the medicines, but on the clinical situation of the patients.

- The reviewer expressed the same concerns as reviewer 1. Please see previous responses (#01, #02 and #05). Basically, we do not compare prices for pensioners and non-pensioners within all drugs, but in specific homogeneous therapeutic groups with similar indications for pensioners and non-pensioners (the price differences within statins, antidepressive drugs, ACEIs and ARBs, beta-blockers, and so on -with some mentioned exceptions- are not related to patient severity).

#13. Reviewer 2. Major Compulsory Revisions #2. Another situation that affects prescription in primary care is that has been called “induced prescription”: general practitioners are somehow forced to prescribe medications that have been indicated by specialists. Specialists could have different prescription patterns than family doctors and pensioners (older and sicker people) could be more exposed to this effect than non-pensioners.

- The so-called “induced prescription” is an important phenomenon in Spain and, certainly, specialist doctors have different prescription patterns (usually with more “innovative” and brand-name drugs) than GPs and, additionally, they are not included in the incentive policies. It is also reasonable that they treat patients with more severe conditions. We agree with the reviewer that this phenomenon could contribute to the price discrimination of drugs with different co-payment schemes. We have included a new sentence about this issue in the discussion section.

#14. Reviewer 2. Major Compulsory Revisions #3. The third issue to consider is that the physician agency relationship is based on two factors: the information asymmetry existing in the patient-doctor relationship, and the existence of incentives that induce or persuade the doctors, in this case, to modify their prescribing behaviour. Although the authors do mention the possibility of those incentives, they do not seem to be so strong to really explain the differently use of medicines in the groups that are compared.

- Your comments and those from the other referees have convinced us to be less “ambitious” in theoretical explanations (agency relationships) and to limit ourselves to testing an empirical fact that could have different causal explanations but that has in any case important policy consequences: that doctors in Spain distinguish prices between groups of patients according to copayment schemes. Therefore, we have eliminated some specific references to the agency relationship from the title and from the main text and
abstract. Instead, we refer to GP sensitivity to prices paid by patients (please see the tracked manuscript). In the discussion section we argue that these patterns of price differentials may be due to different causes and mechanisms (see response #03).

#15. Reviewer 2. Major Compulsory Revisions #4. These comments frame the main recommendation of this review: the data analyzed has serious limitations to be used to test hypothesis. These data could allow for proposing hypothesis that further research could explain. Therefore, authors should reorient not only the objective but also the tone of the manuscript. Instead of testing the hypothesis of the existence of the agency relationship, the paper should discuss which factors could explain primary care doctors’ prescribing behaviour and to what extent and in which conditions could be explained by the physician agency relationship.

- Thank you for the suggestion. We have changed the manuscript as you suggest. Please see the tracked version.

#16. Reviewer 2. Major Compulsory Revisions #5. In another dimension, it has also to be mentioned that the manuscript is too long and too dense, not easy to read. It should be shortened and make more accessible to the reader. Also, tables and figures are not clear.

- We have revised the whole manuscript in an attempt to improve readability. We have also revised tables and the figure (there is only one). And we also have tried to maintain the length despite the additional comments needed because of the reviewer’s requirements.

Reviewer 3: Andrew Sfekas

#17. Reviewer 3. Previous comment. The purpose of this paper was to determine whether physicians act as agents for their patients. The actual meaning of “agency” in this context is left undefined. The authors do provide a partial concept of agency in the context of the doctor and the government (the doctor would consider the prescription’s effect on the total health care budget).

The specific hypotheses tested are that: 1) the total average price of prescribed drugs will be higher when consumers face a 0 price, relative to when consumers face a positive price; 2) the difference in average price between 0 cost to consumers and positive cost to consumers will be lower when the cost is lower; 3) the difference in average price will be higher when the price of treatment is higher. On the third hypothesis, it is somewhat unclear what is meant by the price of treatment.

- Price is always the regulated, fixed sale price as labelled on the box. What varies is the part of the price that different patients (pensioners and non-pensioners) have to pay out-of-pocket. We clarify in the new version what the price of treatment is in the third hypothesis. Also, in order to avoid confusion, we have changed “treatments” for “drugs” in the main text.

#18. Reviewer 3. Compulsory Revisions #1. The paper intends to test the agency relationship between physicians and patients, but the relationship itself is not spelled out. Presumably the question is whether the physician is maximizing the consumer’s preferences, which would involve the cost of treatment. This would perhaps be in contrast to a situation in which the
physician is an agent for the government (and therefore considers the cost of treatment even when the price to consumers is 0) or him/herself only, in which case the physician may wish to maximize reputation by prescribing the most effective drug regardless of cost. I would like to see that spelled out in greater detail.

- Your comments and those from the other referees have convinced us to be less ambitious in theoretical explanations (agency relationships) and limit ourselves to testing an empirical fact that could have different causal explanations but that has, in any case, important policy consequences: that doctors in Spain distinguish prices between groups of patients according to copayment regimes. Therefore, we have eliminated some specific references to the agency relationship from the title and from the main text and abstract. Instead, we refer to GP sensitivity to prices paid by patients (please see the tracked manuscript). In the discussion section we argue that these patterns of price differentials may be due to different causes and mechanisms (see response #03 and #14)

#19. Reviewer 3. Compulsory Revisions #2. The authors acknowledge that the data are from prescriptions actually filled, not prescriptions written. If physicians wrote out the same prescriptions for everyone, and non-pensioners tend not to fill the more expensive ones, the results would be the same--average price for non-pensioners is less than average price for pensioners. However, the results would be due to the fact that consumers are cost-conscious, rather than that physicians consider the cost to consumers. I would consider this to be the main empirical problem in the paper.

- We agree with the reviewer. This point has been emphasised as a limitation in the discussion section.

#20. Reviewer 3. Compulsory Revisions #3. Shouldn’t I expect pensioners to be older and retired, and therefore to require more expensive drugs? Without some additional controls, it seems like it would be hard to attribute a price difference to agency.

- This question expresses the same concerns as the previous reviewers. See previous responses (#01, #02, #05 and #12) and changes. Basically, we do not compare prices for pensioners and non-pensioners within all drugs, but in specific homogeneous therapeutic groups with similar indications for pensioners and non-pensioners (the price differences within statins, antidepressive drugs, ACEIs and ARBs, beta-blockers and so on (with some mentioned exceptions) are not related with patient severity.

#21. Reviewer 3. Compulsory Revisions #4. One of the authors’ hypotheses is that the price difference should be less for the drugs with reduced copay. Of course that would be holding all else equal. Why are these drugs reduced copay, and what does that imply for the model? I would like to see some explanation of how drugs end up in either category.

- In Spain, drugs for treating chronic conditions have reduced copayments in order to avoid charging patients with unaffordable payments over long time periods. But in practice some drugs for chronic conditions (for instance, those for lowering cholesterol) do not have the benefit of copayment reduction. In practice, categorization is made by the central government according to non explicit specific criteria for any particular case. We clarify this point in the new version of the manuscript.
#22. Reviewer 3. Compulsory Revisions #5. I am not sure what the price of treatment refers to in models M2 and M3, so it's difficult to evaluate those results.

- Price of treatment is a synonym of price of the drug. **We clarify this point in order to make clearer the manuscript.**

Additionally, we have revised the whole manuscript to correct style and typographical errors and to adapt it to the style rules of BMC journals.

We very much appreciate the comments made by the referees, which we believe have been extremely useful in improving our manuscript.

Thank you for your interest in our paper. Please do not hesitate to contact us for any further clarification.

Yours sincerely,

On behalf of all the authors,

Beatriz González López-Valcarcel.
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