PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with health literacy in multimorbid patients in primary care: a cross sectional study in Switzerland
AUTHORS	N'GORAN, A. Alexandra; Pasquier, Jérôme; Deruaz-Luyet, Anouk; Burnand, Bernard; Haller, Dagmar; Neuner-Jehle, Stefan; Zeller, Andreas; Streit, Sven; Herzig, Lilli; Bodenmann, Patrick

VERSION 1 – REVIEW

REVIEWER	Catherine Hudon Université de Sherbrooke Canada
REVIEW RETURNED	10-Jul-2017

GENERAL COMMENTS

General comments:

This article aimed to identify factors associated with health literacy in multimorbid patients. Health literacy is an important topic and the aim of this research is relevant. The article seems promising. However, it would be necessary to state clearly what were the independent, dependent and covariables in the regression model. This clarification would help the reader better understand the study.

Specific comments:

Abstract

- Page 3: please, precise the independent, dependent and covariables in the regression model.

Introduction

- Page 6: « Healthcare providers should be conscious of their patients' health literacy skills so as to ensure that health information is communicated effectively to help manage long-term conditions. » Please, add a reference.
- Page 6: « Studies have assessed health literacy in different ways, for example, the relationships between health literacy and multimorbidity in primary care settings, or the factors influencing health literacy among less well-educated young people and their consequences. » Please summarize main results of these studies.

- Page 6: « However, to the best of our knowledge, no study has yet assessed the factors of association between health literacy and multimorbid patients. » Please, clarify this sentence.

	Methods - Page 7: Please, present the psychometric properties of the HLS-EU 6. - Page 8: The number of chronic conditions was measured with which questionnaire? Validated? - Page 9: Same question for the number of medical visits in the last year and TBQ. - Page 9: Please, explain a little bit more for the nurse question. - Page 9: Usually, the CIRS (Lin’s version) needs a chart review. Please, explain how it was used with appropriate references. Data analysis - Page 10: Please, be clear on the independent and dependent variables. In my point of view, health literacy should be an independent variable that could explain a dependant variable...not the inverse. Results - Page 12: What is the final model? Discussion - Page 13: Better explanation of independent and dependent variables would help to well understand the discussion. Many paragraphs in the discussion and the conclusion should be written again with this in mind.

REVIEWER	Robin J. Jacobs, PhD, MSW, MS, MPH Baylor College of Medicine United States
REVIEW RETURNED	26-Jul-2017

GENERAL COMMENTS	This purpose of this study was to investigate factors associated with health literacy in patients (N = 888) being seen in primary care settings who have multimorbid chronic conditions in Switzerland. Results indicated there were significant associations between low health literacy scores and treatment burden scores, marital status, moderate problems with mobility, and severe problems with anxiety/depression. Due to the importance of treatment for multimorbidity, which presents complex issues related to patient outcomes, this manuscript has the potential to make a contribution to the literature. It is this reviewers' aim to provide feedback on how to improve the potential contribution of this manuscript. The introduction / literature adequately addresses the study topic. The methods and analysis conducted are appropriate for the study. I commend the authors for addressing an important health concern and to better understand the association between health literacy and problems associated with multimorbidity in primary care patients. Limitations are appropriately addressed. This well-written manuscript presents pertinent information has the potential to make a contribution to the literature.

	The mean age of the sample was 73 years, which indicates the findings may be more relevant to an older patient population versus a younger one. This distinction should be addressed in the paper / discussion. If the mean number of chronic conditions was 4, why did the authors decide on including only those patients with 3 chronic conditions? The rational for this number (i.e., 3) needs to be explained. Also, were distinctions made between the type of condition (e.g., diabetes) or combination of conditions? More information about the criteria for selection for analysis wood be helpful to the reader. I commend the authors for addressing an important health concern and to better understand the health literacy as it might be addressed in primary care settings with multimorbid patients. This manuscript contains pertinent information, is well organized and presented (from the literature review/intro to the conclusion) and has the potential to make a contribution to the literature.

REVIEWER	Henrik Støvring Department of Public Health - Biostatistics Aarhus University Denmark
REVIEW RETURNED	17-Aug-2017

GENERAL COMMENTS	The presentation of the study design and analysis is generally well-written and transparent. From a statistical point of view, I do however have some substantial issues with the paper: 1. Patients are sampled at visits to a GPs practice. While GPs are sampled randomly, this is not true of patients. The selection mechanism for patients is to identify a random patient visit on a specified day, check whether the patient satisfies inclusion criterias, and if not then keep checking subsequent patients until a suitable patient can be included. Among all eligible patients this sampling procedure favors patients with more GP visits - they will have a higher probability of being included. While this is surely intended and may have improved feasibility, it could pose problems for the conclusions, if health literacy is somehow associated with frequency of GP visits and/or the various patient characteristics studied in relation to health literacy. At the very least this should be discussed in the paper (selection bias is mentioned, but not this particular one), and it would be nice if authors could somehow quantify how different their sampled population is from the relevant background population of patients with multimorbidity. Perhaps this could also help us understand why different studies have found conflicting results regarding the use of healthcare services and health literacy - is it merely a question of how patients are sampled in the different studies? 2. As authors note, a substantial group of included patients do not provide complete answers regarding their health literacy. As such it is a strength that authors address this with analyses based on multiple imputation. However, I would like more information on the amount of missing information *per patient*, not only with respect to the different questions in the questionnaire. In other words, what is the median number of questions incompletely

answered per patient and what is the range or distribution of this number among patients included in the analyses? Also I am not sure from the paper whether patients who did not answer any questions on health literacy were included in the analyses? I get the impression that patients had to answer at least 5 of 6 questions to be included, but if so, this should be explicitly stated along with information on how many were excluded based on this criteria. Indeed a flow-chart of the various steps in the inclusion process would help the reader.

3. More importantly though, I think the imputation of "Do not know" values is problematic. As an extreme version of this problem consider a person asked "Do you find this sentence difficult to understand?" and the person replies "I don't know". If we were to impute this answer with values from "Very easy to understand" to "Very difficult to understand" I cannot contemplate any scenario, where we would state that the actual, but unobserved answer behind the stated "I don't know" is "Very easy to understand". While less extreme in the health literacy situation, I still find it very hard to understand how a don't know answer to a question on "How easy do you find it to use information the doctor gives you to make decisions about your illness?" should not carry information in itself on the question asked. Rather, it would to me seem to indicate that patients indeed might have difficulties in using the information. How can this be addressed? I would be interested in seeing if a don't know answer for one question was more likely among patients with low health literacy on the other questions. Further, one might speculate that the imputed value could not be "very easy" or "easy", and one could therefore restrict imputed values to the remaining answer categories, possibly only as a sub-analysis. Finally I think this issue should be extensively addressed in the discussion.

A more minor problem is that many patient characteristics are included in the final model. While it is an asset that authors have not only included those with statistical significance, there are many associations and therefore a substantial risk of type I errors - claiming to have found an association, which is actually just occurring by chance in this dataset. This is the classic multiple testing problem. Authors adequately state that their analysis is explorative in nature and should be confirmed in future studies. They do however still in their Discussion point to various associations as being "interesting" or "important" despite small effect sizes and borderline significance. Further explicit caution by authors should be considered.

Finally, I think there must be typos in Table 3: For "Anxiety/depression" confidence intervals overlap zero and yet are highly significant. The problem is likely omitted minus signs on the upper limits of confidence intervals.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Catherine Hudon
Institution and Country: Université de Sherbrooke, Canada
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
See attached document
Predictors of health literacy in multimorbid patients in primary care: a cross-sectional study in Switzerland
Review bmjopen-2017-018281

3. General comments:
This article aimed to identify factors associated with health literacy in multimorbid patients. Health literacy is an important topic and the aim of this research is relevant. The article seems promising. However, it would be necessary to state clearly what were the independent, dependent and covariables in the regression model. This clarification would help the reader better understand the study.

Authors reply:

We understand the reviewer's concern. Because we wanted to understand which variables were associated with lower health literacy, we decided to use the HLS-EU score as the dependent variable (the mean of six health literacy items/questions). All other variables were used as independent variables. Of course, using another model, it would also have been possible to determine how HL influences those other variables, but this was not the aim of our study. (More details about our replies to this question in comment 9 and 13 below):
To be clearer, we have specified in the method section, on page 8:
2.2 Covariates
“All variables are described elsewhere. (26) Briefly, our analyses used the following variables:
2.1.1 Dependent variable: as we wished to understand the determinants associated with lower health literacy scores, we chose the HLS-EU as the dependent variable.
2.1.2 Independent variables includes all other variables as: age, sex, marital status, educational level, number of chronic conditions, number of drugs, number of medical visits in the last year, number of hospitalizations in the last year, Dipcare questionnaire for deprivation assessment (3 dimensions), treatment burden questionnaire (TBQ), nurse, paramedical therapist, homecare, number of specialists involved in patient’s care, EQ5D3L composed of five dimensions of health and using a visual analogue scale, the severity index derived from the cumulative illness rating scale (CIRS).”

Specific comments:
4. Abstract
- Page 3: please, precise the independent, dependent and covariables in the regression model.

Authors reply:
As requested, in the abstract’s method section, we added: “As we wished to understand the determinants associated with lower health literacy, the HLS-EU 6 score was the only dependent variable; all other covariates were considered independent.”

5. Introduction
- Page 6: « Healthcare providers should be conscious of their patients’ health literacy skills so as to ensure that health information is communicated effectively to help manage longterm conditions. » Please, add a reference.

Authors reply:
As requested, we have actually added 2 references:
- Al Sayah F, Majumdar SR, Williams B, Robertson S, Johnson JA. Health literacy and health outcomes in diabetes: a systematic review. J Gen Intern Med. 2013;28(3):444-52.

- Seligman HK, Wang FF, Palacios JL, Wilson CC, Daher C, Piette JD, et al. Physician notification of their diabetes patients' limited health literacy. A randomized, controlled trial. J Gen Intern Med. 2005;20(11):1001-7.

6. - Page 6: « Studies have assessed health literacy in different ways, for example, the relationships between health literacy and multimorbidity in primary care settings, or the factors influencing health literacy among less well-educated young people and their consequences. »
Please summarize main results of these studies.

- Page 6: « However, to the best of our knowledge, no study has yet assessed the factors of association between health literacy and multimorbid patients. »
Please, clarify this sentence.

Authors reply :
We thank the reviewer for highlighting these points. Our sentences were indeed confusing. We added a summary of the first three studies (Van der Heide, Quenzel and Sorensen) in the first sentence, and reformulated the second.
Page 6 reads now: "The literature shows that health literacy has been assessed in different ways and with contrasting conclusions: e.g. different studies looking at the factors influencing health literacy among less well-educated young people showed a relationship between low health literacy and socioeconomic factors (17, 24, 25). One study evaluating relevant associations between health literacy and multimorbidity (defined as two or more chronic diseases from a list of 11 conditions) in primary care, found none (14). To better understand the determinants associated with low health literacy, the present study aimed to explore all the factors that might be associated with low health literacy in multimorbid patients in primary care with at least three chronic conditions."

7. Methods
- Page 7: Please, present the psychometric properties of the HLS-EU 6.

Authors reply :

HLS-EU 6 is directly derived from the original HLS-EU 47 (Sorensen 2013). The original HLS-EU 47 explores three domains: healthcare, disease prevention and health promotion. In each domain, four matrices were explored: 1.access/obtaining information; 2.understanding information; 3. processing/appraising information; and 4. applying/using information. The HLS-EU 6 is a validated short form (Pelikan 2014) with two of the original questions remaining in each domain. Le Prof Pelikan provided a validated French and a German translation.
In the measurement section, pg 7, we added: "The original HLS-EU 47 explored three domains: 1. healthcare; 2. disease prevention; and 3. health promotion. Each domain explored four matrices: accessing/obtaining information; understanding information; processing/appraising information; and applying/using information.
The HLS-EU 6 is a validated short form with two of the original questions remaining in each domain (30-32)." Validated French and German versions of the HLS-EU 6 were available.

- Page 8: The number of chronic conditions was measured with which questionnaire? Validated?

Authors reply:
The chronic conditions included were based on the ICPC2 classification. We established a list of 75 chronic conditions relevant to multimorbidity in primary care and developed especially for our study (reference N'Goran). All included chronic conditions were coded on with the ICPC 2.

In the methods section, pg 7, we added: “All multimorbid patients above 18 years old and suffering from at least three of the 75 chronic conditions on a predefined list based on the International Classification of Primary Care 2 (ICPC 2) were considered eligible”
And on pg 9: number of chronic conditions (based on ICPC 2)

- Page 9: Same question for the number of medical visits in the last year and TBQ.

Authors reply:
Numbers of medical visits were declared by GPs on the basis of their medical records. No special questionnaire was used.
We added pg 9: “number of medical visits in the last year (based on GPs’ medical records)”

TBQ: Tran and Montori developed the TBQ in 2012, as a measure of the burden of treatment. This subjective estimation, on a scale of 0 to 10 (TBQ), was developed to assess the overall burden related to the treatment of chronic conditions. It consists of 15 questions, the answers for which are each scored from 0 to 10, with 0 corresponding to no burden and 10 to a very important/considerable burden. The global (summed) treatment burden score from 0 to 150. No Swiss population-based data exists for this questionnaire, but it has been validated for France.

Page 9: Please, explain a little bit more for the nurse question.

Authors reply:
In the telephone interview, the research assistant asked three questions about the home care which the patient might receive: 1) does he/she receive any medical help from a home-nursing institution (we specified all the different systems that exist across Switzerland), whether governmental or private; 2) does he/she receive help for home care (cleaner, etc.); and 3) does he/she receive meals at home. Here, the nurse question relates only to the first question, i.e. help by a home-nursing institution, which includes the care provided by qualified nurses, but also other types of care such as help for showering but also social assistance by the same system (see published protocol).

We added some precisions pg 9 on the number of medical visits and the nurse question
- number of medical visits in the last year (based on GPs’ medical records)
- medical help from a home nurse

- Page 9: Usually, the CIRS (Lin’s version) needs a chart review. Please, explain how it was used with appropriate references.

Authors reply:
As specified in the published protocol (Déruaz-Luyet et al BMJOpen 2015), for each patient enrolled, GPs provided a quantitative estimate of the impairment to each of the 13 organ systems, using the cumulative illness rating scale (CIRS) on his paper-based questionnaire. GPs completed this part of the questionnaire using information from each patient’s medical file.
9. Data analysis
- Page 10: Please, be clear on the independent and dependent variables. In my point of view, health literacy should be an independent variable that could explain a dependant variable...not the inverse.

Authors reply (please refer also to question 3, « general comments » and question 13 « discussion »

Our aim was to determine which variables were associated with health literacy in patients with multimorbidity. This is why we considered health literacy as the dependent variable and all other variables as independent. This really relates to our research question. We fully agree that health literacy could be considered an independent variable of healthcare processes or health outcomes. However, such questions were not the purpose of the analyses we present in this manuscript. Our analyses are exploratory and not based on a priori hypotheses, neither on a conceptual model.

10. Results
- Page 12: What is the final model?
-
Authors reply :

As specified before, in our opinion, the dependent variable is the health literacy score, and the final model is the multivariate regression where the dependent variable is the health literacy score. We first carried out a stepwise selection of independent variables as a sensitivity analysis (results not shown). The selected variables had similar coefficients to the complete final model. That's why all the variables appearing in Table 3 are the independent variables.

11. Discussion
- Page 13: Better explanation of independent and dependent variables would help to well understand the discussion. Many paragraphs in the discussion and the conclusion should be written again with this in mind.

Authors reply:
We now understand and agree that the discussion of our results needs to be clearer. The association between health literacy and other variables can be explored in two ways: determinants associated with health literacy as we explored in our study, or health literacy associated with different variables, as often described in literature. However, it would usually be impossible to identify causal associations, and those associations are most often descriptive in nature.
We identified a list of unclear sentences and references, and we have revised our entire discussion in light of this.
- "However, our exploratory study was unable to determine any causal association between health literacy and the treatment burden. But our results could also be considered from another angle, that has been taken in other analyses"
- "Furthermore, low health literacy, used as an independent variable, has been found to be associated with a reduced ability of adults with coronary heart disease to identify medication (42), poor health outcomes (14, 19, 43), and a more significant use of healthcare (44). These three factors can also be linked to multimorbidity and may have an impact on the overall treatment burden."
- "This result is not concordant with the study by Green et al. (46), however, which found no association between limited health literacy and depression in patients receiving chronic hemodialysis treatment, but this difference might be explained by the differences in the study populations, how health literacy was assessed and the fact that his study used health literacy as independent variable."
- "These results are inconsistent due to differences in the study populations (i.e. our study population was composed of multimorbid patients in primary care settings) and methodologies (other studies considered health literacy as an independent variable)."

Reviewer: 2
Reviewer Name: Robin J. Jacobs, PhD, MSW, MS, MPH
Institution and Country: Baylor College of Medicine, United States
Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below
This purpose of this study was to investigate factors associated with health literacy in patients (N = 888) being seen in primary care settings who have multimorbid chronic conditions in Switzerland. Results indicated there were significant associations between low health literacy scores and treatment burden scores, marital status, moderate problems with mobility, and severe problems with

anxiety/depression. Due to the importance of treatment for multimorbidity, which presents complex issues related to patient outcomes, this manuscript has the potential to make a contribution to the literature. It is this reviewers' aim to provide feedback on how to improve the potential contribution of this manuscript.

The introduction / literature adequately addresses the study topic. The methods and analysis conducted are appropriate for the study. I commend the authors for addressing an important health concern and to better understand the association between health literacy and problems associated with multimorbidity in primary care patients. Limitations are appropriately addressed. This well-written manuscript presents pertinent information has the potential to make a contribution to the literature.

12. The mean age of the sample was 73 years, which indicates the findings may be more relevant to an older patient population versus a younger one. This distinction should be addressed in the paper / discussion.

Authors reply:
Age was included in the multivariate model, and we did not observe a significant association between age and health literacy. But age groups were not equally represented throughout the sample. Indeed, the average age of our patient population was relatively high but, on the one hand, the average age of the Swiss population is elevated and, on the other hand, age is associated with multimorbidity.

We added in the discussion: pg 14 “However, our study revealed no association between HL and age”.

13. If the mean number of chronic conditions was 4, why did the authors decide on including only those patients with 3 chronic conditions? The rational for this number (i.e., 3) needs to be explained. Also, were distinctions made between the type of condition (e.g., diabetes) or combination of conditions? More information about the criteria for selection for analysis wood be helpful to the reader.

Authors reply:
The definition of multimorbidity varies throughout the literature, but a common definition can be two or more, or three or more chronic conditions. In research, the definition depends on the aims, methodology, population, lists and numbers of included chronic conditions, which usually contains silent risk factors as well as symptomatic conditions. In primary care, multimorbidity is the norm rather than the exception (Fortin), and we wanted to include more complex patients in order to target a population whose management is more challenging to GPs—this is why we used the definition of three or more chronic conditions.
To identify patients eligible for our study, we used a list of 75 chronic conditions, specifically developed to identify chronic conditions relevant to multimorbidity in primary care, and we set the limit to define multimorbidity as 3 or more chronic conditions within this list.
In the methods, pg 7, we specified: “The study was designed to assess multimorbidity in patients in a primary care setting in order to target a population whose management would be more challenging to GPs. The detailed study protocol, dataset description and initial results have been published elsewhere.”

14. I commend the authors for addressing an important health concern and to better understand the health literacy as it might be addressed in primary care settings with multimorbid patients.
This manuscript contains pertinent information, is well organized and presented (from the literature review/intro to the conclusion) and has the potential to make a contribution to the literature.

Reviewer: 3
Reviewer Name: Henrik Støvring
Institution and Country: Department of Public Health - Biostatistics, Aarhus University, Denmark
Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below
The presentation of the study design and analysis is generally well-written and transparent. From a statistical point of view, I do however have some substantial issues with the paper:

15. Patients are sampled at visits to a GPs practice. While GPs are sampled randomly, this is not true of patients. The selection mechanism for patients is to identify a random patient visit on a specified day, check whether the patient satisfies inclusion criterias, and if not then keep checking subsequent patients until a suitable patient can be included. Among all eligible patients this sampling procedure favors patients with more GP visits - they will have a higher probability of being included. While this is surely intended and may have improved feasibility, it could pose problems for the conclusions if health literacy is somehow associated with frequency of GP visits and/or the various patient characteristics studied in relation to health literacy. At the very least this should be discussed in the paper (selection bias is mentioned, but not this particular one), and it would be nice if authors could somehow quantify how different their sampled population is from the relevant background population of patients with multimorbidity. Perhaps this could also help us understand why different studies have found conflicting results regarding the use of healthcare services and health literacy - is it merely a question of how patients are sampled in the different studies?

Authors reply:
We thank the reviewer for this pertinent comment. As better described in the published protocol, the GPs are not randomly sampled, but the inclusion of patients was sufficiently random to limit the possibility that GPs select specific patients. However, as the reviewer proposed, patient selection could introduce a potential selection bias by oversampling frequent attendees. However, the number of visits was one of our covariates and our analyses found no association between HL and the number of visits. We believe that this potential selection bias is not an important limitation.
Furthermore, references to the two directions of this association can be found in the literature:
On the one hand, multimorbid persons with low HL may make more visits especially in emergency settings (e.g. in Herndon: “Health literacy and emergency department outcomes, a systematic review” Annals of Emergency, 2011, or Griffey RT: “Is low health literacy associated with increased emergency department utilization and recidivism?” Acad Emerg Med 2014.
On the other hand, persons with low HL also have low access to the health system, as shown by Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K.: “Low health literacy and health outcomes: an updated systematic review.” Annals of Internal Medicine. 2011;155(2):97-107.
However, little is known about the frequency of consultation and health literacy in the primary care settings.
In the limitations, pg 17, we added: “Furthermore, we cannot exclude a potential selection bias, as patients who consulted more frequently had a higher chance of being included. However, we found no association between the frequency of consultations and health literacy in our final model.”

16. As authors note, a substantial group of included patients do not provide complete answers regarding their health literacy. As such it is a strength that authors address this with analyses based on multiple imputation. However, I would like more information on the amount of missing information *per patient*, not only with respect to the different questions in the questionnaire. In other words, what is the median number of questions incompletely answered per patient and what is the range or distribution of this number among patients included in the analyses? Also I am not sure from the paper whether patients who did not answer any questions on health literacy were included in the analyses? I get the impression that patients had to answer at least 5 of 6 questions to be included, but

if so, this should be explicitly stated along with information on how many were excluded based on this criteria. Indeed a flow-chart of the various steps in the inclusion process would help the reader.

Authors reply :
We thank the reviewer for underlining these points. We agree that some of our information about the use of incomplete answers was not precise enough.
All missing values were imputed and all respondents were included in the analysis. As a sensitivity analysis, we evaluated the same model using the respondents who answered at least 5 of the 6 HL questions and who had no missing values in any covariate (431 respondents). In this analysis, the HL score (mean of the HL variable) was computed ignoring the missing values. We did not report the results of the sensitivity analysis, but it gave similar results of the one based on multiple imputations.
In the abstract's main measures section we wrote: "This comprises six items scored from 1 to 4 (very difficult = 1, fairly difficult = 2, fairly easy = 3, very easy = 4), and the total health literacy score is computed as their mean."
And in the method section, pg 8, we wrote: "This fifth alternative was coded as a missing value. The health literacy score was thus calculated as the mean of the six health literacy items, scored from 1 to 4, after imputation of the missing values (see the Statistical Analyses section below "
And in the limitation, pg 17: "Third, the health literacy score contained a lot of missing values, and we cannot exclude that the cause of that missing data was related to health literacy itself. However, we examined whether the mean of the available HL items was associated with the number of missing HL items, and this was not the case."

17. More importantly though, I think the imputation of "Do not know" values is problematic. As an extreme version of this problem consider a person asked "Do you find this sentence difficult to understand?" and the person replies "I don't know". If we were to impute this answer with values from "Very easy to understand" to "Very difficult to understand" I cannot contemplate any scenario, where we would state that the actual, but unobserved answer behind the stated "I don't know" is "Very easy to understand". While less extreme in the health literacy situation, I still find it very hard to understand how a don't know answer to a question on "How easy do you find it to use information the doctor gives you to make decisions about your illness?" should not carry information in itself on the question asked. Rather, it would to me seem to indicate that patients indeed might have difficulties in using the information. How can this be addressed? I would be interested in seeing if a don't know answer for one question was more likely among patients with low health literacy on the other questions. Further, one might speculate that the imputed value could not be "very easy" or "easy", and one could therefore restrict imputed values to the remaining answer categories, possibly only as a sub-analysis. Finally I think this issue should be extensively addressed in the discussion.

Authors reply:
We thank the reviewer for this very interesting comment. We discussed the significance of the "I don't' know" answer a lot within our team, and we agree that the hypothesis of an association between the "don't know" answer and low health literacy is possible. However, other hypothesis exists too: the "don't know" answer may also mean that the person is not interested in the question in itself. Indeed, if someone does not have a psychological problem, he cannot be concerned by a question about how difficult it is to find information about this question. As it is impossible to get an answer about the significance of the "don't know" answers, we prefer not to introduce this question into our discussion. Furthermore, we have tried to be clearer in both the abstract and the methods section about the possible answers to the health literacy items.
Pg 8 now reads:
"The possible responses were as follows: very difficult = 1, fairly difficult = 2, fairly easy = 3, very easy = 4 and a fifth alternative for when participants did not answer or did not have a definite answer, coded as a missing value. The health literacy score was thus calculated as the mean of the six health

literacy items, scored from 1 to 4, after imputation of the missing values (see the Statistical Analyses section below) (31).”

And you will find further information about our analyses of this topic in the following table giving mean health literacy scores stratified by the number of missing health literacy items. The score is computed by omitting the missing items. If all the items are missing (2 cases) the score is undetermined. The health literacy score calculated with the available items does not seem to depend on the number of missing values.

```
missing_HL_items_nb nobs HL_min HL_mean HL_sd HL_median HL_iqr HL_max
0 311 1.33 2.83 0.48 2.83 0.67 4
1 200 1.6 2.87 0.44 2.8 0.4 4
2 175 2 2.87 0.43 2.75 0.5 4
3 117 1.67 2.95 0.51 3 0.67 4
4 59 2.5 3.12 0.48 3 0.5 4
5 24 2 3.04 0.46 3 0 4
6 2
```

18. A more minor problem is that many patient characteristics are included in the final model. While it is an asset that authors have not only included those with statistical significance, there are many associations and therefore a substantial risk of type I errors - claiming to have found an association, which is actually just occurring by chance in this dataset. This is the classic multiple testing problem. Authors adequately state that their analysis is explorative in nature and should be confirmed in future studies. They do however still in their Discussion point to various associations as being "interesting" or "important" despite small effect sizes and borderline significance. Further explicit caution by authors should be considered.

Authors reply:
We carried out a stepwise selection of independent variables as a sensitivity analysis. The selected variables had similar coefficients to the complete model.
We added in the statistical analyses: As a sensitivity analysis, we carried out a complete case analysis, and this gave similar results.

19. Finally, I think there must be typos in Table 3: For "Anxiety/depression" confidence intervals overlap zero and yet are highly significant. The problem is likely omitted minus signs on the upper limits of confidence intervals.

Authors reply :
There are no typos. The confidence intervals do not overlap 0. However, the table’s columns were not large enough and the minus signs appeared overlaid on the numbers in some versions, due to a formatting problem. We have now corrected this.

VERSION 2 – REVIEW

REVIEWER	Catherine Hudon Université de Sherbrooke Canada
REVIEW RETURNED	20-Oct-2017

GENERAL COMMENTS	General comments:

	Authors addressed many comments of my previous review and presented an improved manuscript. However, major revisions are still required, especially in the Methods and Discussion. Specific comments: Title - Since the cross-sectional design does not allow evaluating causality, the word « Predictors» should be replaced by « Factors associated with » or such kind of expression. Introduction - Page 6: « Additionally, health literacy is a prerequisite for patient activation and shared decision-making. » Please, add a reference. Methods - Page 7: The data collection process is not clear. Data came from a national cross-sectional survey (self-administered questionnaire), so why the number of medical visits in the last year is based on GP's medical records? We still need precisions about how were measured many independent variables: number of chronic conditions, number of drugs, number of hospitalisations in the last year, medical help from a home nurse, number of specialists involved in patient's care. Validity of the questionnaire is crucial, and it is not possible to judge in the current version. - Page 7: We also need more information about recruitment of the multimorbid patients. - Page 8: Please add references for the French and German versions of the HLS-EU 6. Data analysis - « Univariate and multivariate linear regressions were carried out to identify predictors of health literacy. » Again, the word « predictors » should be replaced by « variables associated with ». Discussion - Page 13: This section needs major revisions. « This could be explained by the fact that multimorbid patients, facing a high treatment burden and several associated diseases at once, are so concerned about simply coping with their care procedures and treatment that they do not have time to improve their literacy and truly understand those medical acts. This is a common result of polypharmacy, several different treatment procedures and

	care regimens, and numerous administrative procedures. When we look at all of these elements together, patients faced with the complex situation of a high treatment burden may well become confused: there are too many things happening at the same time for them to be able to understand and manage them effectively. They therefore have neither the time nor the energy to improve their health literacy from its initial low level. » Honestly, I find theses hypothesis pretty weak. The cross-sectional design does not allow concluding on the sense of the association. The hypothesis that low literacy be associated with high illness burden seems more logical than the inverse. - Same comment for the last paragraph of page 14. - Instead of trying hypothesis, authors should compare their results to results of other articles and explain the implication of their findings. Conclusion - The conclusion should be more concise and answer the objective of the study.

REVIEWER	Henrik Støvring Department of Public Health Aarhus University Denmark
REVIEW RETURNED	07-Nov-2017

GENERAL COMMENTS	Authors have adequately addressed my concerns, and I have nothing further to add.

VERSION 2 – AUTHOR RESPONSE

General comments:
Authors addressed many comments of my previous review and presented an improved manuscript. However, major revisions are still required, especially in the Methods and Discussion.

Specific comments:

1. Title
Since the cross-sectional design does not allow evaluating causality, the word “Predictors” should be replaced by “Factors associated with” or such kind of expression.

Authors reply:
We changed the word “predictor” to “factor”» in the title.

Introduction

2. Page 6: “Additionally, health literacy is a prerequisite for patient activation and shared decision-making.” Please, add a reference.

Authors reply:
We added the following references:
Durand AM: Do interventions designed to support shared decision-making reduce health inequalities? A systematic review and meta-analysis.

Sian K Smith: Insights into the concept and measurement of health literacy from a study of shared decision-making in a low literacy population.

Sian K Smith: Skill set or mind set? Associations between health literacy, patient activation and health.

3. Methods

Page 7: The data collection process is not clear. Data came from a national cross-sectional survey (self-administered questionnaire), so why the number of medical visits in the last year is based on GP’s medical records? We still need precisions about how were measured many independent variables: number of chronic conditions, number of drugs, number of hospitalisations in the last year, medical help from a home nurse, number of specialists involved in patient’s care. Validity of the questionnaire is crucial, and it is not possible to judge in the current version.

Authors reply:
As specified in the Methods section, the whole protocol and the first results have been published elsewhere. But we have nevertheless added some more details in the Methods section (see answer below).

Indeed, for each patient included, GPs completed a paper-based questionnaire, whereas each enrolled patient answered a telephone-based questionnaire.

Our independent variables came from both GPs’ questionnaires and patient interviews. If we used validated questionnaires for most of the research questions, we think that some of them—such as the number of chronic conditions or the number of hospitalisations etc.
—do not necessarily need a validated questionnaire (there is no scoring). Therefore, we only ask simple questions to the GPs who were able to base their answers on medical records.

For more clarity, we have now separated the list in independent variables by whether they were in the GP and patient questionnaire.

The following independent variables came from GPs’ questionnaires and their medical record:
- The number of chronic conditions coded by the GP that were on the predefined list of 75 chronic conditions (reference: N’Goran)
- The number of drugs listed by GPs, by organic system (general, blood, immune, digestive, cardiovascular, respiratory, neurological, endocrine, eye, ear, psychological, musculoskeletal), on the basis of their medical records and coded by substance.
- The number of hospitalisations listed by GPs as per their medical records.

4. Page 7: We also need more information about recruitment of the multimorbid patients.

Authors reply:

As specified above, all this information can be found in a previously published protocol and first results. The sampling section of the published protocol reads: “Recruitment of patients: Each GP will include 10 patients meeting the inclusion criteria. Recruitment will take part over a maximum period of 10 weeks per GP. The data collection process will start on 12 January 2015 and will end on 30 September 2015. Each GP will be provided a randomisation calendar specifying which patient to enrol for each half-day of the recruitment weeks. We selected half-days for the recruitment of patients to match GPs’ schedule as accurately as possible, and to take into account the fact that many GPs work either part-time or have a variety of professional activities (teaching, home visits, etc). We wanted to make sure that the GP was seeing patients at his practice during the entire time slot considered. Patients’ recruitment is based on patients who are scheduled for each half-day of recruitment. The randomisation calendar gives the ordered number of the consultation to consider, and the GP includes the patient of this consultation if he/she meets the inclusion criteria. If the randomised patient does not meet the inclusion criteria, the next patient who fulfils the inclusion criteria is eligible. If no patient is included at the end of the half-day, the recruitment process will be postponed to the next half-day of consultations. The patient will be asked to consent to participate to a telephone interview questionnaire that will take place within 48 h after the visit to the GP. The patient’ s name and phone number will then be transmitted to a research assistant. If an eligible patient refuses to participate, their date of birth, sex and reason for refusing participation will be documented.”

We added a summary of this information in the Methods section:

“Each GP was provided with a randomisation calendar specifying which patients to enroll on each half-day during the recruitment weeks.”

And

“GPs completed a paper-based questionnaire for each included patient (patient-related variables assessed through the GP survey). Patients enrolled completed a telephone-based questionnaire.”

5. Page 8: Please add references for the French and German versions of the HLS-EU 6.

Authors reply:
The German version of the HLS-EU 6 can be found in the original references (consortium H-E, Pelikan, and Sorensen). When we bought the German and French versions after an e-mail exchange with Prof.
Pelikan, he assured us that there was a validated French version, translated and back-translated by a Belgium consortium. This was the version we used. However, it seems that the validated French version has yet to be published and is only accessible via the authors. We added a reference for this and specified “available by the authors (34).”

6. Data analysis
“Univariate and multivariate linear regressions were carried out to identify predictors of health literacy.” » Again, the word “« predictors” » should be replaced by “« variables.”

Authors reply:
We replaced the word “predictors” by “variables.”

7. Discussion
Page 13: This section needs major revisions.

Honestly, I find theses hypothesis pretty weak. The cross-sectional design does not allow concluding on the sense of the association. The hypothesis that low literacy be associated with high illness burden seems more logical than the inverse.

Authors reply:
We changed the paragraph and introduced some references. The paragraph reads now as follows: “There are no specific references to explain the association found between health literacy and the burden of treatment. As a proxy for treatment burden, some authors have described an association between low health literacy and treatment adherence (45, 46), however, others found no evidence for such an association (47, 48).“

Same comment for the last paragraph of page 14.

Instead of trying hypothesis, authors should compare their results to results of other articles and explain the implication of their findings.

Authors reply:
We changed this particular paragraph that reads now:

“Concerning the association between mobility problems and low health literacy, Matsumoto et al. describes a relationship with different social determinants of health such as housing, employment, transport or social support (54). On the other hand, in a very different population, there was a strong association between low health literacy and obesity in young children with a described lack of physical activity (55). However, we can only speculate as to whether there is any precise explanation of the associations between anxiety, depression, mobility and health literacy. Furthermore, due to its design, the study’s findings cannot determine a causal association.
Anxiety, depression and mobility are just some of the detereminants of quality of life, and the literature reveals very controversial results concerning the association between health literacy and quality of life. It seems that such associations may depend on certain other aspects, such as specific chronic diseases or the cultural characteristics of the population studied (56). Thus, although we found that some of the determinants of quality of life are factors associated with low health literacy, we believe that further studies are necessary to better understand the underlying reasons for the controversial results in the literature. However, it nevertheless seems important to describe factors associated with low health literacy, thus allowing GPs to better identify such patients and to adapt how they inform them about medical problems.”

Conclusion
- The conclusion should be more concise and answer the objective of the study.

Authors reply:
We reformulated and shortened the conclusion. It reads now:

The present study highlights factors associated with health literacy in multimorbid patients in primary care: a high treatment burden, altered quality of life by problems with anxiety or depression and poor mobility were associated with a low level of health literacy. This is a useful information that could guide GPs in their daily practice and help them to better identify patients at risk of having low health literacy. Even though, with the current state of knowledge, we cannot demonstrate causal relationships between multimorbidity and the treatment burden, GPs should carefully weigh up how best to transmit clinical information to patients whom they believe to be at risk of low health literacy.