**Author’s response to reviews**

**Title:** Adherence to treatment and related factors among patients with chronic conditions in primary care: A cross-sectional study

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Ref: FAMP-D-19-00153

Title: "Adherence to treatment and related factors among patients with chronic conditions in primary care: A cross-sectional study"

Journal: BMC Family Practice

**EDITOR COMMENTS**

Comment:

1) In the figure - the vertical line should be at 1 and not at zero. To see whether the OR is in favor (>1) or not in favor (<1)
Response:

We appreciate the concern of the editor and we have addressed this matter (figures section, Figure 1).

REVIEWER COMMENTS

R Nascimento (Reviewer 1)

Comment:

1) I think that tables 1 and 2 are too long and so difficult to analyze. I would suggest to split the table 1 in two tables: first one with the social and economic characteristics, healthcare team and system related factors; and a second table with health conditions, therapy related factors and patient related factors. The same suggestion to table 2 - present just the multivariate logistic regression. The p-value of the bivariate analyses could be inserted in table 1.

Response:

We want to thank the reviewer for the suggestions. We have presented social and economic-, healthcare team and system-, and condition-related factors in Table 1, and therapy- and patient-related factors in Table 2. Furthermore, we have included the results of the bivariate analyses in both tables (Table 1 and Table 2) and have just presented the multivariable logistic regression in Table 3 as the reviewer suggested.

Comment:

2) The prevalence of high, medium and low adherence could be presented as a table or figure and not as a supplementary table.

Response:

We would like to include Table s2 (Level of Adherence and Likely Causes of Non-Adherence according the Morisky-Green-Levine Questionnaire) in the Supplementary Material section because all the information displayed in the table is explained in the manuscript (results section, sample characteristics). Thus, we consider this table is not essential to understanding the conclusions of the paper but complements to the article content.
Comment:
3) Regarding to the discussion, I would suggest a reformulation of the first paragraph which presents just results showed before. The first phrase of the second paragraph is a little confused and needs adjustments.

Response:
We appreciate the reviewer’s insights and we have reformulated some sentences in the discussion section. However, we believe that the first paragraph of the discussion should summarize the main findings of the study. This is generally recommended by the editors of the journals (1).


Comment:
4) Page 14, line 312 - Discussion about use a single pharmacy to dispensing medication. Is this the only alternative? If is there a robust computerized systems implemented, is it really necessary to use just one pharmacy? I would suggest to improve this discussion and the conclusions.

Response:
Based on our findings and the results of previous studies, we believe that rather having a robust pharmacy-based computer system, the consistent use of a single pharmacy may be an effective approach to foster adherence. We have modified this part of the discussion and have incorporated new arguments and results of studies that support our approach (discussion section, 6th paragraph).

Alex Lustman (Reviewer 2):
Comment:
Major problems - The Morisky-Green-Levine questionnaire was designed as a screening test for adherence, not as a "gold standard" tool for research purposes. As the article states,“ it has ab 81% sensitivity and only a 44% sensitivity. The authors must adress why this method can be applied to their research question when it has such a low sensitivity. Generally the questionnaire
is scored 1 for each no response and a score of 3-4 is considered good adherence. Why did the authors reverse the accepted scoring? Why did the authors only consider 0 as high adherence when most articles use scores of 3 and 4 for as being considered good adherence?

Response:

We want to thank the reviewer for the concerns. Firstly, we want to highlight that there is no method considered as “gold standard” to measure adherence (1). As result, multiple methods (direct and indirect) have used to measure adherence. One of these methods is the Morisky-Green-Levine Questionnaire(2). This method, according to the systematic review conducted by Suliman et al. (3) is one of the most widely accepted to assess medication adherence to chronic conditions. We used this method because is simple, economic, practical, easy of administer, and provides likely reasons for non-adherence. Furthermore, the self-reported Morisky-Green-Levine questionnaire has been translated into more than 80 languages and validated with physiological outcomes for hundreds of specific health conditions (4). Additionally, the Morisky-Green-Levine Questionnaire has also used in many other studies to assess medication adherence in populations suffering from multiple chronic conditions in many other studies (5–8).

Secondly, the reviewer pointed out that the method "has ab 81% sensitivity and only a 44% sensitivity. The authors must address why this method can be applied to their research question when it has such a low sensitivity”. We want to clarify to the reviewer that this method has high sensitivity (81%), and does not have low sensitivity as the reviewer stated. Additionally, we are aware that the method has an acceptable specificity (44%), as we pointed out in the limitations of the study, and various methods are currently available with better psychometric properties. We are also aware that any self-reported method may somewhat underestimate the true extent of non-adherence (1). However, the Morisky-Green Levine has been considered one of the most important methods to measure adherence and has been cited over 5,000 times in peer-reviewed journals since its publication (Google Scholar). Furthermore, this test has been shown to improve their psychometric properties, detect poor treatment adherence in patients with depression (9), and was more sensitive to detect non-adherence than the pill count method in patients with Parkinson’s Disease (10). Overall, we consider the Morisky-Green-Levine test a useful method for research (4).

Regarding the scoring of the scale, we used the original scale published in the validation of the method (2) and we did not reverse any score. According to the original publication, each “no” response receives a score of “0”, and each “yes” response receives a score of “1”, resulting high adherence in a total score of “0”; medium adherence in a score of “1-2”, and low adherence in a score of “3-4” (page 69, Table 2, original publication Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence). If a score of “3-4” is considered ‘good adherence’ as the reviewer suggested, then, a patient who forgets to take his medicine, is careless at times about taking his medicine, and stops taking his
Comment:

Minor-

1 The English throughout the article needs correcting.

Response:

The manuscript has now been carefully reviewed by an editor to ensure that it reads well and is grammatically correct.

Comment:

2 Please describe how the 2 sites chosen are representative of primary health care clinics throughout Spain

Response:

The 2 sites chosen to conduct the study are representative of primary healthcare centers of Spain because all the healthcare centers in Spain operate on the same principles to maximum accessibility and equity within the national territory and because they represented the main centers of the Health Area of Soria, one of the 52 provincial capitals of Spain. We have now incorporated the information in the manuscript: “The Spanish National Health System (SNHS) provides universal health coverage to all Spanish citizens and is structured into two healthcare levels: Primary Health Care and Specialist Care. Primary Health Care is distributed in Health Areas that provide basic health care services through one or more healthcare centers. All the healthcare centers operate on the same principles to ensure maximum accessibility and equity mean within the national territory. Healthcare centers in Spain offer services free of charge at the point of delivery such as consultations, health education, laboratory tests, physical therapy, and x-ray exams. Currently, the facilities of the study are the main healthcare centers of the Health Area of Soria, and guarantee healthcare services to an estimated population of 25,000.” (methods section, study design and settings).

Comment:

3 Why did you choose 75% adherence levels for the sampling population when in the conclusion you bring a number of papers with 50% adherence rates
Response:

We chose a 75% of prevalence of medication non-adherence based on the results, methodology, and population of previous studies that we referenced in the manuscript: We accepted an expected proportion of the participants not adhering to prescribed medications of 75% [22, 23] (methods section, population and sampling). These studies were conducted in Spain and Italy (country with a similar healthcare system to Spain), among people with multiple chronic conditions, and used the same instrument to measure adherence (the Morisky-Green-Levine Questionnaire). We considered these studies were more appropriate than others to set a reference level of non-adherence.

Comment:

4 Were the various questionnaires validated in Spanish?

Response:

We appreciate reviewer’ concern. We used the Spanish validated version of "Medication Assessment Questionnaire"(11) and we have now incorporated this information in the manuscript: “Self-reported adherence was determined using the Spanish validated version [25] of the four-item Morisky-Green-Levine Medication Assessment Questionnaire [26]” (methods section, measurement of exposure and covariates). The questionnaire used to collect patients’ socio-demographic characteristics and information related to adherence factors was designed after a discussion by an expert group in medication-adherence (five primary care physicians, two pharmacists, and one statistician) to ensure validity. This information was previously reflected in the manuscript: “A questionnaire, previously designed by an expert group in medication-adherence, was used to obtain information about patients’ socio-demographic characteristics and factors related to adherence. Prior to its implementation, investigators piloted the survey on 30 subjects to ensure it was easily understood, well-defined, and accurately addressed the study goals” (methods section, data collection).

Comment:

5 Eligible subjects were aged 18 and older, yet the youngest subject interviewed was 52, is this representative?
Response:

We do not know why the reviewer pointed out that the youngest interviewed was 52 years. We did not provide any information about participants’ age range because we believe it was not relevant information. We did provide the mean age (in years) and standard deviation of participants: 65.79 ± 13.7 (Table 1). Actually, the age of the younger participant was 20 years old, but again, we did not include this information because we believe does not lead to a better understanding of the study.

Comment:

6 Should "medium adherance rates " be included in the "poor adherance" group?

Response:

An extensive number of studies that used the Morisky scale has categorized any score above zero as non-adherent (6–8,12,13). We believe this classification is appropriate given the analyses of our study.

Comment:

7As this was a cross sectional study, association can be implied NOT prediction, please correct throughout the article.

Response:

We appreciate the insights of the reviewer and we have replaced the term “predictor” for the term “factors” through the manuscript.

Comment:

8 "Prevalance rate" is not the correct term, please rewrite the sentences that talk about prevelance to adherance

Response:

We thank the reviewer for the suggestion and have modified this term through the manuscript.
Comment:

9 The MORISKY-Green-Levine questionnaire is a good screening tool with 81% specificity, but as a research tool to confirm compliance it is weak with a 44% sensitivity.

Response:

Again, this method has high sensitivity (81%) and an acceptable specificity (44%), and does not have 81% specificity and 44% sensitivity as the reviewer pointed out. The high sensitivity of the method indicates its ability to detect a sizeable number of true non-adherent patients. On the other hand, its acceptable specificity means that a number of patients who are adherent are likely to self-report non-adherent. However, it is generally accepted that patients tell the truth when they report that they have not taken their medication (14).

Comment:

10 Table 1 and 2 can be combined.

Response:

We have combined Table 1 and Table 2 as the reviewer suggested and we have also split the factors in two tables as suggested by reviewer #1. We have presented social and economic-, healthcare team and system-, and condition-related factors in Table 1, and therapy- and patient-related factors in Table 2. The result of the bivariate analysis is presented in both tables (Table 1 and Table 2) and we have just presented the multivariable logistic regression in Table 3.

REFERENCES


