ARTICLE DETAILS

TITLE (PROVISIONAL) | Development of a novel instrument for assessing intentional non-adherence to official medical recommendations (iNAR-12): a sequential mixed-methods study in Serbia


GENERAL COMMENTS | I appreciate the opportunity to review the manuscript (Intentional non-adherence to official medical recommendations: An irrational choice or negative experience with the healthcare system?). I hope that my comments below can help the authors to strengthen their submission.

Introduction
The introduction is not clear and need to be revised. For instance, is the gap in knowledge the study tries to fill is non-adherence to medical recommendations versus current focus on medication or intentional non adherence? The introduction provides summary of many references about the extent/types of non-adherence but do not discuss adherence in the context of theories and frameworks. Many systematic reviews on the factors associated with adherence are published yet not referenced e.g. Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic reviews. Syst Rev. 2019;8(1):1–17.7.

Methodology
Focus group: the reader is referred to a detailed report in Serbian, but basic information needs to reported in the manuscript to help judging the validity of the focus group findings. For instance, who conducted the focus group? How were participants selected? Why participants’ background from neurology, pulmonology, gynecology, and forensic not a cardiology or endocrinology or a pharmacy? Did they used an interview guide? Prompt questions? Duration of the focus group? Was one focus group enough? Derivation of themes?
Literature review: the purpose of the review appears to be “to inform inclusion of any additional items” which items? The methods started by “To compile a comprehensive initial pool of non-adherence behaviors” does items refer to behaviours? Again, more details are needed to judge the quality of the review. The keywords used would yield thousands of hits what criteria was used to include or exclude evidence? What papers were included and used to created the list of non-adherence behaviours? Why the authors opted for conducting literature review despite that a number of high quality systematic reviews are published on adherence?

Page 11 line 42: “intentionally decided not to follow a recommendation or to avoid/delay seeking treatment, rather than forgetting or failing to do something due to insufficient self-discipline” I find the sentence forgetting or failing to do something due to insufficient self-discipline is over simplifications of unintentional adherence and offending to the patient. Please refer to Lehane and McCarthy 2006 were they discuss three factors related to unintentional adherence: patient factors, treatment factors and patient/professional factors.

Page 12 line 8: “intentional non-adherence, as opposed to habitual non-adherence”, is habitual non adherence the same as unintentional non adherence? In page 9-10 habitual was explained as behaviors that are lifestyle-related e.g. smoking? If not, did the 8 members rate intentional non adherence and habitual non adherence only? What about unintentional non adherence?

Page 12 line 52: the sample size is nor clear if collection was terminated at 475 how did the authors reach a sample of 646

Results

Table 1 How was the mean of behaviours calculated? Do behaviours have scores? Or do the authors % of those who responded to each behaviour?

The final 12 items include “refused to change my lifestyle habits (e.g. my diet or physical activity) as recommended by a doctor” although in the methodology page 8 the author stated “Therefore, we have not included adhering to health behaviors that are lifestyle-related, hence likely to be more habitual.” Furthermore, what is the difference between diet in item 12 and smoking as habitual non-adherence?

It is not clear how item 7 “did not take prescribed therapy” is an intentional behaviour versus other items in commonly used adherence measurement instrument e.g. did you take your medicine yesterday?

Table 2 how the Mean and Sd for iNAR was calculated? Is the correlation between iNAR-12 and item 1 is o.72? what is item 1? I assumed it is iNAR-12?

Discussion

I am not sure that the study “developed a novel measure of intentional non-adherence to medical recommendations”. Reading the manuscript, a number of health behaviours were identified and the degree of non-adherence to these behaviours was correlated to certain factors such as experience and passivity.

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**GENERAL COMMENTS**

Thank you for the opportunity to review this manuscript, which elucidates a relevant subject.

Authors Purić, D. et al. have developed a novel instrument measuring intentional non-adherence behaviour to medical recommendations and evaluated over 500 participants using the instrument.

The study is relevant as a greater knowledge of factors that influence intentional non-adherence may be used in the future to achieve treatment adherence and thereby improve the general health of the population. The survey is well conducted and analysed. However, I missed a discussion on whether or not the most relevant population was surveyed.

Major issues

Limitations: In the abstract, you describe the aim: “We aimed to (1) develop a novel instrument capturing intentional non-adherence (iNAR) suitable to the general population, consisting of non-adherence to prescribed therapy, self-medication, and avoidance to seek medical treatment”. The population who answered the questionnaire were primarily younger, well-educated women (39 years, 74% women, education duration 17 years). In my opinion, the problem with medical non-adherence is larger for the older population, who often have a higher degree of morbidity. It is not unreasonable to assume that you might have found different results if you had surveyed older men with short education. Perhaps the survey distribution through social media affected the population of responders. I recommend adding a line or two in the limitations section describing if the population you surveyed fit the aim of assessing medical non-adherence in the general population. This should also be discussed in the discussion section.

Habitual non-adherence: I find the term ‘Habitual non-adherence’ to be a bit misleading in how the term is used in this article. To me, adherence differs from compliance in that adherence presumes the patient's agreement with the recommendations, whereas compliance implies patient passivity (ref Brown). You use the WHO definition of adherence, “the extent to which a person's behaviour… corresponds with agreed recommendations from a healthcare provider” The way I see it, not following public health advice is non-compliance and not non-adherence since the patients did not agree to follow the public recommendations in the first place. I suggest you remove the term ‘habitual non-adherence’ from the article and instead use ‘not following public health advice’ or ‘habitual non-compliance’.


Minor issues

iNAR is defined on several pages (nr 3 of 43 (abstract), 4 of 43 (Strengths and limitations), 9 of 43 (Current study), 12 of 43 (methods)).

Abstract
Line 17: I am unsure what you mean by “and to a set of healthcare-related beliefs and experiences”. I recommend paraphrasing this part of the aim (3).

Line 22: What is a public health expert?

Conclusions: you conclude that you have constructed a comprehensive measure of iNAR behaviours, but the health-related variables only account for 14% of the variance in iNAR behaviour.

Introduction

Page 5 of 43, line 15: Please describe who the public health expert is.

You describe that the problem with non-adherence leads to poorer health outcomes, a decreased quality of life, premature mortality and a higher burden on healthcare systems. Achieving treatment adherence can have a far greater impact on improving population health. Your study is not solely focused on adherence to medication therapy, as it also investigates the use of sunscreen, child vaccinations and gynaecology visits (situations where the consequence of non-adherence will likely be smaller compared to medicinal non-adherence (e.g. failure to take insulin)). Were all iNAR items weighted evenly when calculating the overall iNAR score?

Habitual non-adherence: I am unsure why you included ‘Habitual non-adherence’ in your study. As I understand it, you use the term to compare if predictors of intentional non-adherence to medical treatment were the same as those related to not following public health advice (smoking, use of sunscreen, unhealthy diet). However, you compare intentional non-adherence to smoking alone. In the introduction or method section, I recommend that you elaborate on why smoking was the only outcome chosen to represent ‘Habitual non-adherence’.

Page 7 of 43, Line 26: I recommend paraphrasing ‘more adherence’ to a higher degree of adherence.

Methods:

Page 11 of 43, line 17: Please describe who the public health expert is (education, job title).

Page 11 of 43, line 42: please describe the snowball method. Did participants invite others to participate via social media? Were there any efforts to ensure that participants represented the general public?

Page 12 of 43, line 3: what were the three attention checks? The method section should include a description of what the attention checks entailed.

Page 12 of 43, lines 12-15: what was the percentage of people with chronic medical conditions?

If the point of the study is to learn more about what factors influence medication behaviours, why did it not exclude participants without a chronic condition?
Results:

Three of the 22 iNAR questions (10-13) are regarding the use of prescription medications without them being prescribed. In Denmark, it is not possible to purchase prescription medications without a prescription. Could you please clarify if this is a common behaviour in Serbia and how it can occur? You might consider adding a couple of lines in the background section describing the health care system in Serbia so that readers can view the results in relation to the setting.

Population: I missed a description of the morbidity of the population surveyed. Why did you not record the number of prescribed medications or the number of medications used by the participants? From the Instrument NAR TCAM (English).pdf file in OSF, I can see that you asked participants if they were suffering from any long-term/chronic health problems that entail long-term therapy. How many participants had chronic health problems? What was the average number of chronic health problems? This is relevant information that should be reported clearly in the result section, especially since you find a significant correlation between iNAR and the presence of chronic disease. I suggest adding a table presenting population characteristics (age, sex, education, number of co-morbidities, number of medications).

Were there a correlation between iNAR behaviours and age, sex and educational level?

Page 22 of 43: In the section ‘Contrasting predictors of intentional and habitual non-adherence’, You write, “The model, in total, explained 14% of the variance, with negative experiences with the healthcare system and chronic disease contributing positively, and health self-evaluation and normalization of patient passivity contributing negatively to prediction.” Is a model that explains 14% of the variance a good model? I miss a description of whether the model was good at anticipating factors related to intention non-adherence. If the model only accounts for 14%, do the authors have a hypothesis for relevant items that were not included?

When comparing the protocol on OSF to your publication, several measured variables are not reported in the paper (e.g., Political orientation; religiousness; Adherence Barriers Questionnaire). Why did you not report all outcomes measured? I suggest adding the information to the document ‘Transparent changes from the preregistration’ on OSF or presenting them in your result section.

It is relevant to the study to know the extent of intentional non-adherence and not only the predictors of intentional non-adherence. I am unsure if this information is presented in Tables 1 and 2. I miss a result table presenting the number/percentages of participants who had non-adhering behaviours (self-medication, changing or adapting the prescribed therapy without or contrary to medical advice, avoiding going to the physician). Is this presented in table 1? I am unsure if column M in table 1 is mean or median. This should be explained in the table note. Example: table 1, question 12, does M 0.44 mean that 44% of participants had taken an anxiolytic even though a doctor had not prescribed it to them?

Discussion
I miss some discussion on whether intentional non-adherence can be rational. Sometimes a patient will stop taking a medication because it is no longer needed (sleeps fine without a sleep medication), or due to an unactable side effect, or because they cannot afford treatment. Did your study examine the reasons for intentional non-adherence? I believe this information is relevant when designing future interventions aimed at reducing intentional non-adherence. If reasons for non-adherence are measured via the Adherence Barriers Questionnaire, I believe the information should be presented in your paper.

REVIEWER
Nieuwkerk, Pythia
Academic Medical Center / University of Amsterdam, Medical Psychology

REVIEW RETURNED
20-Feb-2023

GENERAL COMMENTS
Non-adherence to medical recommendations is a widespread problem. It is expected that much health gain can be achieved by better understanding and intervening in non-adherence. Intentional non-adherence (the subject of this paper) has received less attention than unintentional non-adherence. Therefore I found the subject of this paper interesting and relevant.

However, I found the scope on the reasons for intentional non-adherence quite narrow. This is illustrated by the title of the paper which suggests that there are two possible causes for intentional non-adherence: an irrational choice or negative experience with the healthcare system.

There is quite some literature (for example from Rob Horne and John Weinman) showing that intentional non-adherence often arises from different perceptions of illness than hold by conventional medicine and/or by making a different trade-off between anticipated or experienced benefits and burden of medical advice (e.g. concerns about potential negative effects, costs). Patients may harbor significant, unresolved doubts and concerns about prescribed medicines/medical recommendations suggesting a fault-line between patients’ and prescribers’ cultural perceptions of the treatment/medical advice. Viewed from the perspective of biomedicine, non-adherence may seem irrational. However, from the patients’ perspective, non-adherence may be a ‘common-sense’ response to their implicit appraisal of medical recommendations.

I missed this patient perspective throughout the manuscript. Throughout the manuscript, intentional non-adherence is referred to as “irrational” or an “irrational mindset” and patients’ perceptions as “unfounded beliefs”. I am afraid this will not help to increase understanding between the biomedical- and the patient perspective.

The objective of the paper is to develop a novel instrument measuring intentional non-adherence behavior to medical recommendations. From an original list of 22 items, a total of 12 items were included in the final instrument. Out of these 12 items, a total of 3 items ask about taking antibiotics/anxiolytic/some other prescription drug even though a doctor did not prescribe it. These 3 items would not be applicable for use in countries where people do not have access to prescription medicines without the prescription of a doctor (would be impossible to be non-adherent...
Another 4 items ask about medication non-adherence (not taking meds, stop earlier than prescribed, skipping some of the prescribed medicines but not all, changing the dosage of medicines). These non-adherence behaviors are also covered by the already existing Medication Adherence report Scale (MARS) (Chan AHY, Horne R, Hankins M, Chisari C. The medication adherence report scale: a measurement tool for eliciting patients’ reports of nonadherence. Br J Clin Pharmacol. 2020; 86:1281–1288). This means that there would be 5 items that are broadly applicable and that ask unique information about intentional non-adherence.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Sinaa Al-Aqeel, King Saud University

Comments to the Author:

I appreciate the opportunity to review the manuscript (Intentional non-adherence to official medical recommendations: An irrational choice or negative experience with the healthcare system?). I hope that my comments below can help the authors to strengthen their submission

R1.1: Introduction

The introduction is not clear and need to be revised. For instance, is the gap in knowledge the study tries to fill is non-adherence to medical recommendations versus current focus on medication or intentional non-adherence? The introduction provides summary of many references about the extent/types of non-adherence but do not discuss adherence in the context of theories and frameworks. Many systematic reviews on the factors associated with adherence are published yet not referenced e.g.


Response: The gap in the knowledge covers both aspects - non-adherence to medical recommendations (versus medication recommendations only) as well as intentional reasons (versus unintentional). We have clarified this in the Introduction section, especially in the Reasons for non-adherence subsection. In this subsection we also discuss theoretical frameworks of non-adherence, and have added the suggested references.

R1.2: Methodology

Focus group: the reader is referred to a detailed report in Serbian, but basic information needs to reported in the manuscript to help judging the validity of the focus group findings. For instance, who conducted the focus
group? How were participants selected? Why participants’ background from neurology, pulmonology, gynecology, and forensic not a cardiology or endocrinology or a pharmacy? Did they used an interview guide? Prompt questions? Duration of the focus group? Was one focus group enough? Derivation of themes?

Response: We have now provided more detail in the manuscript, following the issues raised by the reviewer in the Input from medical experts section.

R1.3: Literature review: the purpose of the review appears to be “to inform inclusion of any additional items” which items? The methods started by “To compile a comprehensive initial pool of non-adherence behaviors” does items refer to behaviours?

Again, more details are needed to judge the quality of the review. The keywords used would yield thousands of hits what criteria was used to include or exclude evidence? What papers were included and used to created the list of non-adherence behaviours?

Why the authors opted for conducting literature review despite that a number of high quality systematic reviews are published on adherence?

Response: To clarify in line with the comment, we rephrased the initial formulation to “to inform the inclusion of any additional behaviors that were not mentioned by the experts.”

We did not aim to conduct a comprehensive literature review on the general topic of adherence. Rather, our literature search had a quite specific focus on intentional non-adherence as we sought to operationalize it. For this reason we included terms such as instrument, assessment, measurement in our search strategy, which we now make clear in the text. We searched for items/behaviors that would be relevant for intentional non-adherence in the general population. We highlighted this additionally in the Literature search section.

R1.4: Page 11 line 42: “intentionally decided not to follow a recommendation or to avoid/delay seeking treatment, rather than forgetting or failing to do something due to insufficient self-discipline” I find the sentence forgetting or failing to do something due to insufficient self-discipline is over simplifications of unintentional adherence and offending to the patient. Please refer to Lehane and McCarthy 2006 were they discuss three factors related to unintentional adherence: patient factors, treatment factors and patient/professional factors.

Response: We agree with the reviewer and have now revised this sentence to mention the factors from Lehane and McCarthy (2007) in the Literature search section.

R1.5: page 12 line 8: “intentional non-adherence, as opposed to habitual non-adherence”, is habitual non adherence the same as unintentional non adherence? In page 9-10 habitual was explained as behaviors that are lifestyle-related e.g. smoking? If not, did the 8 members rate intentional non adherence and habitual non adherence only? What about unintentional non adherence?

Response: Thank you for this comment, it is important to address this issue. In our paper we don’t focus on unintentional non-adherence which refers to not adhering due to socioeconomic, educational, cognitive or other barriers. We do focus on psychologically determined non-adherence behaviors, and contrast intentional non-adherence to lifestyle related behaviors that are contrary to official medical recommendations, such as
smoking. We didn’t consider habitual non-adherence to be the same as unintentional non-adherence. To avoid further confusion, we have now omitted the term habitual from the manuscript.

**R1.6:** Page 12 line 52: the sample size is nor clear if collection was terminated at 475 how did the authors reach a sample of 646

Response: We have now clarified that we had two conditions (optimal sample size reached and no new entries in the database for five consecutive days).

Results

**R1.7:** Table 1 How was the mean of behaviours calculated? Do behaviours have scores? Or do the authors % of those who responded to each behaviour?

Response: Initially the mean of behaviours was calculated as the average proportion of NAR behaviors across all behaviors (M for iNAR in Table 2), i.e. as the average iNAR prevalence. To increase clarity we have now changed the proportions to percentages for all iNAR behaviors (M in Table 1) as well as average iNAR prevalence (Table 2) and added explanation of average iNAR values above Table 1.

**R1.8:** The final 12 items include “refused to change my lifestyle habits (e.g. my diet or physical activity) as recommended by a doctor” although in the methodology page 8 the author stated “Therefore, we have not included adhering to health behaviors that are lifestyle-related, hence likely to be more habitual.” Furthermore, what is the difference between diet in item 12 and smoking as habitual non-adherence?

Response: We did include the item reviewer refers to in our instrument because, even though it is lifestyle related, it is a consequence of decision-making (someone deliberately refuses to follow a medical recommendation), whilst people typically smoke because they are addicted and unable to stop. We discuss the issue of habitual non-adherence in R1.5 in detail.

**R1.9:** It is not clear how item 7 “did not take prescribed therapy” is an intentional behaviour versus other items in commonly used adherence measurement instrument e.g. did you take your medicine yesterday?

Response: We understand the reviewer’s concern. However, this item loaded highly (w > .60) onto the common factor reflecting intentional non-adherence implying it shared substantial variance with other explicitly intentional non-adherence behaviors. We also believe the respondents had intentional non-adherence in mind when they answered this question, because the instruction and other items provided that context. In addition, the way the question was worded in Serbian suggested intention more than its English counterpart. Following the reviewer’s comment, however, we amended the wording of the item to emphasize that this is an intentional choice “I decided (not to take the prescribed therapy)” and included this reworded item in the final version of the instrument made available for future use (uploaded at the OSF platform: https://osf.io/ka4nx).
R1.10: Table 2 how the Mean and Sd for iNAR was calculated? Is the correlation between iNAR-12 and item 1 is 0.72? what is item 1? I assumed it is iNAR-12?

Response: We calculated the mean as the mean of responses on the 12 iNAR behaviors and we now report these scores as percentages instead of proportions for clarity (e.g. if a participant reported experiencing 4 out of 12 iNAR behaviors, their iNAR score would be 33.33%; the mean and SD are reported as the mean and SD of this measure for all participants). Please see our response for comment R1.9 above.

Table 2 is a correlation matrix, so the rows correspond to the columns of the table (i.e. 1 is iNAR-12, 2 is Age, 3 is Education etc.). We report the reliability (via Cronbach’s Alpha) of each measure on the diagonal of the correlation matrix. Hence, the 0.72 is the Cronbach’s Alpha for the iNAR-12 scale. This is outlined in the Note for the table, but we have added it to the title of the table as well, to avoid confusion.

R1.11: Discussion

I am not sure that the study “developed a novel measure of intentional non-adherence to medical recommendations” . Reading the manuscript, a number of health behaviours were identified and the degree of non-adherence to these behaviours was correlated to certain factors such as experience and passivity.

Response: The reviewer is right that some of these behaviors might have been captured by some other assessment tools, however, our instrument is novel in that it systematically captures a wide range of non-adherence behaviors in a single measure, thus allowing us to encapsulate this type of behavior with a single score. Previously developed measures, to the best of our knowledge, focus mainly on a particular subset of non-adherence behaviors. Additionally, we examine the psychometric properties and the factorial validity of this scale, finding that it satisfies expected standards and showing that these diverse types of non-adherence can be subsumed under a single latent dimension. This also allows other researchers to use this scale if they want to assess intentional non-adherence reliably.

Reviewer: 2
Ms. Cille Buelow, Bispebjerg Hospital

Comments to the Author:

Thank you for the opportunity to review this manuscript, which elucidates a relevant subject.

Authors Purić, D. et al. have developed a novel instrument measuring intentional non-adherence behaviour to medical recommendations and evaluated over 500 participants using the instrument.

The study is relevant as a greater knowledge of factors that influence intentional non-adherence may be used in the future to achieve treatment adherence and thereby improve the general health of the population. The survey is well conducted and analysed. However, I missed a discussion on whether or not the most relevant population was surveyed.
Major issues

R2.1: Limitations: In the abstract, you describe the aim: “We aimed to (1) develop a novel instrument capturing intentional non-adherence (iNAR) suitable to the general population, consisting of non-adherence to prescribed therapy, self-medication, and avoidance to seek medical treatment”. The population who answered the questionnaire were primarily younger, well-educated women (39 years, 74% women, education duration 17 years). In my opinion, the problem with medical non-adherence is larger for the older population, who often have a higher degree of morbidity. It is not unreasonable to assume that you might have found different results if you had surveyed older men with short education. Perhaps the survey distribution through social media affected the population of responders. I recommend adding a line or two in the limitations section describing if the population you surveyed fit the aim of assessing medical non-adherence in the general population. This should also be discussed in the discussion section.

Response: We agree with you that a representative sample would increase the generalizability of the results, as it is known that gender disparities, as well as differences between age groups exist in medical non-adherence. We added text recognizing these limitations in the Limitations and Future Research section of the manuscript. Please also see our response to comment E1.2 for more details.

R2.2: Habitual non-adherence: I find the term ‘Habitual non-adherence’ to be a bit misleading in how the term is used in this article. To me, adherence differs from compliance in that adherence presumes the patient’s agreement with the recommendations, whereas compliance implies patient passivity (ref Brown). You use the WHO definition of adherence, “the extent to which a person’s behaviour... corresponds with agreed recommendations from a healthcare provider” The way I see it, not following public health advice is non-compliance and not non-adherence since the patients did not agree to follow the public recommendations in the first place. I suggest you remove the term ‘habitual non-adherence’ from the article and instead use ‘not following public health advice’ or ‘habitual non-compliance’.


Response: We appreciate the suggestion and have thoroughly discussed it within the team. The conceptual issues with the terms adherence and compliance are a challenge, with a big part stemming from the fact that these terms are used both to describe clinically relevant health behavior and define normative “good” behavior. As compliance is considered to be implying that a patient should passively obey medical recommendations, we opted for the use of a normatively more adequate term - adherence, for all behaviors we investigated in our study. With this we state that people should have an active role in decisions regarding their health.

We are aware that the agreement with public recommendations is harder to acknowledge than the agreement in patient-physician contact situations. However, we consider both types of contexts to be open to agreement, given that people can agree and disagree with public health recommendations. We would not imply that all people who follow public health recommendations do so because they passively obey the authorities, rather that there are both people who passively obey and people who exert “informed adherence” in this case. The same would be for specific behaviors we are measuring with iNAR. We believe there are people who show informed adherence with the prescribed treatment, with the recommendation to not self-medicate, or to go to regular checkups, as well as people who passively obey in all of these types of behaviors. In this sense we do
not see a crucial difference between the two contexts. When searching the literature, we found a number of recent articles in which authors also use the term adherence for behaviors in relation to public health recommendations (e.g. Inoue-Choi, Ramirez, Fukunaga & Matthews, 2022; Kale, Herbec, Beard et al., 2022; Piercy, 2019). We thus decided to keep our original solution and use adherence for smoking behavior, as well.


Minor issues

**R2.3:** iNAR is defined on several pages (nr 3 of 43 (abstract), 4 of 43 (Strengths and limitations), 9 of 43 (Current study), 12 of 43 (methods)).

Response: We have now removed the definition from the methods as well as strengths and limitations, however the abstract, and current study can be a standalone section so we have left the definitions there.

**R2.4:** Abstract

Line 17: I am unsure what you mean by “and to a set of healthcare-related beliefs and experiences”. I recommend paraphrasing this part of the aim (3).

Response: We have now added an example of such beliefs and experiences for clarification.

**R2.5:** Line 22: What is a public health expert?

Response: The participant that we label a public health expert is affiliated with the Department of Social Medicine at the Faculty of Medicine, and teaches Master’s and PhD level public health courses. They also hold a PhD in Public health. We have added this clarification in the manuscript as well.

**R2.6:** Conclusions: you conclude that you have constructed a comprehensive measure of iNAR behaviours, but the health-related variables only account for 14% of the variance in iNAR behaviour.

Response: We agree with the reviewer that the percentage of explained variance is not large, however, it is also not negligible. Additionally, by comprehensive we primarily mean that it includes a variety of behaviors suitable for the general population. Moreover, one of the main premises of our study is that intentional non-adherence is not primarily rooted in health-related variables, which is why we set out to explore how it relates to other sets of predictors as well (socio-demographics, healthcare-related beliefs and experiences, and
irrational beliefs). Our results point to the need to further explore the factors that could contribute to the prediction of intentional non-adherence. Please also see our response to point **R2.19** below.

Introduction

**R2.7:** Page 5 of 43, line 15: Please describe who the public health expert is.

Response: Please see our response to comment **R2.5** above.

**R2.8:** You describe that the problem with non-adherence leads to poorer health outcomes, a decreased quality of life, premature mortality and a higher burden on healthcare systems. Achieving treatment adherence can have a far greater impact on improving population health. Your study is not solely focused on adherence to medication therapy, as it also investigates the use of sunscreen, child vaccinations and gynecology visits (situations where the consequence of non-adherence will likely be smaller compared to medicinal non-adherence (e.g. failure to take insulin)). Were all iNAR items weighted evenly when calculating the overall iNAR score?

Response: The reviewer is right that these two types of non-adherence are different. Our data corroborates this as well - the listed behaviors (such as vaccination or sunscreen use) turned out to be different than the rest of the iNAR behaviors, which is why we do not include them in the final scale and do not treat them as part of the iNAR construct.

All of the items that are a part of our final scale which captures, on top of medication non-adherence, self-medication and avoiding treatment, are weighted equally. This is because our results show that, despite them being diverse, there is a single, underlying dimension in the basis of all of them. In addition, we think that it would be difficult to weigh the non-adherence items by the severity of their consequences as, for example, non-adhering to public health recommendations can have detrimental populational effects as well. We thus decided to treat this type of non-adherence as a unitary construct. We have also added information on how the total score should be calculated in the manuscript.

**R2.9:** Habitual non-adherence: I am unsure why you included ‘Habitual non-adherence’ in your study. As I understand it, you use the term to compare if predictors of intentional non-adherence to medical treatment were the same as those related to not following public health advice (smoking, use of sunscreen, unhealthy diet). However, you compare intentional non-adherence to smoking alone. In the introduction or method section, I recommend that you elaborate on why smoking was the only outcome chosen to represent ‘Habitual non-adherence’.

Response: We agree with this comment in that the design would be more comprehensive if we included more measures of this type of non-adherence. There is a sentence in the Limitation section acknowledging this: “Since we used only smoking as a representative of other psychologically determined non-adherence behaviors, future studies could include a more comprehensive set (e.g., sedentary behavior, unhealthy diet) to better disentangle the differences between these two types of non-adherence.”

**R2.10:** Page 7 of 43, Line 26: I recommend paraphrasing ‘more adherence’ to a higher degree of adherence.
Response: We have changed this accordingly.

Methods:

R2.11: Page 11 of 43, line 17: Please describe who the public health expert is (education, job title).

Response: We have included these details in the manuscript - please see our response for comment R2.5 above.

R2.12: Page 11 of 43, line 42: please describe the snowball method. Did participants invite others to participate via social media? Were there any efforts to ensure that participants represented the general public?

Response: We disseminated the invitation for the study via a variety of social media groups, and to personal contacts of the team members. To achieve more socio-demographic diversity, we asked the respondents to further recruit their friends and professional contacts. We added details about the snowball procedure we employed in the study, in the Participants and Procedure section.

R2.13: Page 12 of 43, line 3: what were the three attention checks? The method section should include a description of what the attention checks entailed.

Response: We added the wording of the attention checks we used, in the Participants and procedure section. Since all three items were formulated in the same way (differing only in the response option that should be selected), we have included only one of them in the manuscript, while the exact formulations of all three can be found on the OSF page of the project (in the Preregistration component, https://osf.io/w4s6v/).

R2.14: Page 12 of 43, lines 12-15: what was the percentage of people with chronic medical conditions?

Response: Good point, we added the percentages of the respondents with chronic medical conditions, in the Participants and procedure section.

R2.15: If the point of the study is to learn more about what factors influence medication behaviours, why did it not exclude participants without a chronic condition?

Response: Unlike previous studies on medication adherence, we were interested in investigating a general tendency towards intentional non-adherence, which is independent of individuals’ health status. The behaviors we were interested in are common behaviors in the general population, thus not specific to chronic patients.

Results:
R2.16: Three of the 22 iNAR questions (10-13) are regarding the use of prescription medications without them being prescribed. In Denmark, it is not possible to purchase prescription medications without a prescription. Could you please clarify if this is a common behaviour in Serbia and how it can occur? You might consider adding a couple of lines in the background section describing the health care system in Serbia so that readers can view the results in relation to the setting.

Response: The reviewer is right in that this is common behavior in Serbia (e.g., Tripkovic et al., 2018; Tomas et al., 2017). However, misuse of prescription medicine is not inherent to Serbia only, but is flagged as a global health problem (e.g. Limaye, 2017; Machowska & Stålsby Lundborg, 2019; Munthe et al., 2022; Novak et al., 2016). This is true even for generally high-adherence populations, such as the one of Denmark (Novak et al., 2016). Participants can self-medicate via medications they have previously been prescribed to but did not use up, bring them from another country, use off-shore pharmacies (e.g., Munthe et al., 2022), or rely on social contacts to acquire them (Novak et al., 2016).

We have now also included a selection of these references in the manuscript to further support our inclusion of these items in the scale:


R2.17: Population: I missed a description of the morbidity of the population surveyed. Why did you not record the number of prescribed medications or the number of medications used by the participants? From the Instrument NAR TCAM (English).pdf file in OSF, I can see that you asked participants if they were suffering from any long-term/chronic health problems that entail long-term therapy. How many participants had chronic health problems? What was the average number of chronic health problems? This is relevant information that should be reported clearly in the result section, especially since you find a significant correlation between iNAR and the presence of chronic disease. I suggest adding a table presenting population characteristics (age, sex, education, number of co-morbidities, number of medications)

Response: As our goal was to develop an intentional non-adherence instrument for the general population, and not necessarily people with specific medical conditions, we opted not to measure the number of
prescribed/used medications. The reviewer correctly noted that we had people with chronic medical conditions in the sample, and we have now introduced additional information about them in the Participants and procedure section (percentage of people with one, two, three or more reported conditions and the average number of conditions per respondent). The gender, age and education of the sample are also reported in this section.

R2.18: Were there a correlation between iNAR behaviours and age, sex and educational level?

Response: There were no correlations with either age, sex (gender), educational level, or socioeconomic status. We have now included sex (gender) in the table of intercorrelations (Table 2).

R2.19: Page 22 of 43: In the section ‘Contrasting predictors of intentional and habitual non-adherence’, You write, “The model, in total, explained 14% of the variance, with negative experiences with the healthcare system and chronic disease contributing positively, and health self-evaluation and normalization of patient passivity contributing negatively to prediction.” Is a model that explains 14% of the variance a good model? I miss a description of whether the model was good at anticipating factors related to intention non-adherence. If the model only accounts for 14%, do the authors have a hypothesis for relevant items that were not included?

Response: Thank you for this comment. We feel it is important to note that despite the fact that iNAR was measured relatively reliably, almost a third of its variance can be attributed to error variance, which is not unusual for scales of this type and length. However, when corrected for imperfect measurement of non-adherence, i.e., considering only its reliable variance the predictors accounted for almost a fifth of the variance of non-adherence (20%). What is more, in this study we captured the most general predictors of intentional non-adherence, independent from the specific condition and treatment which could be expected to account for a large percentage of variance.

As there is no cut off value regarding % of variance accounted for we are unable to evaluate our model as good or bad. Still, we added some possible variables that could have an incremental value in prediction of iNAR but were not included in the present study - medical/digital literacy or personality traits (Limitation and Future Research section of the manuscript).

R2.20: When comparing the protocol on OSF to your publication, several measured variables are not reported in the paper (e.g., Political orientation; religiousness; Adherence Barriers Questionnaire). Why did you not report all outcomes measured? I suggest adding the information to the document ‘Transparent changes from the preregistration’ on OSF or presenting them in your result section.

Response: The results presented in this paper are part of a larger project investigating the psychological underpinnings of questionable health behaviors, while the main objective of the study presented here is the development of the iNAR instrument. And while we did register several measures which are not reported in this paper (political orientation, religiousness…), we had no preregistered hypotheses regarding either of these variables. Thus, they constitute the exploratory part of the paper and not reporting them is not considered a divergence from the preregistration. To be completely transparent, we have now outlined these changes in the updated Transparent changes from the preregistration document (https://osf.io/bfman).
As for the Adherence Barriers Questionnaire, we did intend to use it for validation of our instrument, but unfortunately, encountered copyright issues: we realized late that this is a licensed questionnaire, and we were not able to meet the large costs. Consequently, we could not use the data collected with ABQ.

R2.21: It is relevant to the study to know the extent of intentional non-adherence and not only the predictors of intentional non-adherence. I am unsure if this information is presented in Tables 1 and 2. I miss a result table presenting the number/percentages of participants who had non-adhering behaviours (self-medication, changing or adapting the prescribed therapy without or contrary to medical advice, avoiding going to the physician). Is this presented in table 1? I am unsure if column M in table 1 is mean or median. This should be explained in the table note. Example: table 1, question 12, does M 0.44 mean that 44% of participants had taken an anxiolytic even though a doctor had not prescribed it to them?

Response: We have now changed proportions previously reported in the M column of Table 1 to percentages to more clearly reflect the extent of intentional non-adherence or prevalence of each iNAR behavior and added the explanation for these values above Table 1. We thank the reviewer for this comment as the results read better now.

Discussion

R2.22: I miss some discussion on whether intentional non-adherence can be rational. Sometimes a patient will stop taking a medication because it is no longer needed (sleeps fine without a sleep medication), or due to an unactable side effect, or because they cannot afford treatment. Did your study examine the reasons for intentional non-adherence? I believe this information is relevant when designing future interventions aimed at reducing intentional non-adherence. If reasons for non-adherence are measured via the Adherence Barriers Questionnaire, I believe the information should be presented in your paper.

Response: We agree that non-adherence can be rational in some cases, and we have added a sentence to the Discussion section, in the Relationship between iNAR, Irrational Beliefs and Experiences with the Healthcare System subsection to acknowledge this. In the current study, the questions were formulated to show that the behavior was a result of a decision (e.g. ... I decided myself which of the prescribed drugs I would take and which I would not). However, we did not further explore the reasons behind the decisions.

Our initial plan was to explore reasons for non-adherence using ABQ. Unfortunately, we realized late that this was a licensed questionnaire and were unable to meet the costs. Consequently, we decided to drop out the data collected using ABQ. Please see our response to comment R2.20 above.

Reviewer: 3
Ms. Pythia Nieuwkerk, Academic Medical Center / University of Amsterdam

Comments to the Author:

Non-adherence to medical recommendations is a widespread problem. It is expected that much health gain can be achieved by better understanding and intervening in non-adherence. Intentional non-adherence (the
subject of this paper) has received less attention than unintentional non-adherence. Therefore I found the subject of this paper interesting and relevant.

**R3.1:** However, I found the scope on the reasons for intentional non-adherence quite narrow. This is illustrated by the title of the paper which suggests that there are two possible causes for intentional non-adherence: an irrational choice or negative experience with the healthcare system.

Response: When we initially formulated the title, we wanted to contrast these two groups of correlates for intentional non-adherence, and not necessarily to suggest they were the only ones. We agree with the reviewer that the title could be read differently. Following this and editorial suggestions, the title is now reworded to reflect the methods and design of the study, which left no room to spell out the reasons for intentional non-adherence.

**R3.2:** There is quite some literature (for example from Rob Horne and John Weinman) showing that intentional non-adherence often arises from different perceptions of illness than hold by conventional medicine and/or by making a different trade-off between anticipated or experienced benefits and burden of medical advice (e.g. concerns about potential negative effects, costs). Patients may harbor significant, unresolved doubts and concerns about prescribed medicines/medical recommendations suggesting a fault-line between patients’ and prescribers’ cultural perceptions of the treatment/medical advice. Viewed from the perspective of biomedicine, non-adherence may seem irrational. However, from the patients’ perspective, non-adherence may be a ‘common-sense’ response to their implicit appraisal of medical recommendations.

I missed this patient perspective throughout the manuscript. Throughout the manuscript, intentional non-adherence is referred to as “irrational” or an “irrational mindset” and patients’ perceptions as “unfounded beliefs”. I am afraid this will not help to increase understanding between the biomedical- and the patient perspective.

Response: We agree with the reviewer that there are multiple factors influencing adherence and we have now clarified that intentional non-adherence is not always irrational in the Discussion section and acknowledged that this could be rational from the patients perspective (please see response to R2.22). It is possible to rationally not adhere in a specific situation, and adhere in another, however we were interested in psychological dispositions that predispose a person to not adhere in various situations.

While we share the reviewer’s impression that the term “irrational” is affectively charged, it is widely used in psychological literature, along with the term “unfounded” or even “epistemically suspect” beliefs. In our manuscript we defined it quite broadly and made every effort not to stigmatize the respondents who endorsed these beliefs.

As past research has shown that irrational factors such as conspiracy beliefs are related to health behaviors during the COVID 19 pandemic (Teovanovic et al., 2020), we thought it was plausible that such irrational beliefs may extend to other health behaviors as well. Unlike some other health behaviors like use of alternative medicine, the role of irrational beliefs in intentional non-adherence is an understudied topic. We, however, included the patient perspective in the design by adding a set of questions exploring their previous experiences with the healthcare system and their trust in the system. Our results in fact show (and we address this in the Discussion section) that irrational beliefs were not a significant predictor of intentional non-adherence, and that instead, these patient-centered variables (negative healthcare-related beliefs and experiences) were the most prominent predictor.
R3.3: The objective of the paper is to develop a novel instrument measuring intentional non-adherence behavior to medical recommendations. From an original list of 22 items, a total of 12 items were included in the final instrument. Out of these 12 items, a total of 3 items ask about taking antibiotics / anxiolytic / some other prescription drug even though a doctor did not prescribe it. These 3 items would not be applicable for use in countries where people do not have access to prescription medicines without the prescription of a doctor (would be impossible to be non-adherent on these items). Another 4 items ask about medication non-adherence (not taking meds, stop earlier than prescribed, skipping some of the prescribed medicines but not all, changing the dosage of medicines). These non-adherence behaviors are also covered by the already existing Medication Adherence report Scale (MARS) (Chan AHY, Horne R, Hankins M, Chisari C. The medication adherence report scale: a measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol. 2020; 86:1281-1288). This means that there would be 5 items that are broadly applicable and that ask unique information about intentional non-adherence.

Response: Thank you for allowing us to elaborate more on why we think that developing another instrument that assess non-adherence is important. The two major distinctive characteristics of our instrument is a. It measures a specific group of health behaviors, i.e. intentional non-adherence (we have elaborated on that in the text) - our data strongly support the assumption there is one factor underlying these diverse behaviors, and b. It is applicable for the general population (not specific clinical subgroups), as it assesses behaviors that are likely to be experienced by an average respondent at some point in their lifetime. The existing instruments, on the other hand, focused on clinical populations and on their current medication-taking behaviors.

As for the cultural specificity of the items measuring respondents' access to prescription medicine without a prescription, while we agree there are differences in frequency of this behavior between countries, it continues to be a worldwide problem (see our response to comment R2.16 as well). This was highlighted in a recent review (Limaye et al., 2017) in which the authors observed the following prevalence of self-medication (SM): “Antibiotics SM prevalence varied from 1% to 100%. Seventeen studies had low, 21 studies had medium, whereas 7 studies had high prevalence of SM. High antibiotic prevalence was reported from studies done in the developing countries like Indonesia, Sri Lanka, Nigeria, Sudan, Guatemala etc. Greece was the only country belonging to developed nations which showed a high antibiotic SM prevalence - 77%.” Even in Scandinavian countries, although the prevalence of these behaviors is low, it is not zero, while intention for future behaviors is even higher (3.5 and 13% respectively in Muscat et al., 2005). Finally, as these are non-normative behaviors, they tend to be under-reported in self-assessment. Due to all these reasons, we believe it is very important to include them in instruments measuring non-adherence.

*** ***

COI statements:

Reviewer: 1

Competing interests of Reviewer: None.
Reviewer: 2

Competing interests of Reviewer: I have no competing interests.

Reviewer: 3

Competing interests of Reviewer: None.

VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Al-Aqeel, Sinaa</th>
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<td>King Saud University, Clinical Pharmacy</td>
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<td>30-Apr-2023</td>
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| GENERAL COMMENTS    | The authors addressed my comments adequately. |

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<th>REVIEWER</th>
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| GENERAL COMMENTS    | Thank you for the revised manuscript. I believe the authors have answered all comments adequately, and the revision has significantly improved the manuscript. I especially appreciate the alterations to Table 1, which have clarified the result section.

I only have a few minor comments:

Inconsistent hyphenation
There is inconsistency regarding the use of hyphenation throughout your manuscript. Please ensure consistent use of hyphenation.

• socio-demographic/ sociodemographic
• socio-economic/ socioeconomic
• checkup/check-up.

Spelling/typing error:
• Page 8, Methods - Input from medical experts, line three: The word specialties should be spelt specialities
• Page 11, Methods- Patient and public involvement: Please add “the” before the word two, to the sentence “The patients were not involved in the design of the study, however we reached out to two largest patient associations in Serbia at the very beginning, and their representatives attended the stakeholder meetings at later stages.”
• Page 25, line 9: I recommend changing “to seek” to “seeking”
• Page 27, line 2: I recommend rephrasing “Negative correlations with trust in the healthcare system and trust in healthcare practitioners” to “Negative correlations between trust in the healthcare system and trust in healthcare practitioners”
• Page 30, conclusion, fourth line: “advice form” should be “advice from”

In the discussion section, you have added a sentence on the limitations regarding the snowball method “Even though the
snowball sampling procedure led to decreased representativeness and sampling bias, we still had a large and relatively diverse sample.". Here you state that the sample was relatively diverse, but this is not seen in the result section. Please consider adding information to describe the diversity in the result section, perhaps the age range.

VERSION 2 – AUTHOR RESPONSE

Response to reviewers revision 2

Thank you for the revised manuscript. I believe the authors have answered all comments adequately, and the revision has significantly improved the manuscript. I especially appreciate the alterations to Table 1, which have clarified the result section.

We thank the reviewer for their careful reading of our revised manuscript.

I only have a few minor comments:

Inconsistent hyphenation

There is inconsistency regarding the use of hyphenation throughout your manuscript. Please ensure consistent use of hyphenation.

• socio-demographic/ sociodemographic
• socio-economic/ socioeconomic
• checkup/check-up.

We have uniformed the hyphenation throughout the text (sociodemographic, socioeconomic, check-up).

Spelling/typing error:

• Page 8, Methods - Input from medical experts, line three: The word specialties should be spelt specialities
• Page 11, Methods- Patient and public involvement: Please add “the” before the word two, to the sentence “The patients were not involved in the design of the study, however we reached out to two largest patient associations in Serbia at the very beginning, and their representatives attended the stakeholder meetings at later stages.”
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• Page 30, conclusion, fourth line: “advice form” should be “advice from”

We have changed the text accordingly.

In the discussion section, you have added a sentence on the 'limitations regarding the snowball method “Even though the snowball sampling procedure led to decreased representativeness and sampling bias, we still had a large and relatively diverse sample.”. Here you state that the sample was relatively diverse, but this is not seen in the result section. Please consider adding information to describe the diversity in the result section, perhaps the age range.

We thank the reviewer for this comment. We have added the age range and SES range information in the Participants and procedure section, as it fitted there more.