PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Unravelling the role of health literacy in individuals with multimorbidity: A systematic review and meta-analysis

Authors

Chauhan, Arohi; Linares-Jimenez, Fernando Gregorio; Dash, Girish Chandra; de Zeeuw, Janine; Kumawat, Archana; Mahapatra, Pranab; de Winter, Andrea F.; Mohan, Sailesh; van den Akker, Marjan; Pati, Sanghamitra

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Yadav, Uday**
Affiliation	**University of New South Wales**
Date	**17-May-2023**
COI	**NIL**

Thank you for the opportunity to review this important piece. It reads very well but the following points must be considered before being considered.

Introduction:

Chronic disease self-management is compromised when a patient is unable to fully comprehend his or her diagnosis and

treatment.Need more explanation with examples

Line 5-6: Health outcomes (ref 14,22) need to be more explicit.

Multimorbidity is a multidimensional concept that requires support from family and carers as well and their health literacy is very crucial for the self-management. Importantly, also need to make a strength-based point on how people from marginalised and Indigenous identities have limited access to resources - resulting in poor health literacy. You may look into the following papers-

-https://bmjopen.bmj.com/content/10/3/e035700

-https://pubmed.ncbi.nlm.nih.gov/35570271/

-https://bmjopen.bmj.com/content/11/2/e041728

The rationale needs to be more compelling. You need to demonstrate the importance of health literacy in a multimorbidity context. Please see NICE guidelines from UK + https://www.sciencedirect.com/science/article/pii/S2213398422002172

Methods:

-The operational definition for multimorbidity and health literacy needs to be included- [We define health literacy as the ability of an individual to access, understand, evaluate and use health information

to make informed decisions in order to keep or recover one's health. Multimorbidity was defined as the concurrent presence of two or

more chronic conditions (including mental health conditions), independent of the existing or index disease in an individual] This definition is not adequate and needs to be supported by references. A clear definition will help you to form the basis for setting inclusion and exclusion criteria.

- Search period need to be updated to at least Dec 2022(Provided -1st January, 2000 to 31st March, 2022- is bit old)

I just wonder where the search operators are trained in doing so (if yes, need justification)+ If support from a senior librarian was sought during the search process.

-https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0233488- should met your inclusion criteria.

Result section- I feel reporting study population characters like Indigenous/Marginalised or other identities will help the reader understand in which cluster the intervention needs to be prioritised.

Discussion-

Discussion should have a critical appraisal around multimorbidity and health literacy assessment because there are many definitions for both of these elements. What directions are needed? Where these elements need to be assessed, primary care, community etc. or both- who could do that? What would be the benefits?

-Digital technology can be adopted to empower people to take control of their health: Please make sure that your recommendations are based on study findings, and also providing a clear pathway to achieve it will assist researchers and policymakers.

Reviewer **2**

Name **Ostini, Remo**

Affiliation **University of Queensland School of Medicine, Rural Clinical School**

Date **19-Jul-2023**

COI **I have no competing interests.**

Unravelling the role of health literacy

bmjopen-2023-073181

This review only achieves one of its three stated aims. This should be stated explicitly, otherwise the aims bear little relationship to the study that was done and this undermines confidence in the study outcomes.

In the methods, data synthesis and data analysis are not explained clearly – or in the case of the (predominant) narrative analysis component of the study – at all.

The presentation of the results is disjointed.

In part, this is because of the different analysis methods used (meta and narrative analysis) and the range of questions being answered.

The disjointed presentation of the results is exacerbated by the method section not being clear about the analyses to be done and the questions being addressed and the combination of the two – what analysis is used to address which question.

The results also are not presented clearly in terms of the language used and the organisation of the presentation. For example, why are pooled mean meta analyses done on only 2 of the 9 HLQ domains and why the two that were chosen? Similarly, why were only two domains, including one different domain to the previous analyses, used in the association analysis?

Overall, the results are fragmentary and don't take advantage of the strength of the systematic review methodology for pooling data – in either the narrative or the meta-analyses. To some extent this is because of the way the aims are operationalised in the analyses. More realistic aims would address a number of problems with this systematic review.

An example of the lack of pooling is in the results on the relationship between the number of conditions and health literacy, which are based on one study!

More broadly, even though there are 13 studies that use the HLQ in the dataset, it seems only 11 of them are used in the meta analyses and these analyses only address the results for 3 of the 9 HLQ domains.

Subsequently, fifteen studies are used in a narrative analysis of the factors describing the association between health literacy and multimorbidity. This leaves 13 studies that are not used in the data analysis at all and appear to only be used to describe the health literacy of people with comorbidities.

Despite the text claiming that the study will look at the development and severity of multimorbidity, it does not.

Furthermore, the individual and organisational/provider factors that are presented in the results are examples of the association between health literacy and multimorbidity – there is no evidence provided on how they influence that association, despite this being the heading of this section of the analysis.

The problems with language in the way this manuscript is written are particularly pronounced in the discussion, where it is often difficult to know what is being said. This is made more difficult by the discussion not being well organised.

The conclusion has a number of good ideas but they are unconnected in any meaningful sense to the study findings. They are just ideas.

VERSION 1 - AUTHOR RESPONSE

Dear Editor,

Thank you for allowing us to submit a revised version of our manuscript titled “Unravelling the role of health literacy in individuals with multimorbidity: A systematic review and meta-analysis” to BMJ Open. We appreciate the time and effort that both the reviewers and yourself have taken to provide valuable feedback on our manuscript. Your feedback has

helped to improve the quality of the article. Please find our replies in the attached file, with the new or revised text underlined.

Kind regards,

Arohi Chauhan MD and F. Gregorio Linares-Jimenez MD

Reviewer 1 Comments - Dr. Uday Yadav, University of New South Wales

Introduction	
Comment	**Reply**
Chronic disease self-management is compromised when a patient is unable to fully comprehend his or her diagnosis and treatment. Need more explanation with examples.	We would like to thank the reviewer for his comment. We have added examples and provided an explanation for the sentence in question: "In addition, it has been proposed that self-management of chronic disease can be compromised when patients cannot fully understand their diagnosis and treatment. [17-19, 22] For example, patients who meet with different healthcare professionals may struggle to follow all their recommendations and thereby suffer even worse health outcomes.[19, 21] In other instances, patients may seek unnecessary or less effective treatments when they lack or do not understand basic information about their condition. [23]" This change can be found in page 3, line 41-45 of the Marked version
Line 5-6: Health outcomes (ref 14,22) need to be more explicit.	We have revised, here you can find the changes made: "Poor self-management abilities among older adults have also been associated with limited health literacy and a range of adverse health outcomes. [12, 22, 24, 25] People with LHL are more likely to develop diseases such as CKD, and to have poorer prognoses due to more frequent complications or lower quality of life. [26, 27]" This change can be found in page 3, line 46-49 of the Marked version

Multimorbidity is a multidimensional concept that requires support from family and carers as well and their health literacy is very crucial for the self-management. Importantly, also need to make a strength-based point on how people from marginalised and Indigenous identities have limited access to resources - resulting in poor health literacy. You may look into the following papers - https://bmjopen.bmj.com/content/10/3/e035700 [4] - https://pubmed.ncbi.nlm.nih.gov/35570271/ [5] - https://bmjopen.bmj.com/content/11/2/e041728 [6]	Thanking for this relevant comment. We agree with the reviewer that the health literacy levels of the people around them and the access to resources in communities may impact health self-management and health literacy of individuals. Social capital has been studied in similar contexts, and its importance has been made clear. And it is also true that marginalized and indigenous identities may also be disproportionately affected. We have added the following sentences to the introduction acknowledging this: "Multimorbidity constitutes a complex long-term challenge for patients, their family, friends, healthcare providers and systems as it presents patients and the people around them with a steep learning curve about risk, treatment and self-care.[12] Moreover, contextual differences may have a large impact on the learning process of patients; for example, those with marginalised and indigenous identities may have limited access to certain resources that could enhance their health literacy skills. [13, 14]" This change can be found in page 3, line 15-20 of the Marked version
The rationale needs to be more compelling. You need to demonstrate the importance of health literacy in a multimorbidity context. Please see NICE guidelines from UK + https://www.sciencedirect.com/science/article/pii/S2213398422002172	We thank the reviewer for his comment, we agree that the manuscript can benefit from a stronger rationale, we have revised. "Health literacy may be an essential factor associated with the development of multimorbidity. It has been defined as the ability to access, understand, evaluate and use health information to make informed decisions in order to keep or recover one's health, and it has been identified as a key determinant of health.[15] Current health literacy research, focused mainly on patients with specific chronic conditions, shows that limited health literacy is associated with poorer health behaviours and health outcomes, such as earlier onset of disease,

	faster progression of disease, increased rates of hospitalization and higher health-related costs for both individuals and healthcare systems. [12, 16] However, although these similarities suggest the existence of a relationship between health literacy and multimorbidity, research conducted on this potential relationship seems to be limited and has shown mixed results. [17-19]" This change can be found in page 3, line 23-31 of the Marked version
Methods	
Comment	**Reply**
The operational definition for multimorbidity and health literacy needs to be included- [We define health literacy as the ability of an individual to access, understand, evaluate and use health information to make informed decisions in order to keep or recover one's health. Multimorbidity was defined as the concurrent presence of two or more chronic conditions (including mental health conditions), independent of the existing or index disease in an individual] This definition is not adequate and needs to be supported by references. A clear definition will help you to form the basis for setting inclusion and exclusion criteria.	We agree with the reviewer on his appraisal that the definitions in our manuscript may be broad. However, these more flexible definitions were deliberately chosen. For the Health literacy definition, we have added a reference as suggested. And knowing that all of the instruments we might encounter are aiming to measure the same construct based on this definition regardless of the methods, it made sense choosing this definition as it allows for the inclusion of studies using different instruments. The same can't be said about multimorbidity as there are still marked differences between its possible definitions. Yet, we operationalized this definition based on the main differences reported in literature. [7] This definition should avoid excluding valuable articles based on technicalities.
Search period need to be updated to at least Dec 2022 (Provided -1st January, 2000 to 31st March, 2022-	We agree with the reviewer's comment and we have worked on updating the search period, which now ends on the 31st of August 2023.

is bit old)	We have identified 11 new articles, yet our main conclusions have not changed.
I just wonder where the search operators are trained in doing so (if yes, need justification) + If support from a senior librarian was sought during the search process.	Answering to the reviewer's question yes, one of the search operators, FGL, has received formal training in the development of search strategies as part of his graduate studies, during this training the search strategy used for this review was reviewed by a senior librarian.
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0233488 - should met your inclusion criteria.	Thank you for sharing this article with us. We completely agree with it as the referenced article does indeed meet our inclusion criteria and therefore it has been now included in the review, however not in the analysis as the data provided by it is the same as a previously included article by the same authors in which they use the same data sample and report the same values already included. The suggested article also provides an OR for the association between Limited Health Literacy and Multimorbidity using the HLQ tool, yet the tool itself doesn't have cut off points to categorize the levels of Health Literacy, these were set by the author and doesn't allow for comparison with the studies who analysed the association using the HLQ score as a continuous variable.
Results	
Comment	**Reply**
I feel reporting study population characters like Indigenous/Marginalised or other identities will help the reader understand in which cluster the intervention needs to be prioritised.	We agree with the reviewer's comment in which providing this information can be beneficial when discussing further steps in research, yet we have to mention that unfortunately the majority of the articles included in our review do not report this.
Discussion	
Comment	**Reply**

Discussion should have a critical appraisal around multimorbidity and health literacy assessment because there are many definitions for both of these elements. What directions are needed? Where these elements need to be assessed, primary care, community etc. or both- who could do that? What would be the benefits?	We agree with the reviewer's input and we have revised adding the following paragraph to our discussion: "Our systematic review identified a heterogeneous collection of literature that reported different ways of measuring the concepts 'multimorbidity' and 'health literacy'. This was expected for the concept of health literacy, as it was first introduced in 1974 and has since been adapted until a consensus was finally reached regarding its definition. [28, 81] For this same reason, and also because adequate measurement of the construct of health literacy can be context-dependent, it is logical that different tools have, throughout the years, been developed to achieve this goal. [28]" This change can be found in page 13, line 1-6 of the Marked version
Digital technology can be adopted to empower people to take control of their health: Please make sure that your recommendations are based on study findings, and also providing a clear pathway to achieve it will assist researchers and policymakers.	We have revised our recommendations, here you can find the changes made: "This review demonstrated an association between limited health literacy and the number of conditions in patients with multimorbidity. However, across all levels of healthcare further assessment of the impact of different multimorbidity clusters on core health literacy is needed. Being able to identify whether people with limited health literacy and certain multimorbidity patterns are at greater risk of worse health outcomes can lead to the creation of specific interventions to support these patients. [26] Thus, understanding clusters is a potential path toward improving the management of multimorbidity and setting priorities. Alongside this, it is also essential to identify individuals with multimorbidity who have low health literacy. Further needed is a uniform method to classify adequacy of health literacy, taking into account the patient's skills and the complexity of information. A possible course of action for future research could involve validation of tools already

	widely used, like the HLS19-Q12[82], applying these in as many contexts as possible to enable more comprehensive comparison of HL levels. Additionally, research directly focusing on the health outcomes of people with limited health literacy and multimorbidity is needed, including the possibility of mediation analysis to help identify potential targets for intervention. Finally, more longitudinal studies are needed to assess the trajectory of multimorbidity and health literacy, as the chronology of multimorbidity occurrence may also be significantly related to health literacy." This change can be found in page 14, lines 44-49 of the Marked version

Reviewer 2 Comments - Dr. Remo Ostini, University of Queensland School of Medicine

Introduction	
Comment	**Reply**
This review only achieves one of its three stated aims. This should be stated explicitly, otherwise the aims bear little relationship to the study that was done and this undermines confidence in the study outcomes.	We would like to thank the reviewer for bringing this to our attention. However, due to the results of the updated search, we are now able to present evidence related to the three aims this review. The new format of the result section makes clear the way the aims were met.
Methods	
Comment	**Reply**
In the methods, data synthesis and data analysis are not explained clearly – or in the case of the (predominant) narrative analysis component of the study – at all.	We agree with the reviewer's comment and we have revised both the Data synthesis and Data analysis into the following text: **"Data analysis** Because of the heterogeneity between the tools and concepts used to measure health literacy levels and multimorbidity, performance of a quantitative synthesis incorporating all the studies was considered unsuitable. To assess the levels of health literacy among people with multimorbidity, we calculated pooled mean health literacy scores with 95% confidence intervals (CI) per domain from the studies that had used the HLQ tool (n=14). To assess the association between health literacy levels and multimorbidity, in two groups of studies we performed random effects meta-analyses with MetaXL v5.3 (EpiGear) software in MS Excel 2016 and IBM SPSS v27 (one group with studies that used the HLQ tool (n=3) and one with studies that used the HLS-EU tool (n=3)). For dichotomous data we expressed effect sizes as odds ratio, and for continuous data as weighted mean difference. We reported all effect estimates with their 95% CI. We assessed heterogeneity by using

	Cochrane's Q and I2 statistics. Quantitative synthesis was not possible for the remaining articles. Instead, we narratively synthesised these, using "The Causal Pathways Linking Health Literacy to Health Outcomes" model by Paasche-Orlow20. We began by exploring the results of individual studies; we searched for and extracted information dealing with the three main groups of mediators proposed by the model: "Access and Utilization of Health Care", "Provider-Patient Interaction", and "Self-care" and their reported role in the outcome groups: clinical, behavioural, patient-provider communication, and "other"." This change can be found in page 5, lines 44 - 49 of the Marked version
Results	
Comment	**Reply**
The presentation of the results is disjointed. In part, this is because of the different analysis methods used (meta and narrative analysis) and the range of questions being answered.	We would like to thank the reviewer for his insight on the presentation of the results, we have revised this section of the review. You can find these revisions starting in page 6, line 18.
The disjointed presentation of the results is exacerbated by the method section not being clear about the analyses to be done and the questions being addressed and the combination of the two – what analysis is used to address which question.	We have revised and now offer a structure presenting the general characteristics of the studies identified, then we present the quantitative analysis performed on the available data followed by the qualitative information collected, al presented in a way that shows which part of the results obtained helped answer the research questions of our review. You can find these revisions starting in page 6, line 18.

The results also are not presented clearly in terms of the language used and the organisation of the presentation. For example, why are pooled mean meta-analyses done on only 2 of the 9 HLQ domains and why the two that were chosen? Similarly, why were only two domains, including one different domain to the previous analyses, used in the association analysis?	We thank the reviewer for the input, we have revised and performed a more comprehensive analysis of the available data, including the information regarding other domains of the HLQ tool. You can find these revisions starting in page 9, line 18.
Overall, the results are fragmentary and don't take advantage of the strength of the systematic review methodology for pooling data – in either the narrative or the meta-analyses. To some extent this is because of the way the aims are operationalised in the analyses. More realistic aims would address a number of problems with this systematic review.	We believe the input provided is valuable, and we have revised the methods section and made the methodology clearer and we improved the structure of the result section in which we make clear how the original aims of the review were met and to which extent.
An example of the lack of pooling is in the results on the relationship between the number of conditions and health literacy, which are based on one study!	We have revised, and as mentioned we improved the analysis performed and we opted to only mention the results from this particular article without an attempt to pool this data: "Additionally, three studies conducted in the European region observed that the odds of difficulty in understanding health information and actively engaging with healthcare providers increased with the number of physical conditions. The odds also increased when the concept of multimorbidity included a mental health condition. These odds ranged from 1.45 to 7.75 according to the number of physical and mental conditions."

	You can find these revisions starting in page 10, line 1-5.
More broadly, even though there are 13 studies that use the HLQ in the dataset, it seems only 11 of them are used in the meta analyses and these analyses only address the results for 3 of the 9 HLQ domains.	We have revised and present a broader analysis of the available data.
Subsequently, fifteen studies are used in a narrative analysis of the factors describing the association between health literacy and multimorbidity. This leaves 13 studies that are not used in the data analysis at all and appear to only be used to describe the health literacy of people with comorbidities.	We have revised the result section in order to make the presentation of the data clearer on how this was a result of the available data.
Despite the text claiming that the study will look at the development and severity of multimorbidity, it does not.	We appreciate this feedback, and we have revised the language used for this aim.
Furthermore, the individual and organisational/provider factors that are presented in the results are examples of the association between health literacy and multimorbidity – there is no evidence provided on how they influence that association, despite this being the heading of this section of the analysis.	We have revised the result section in order to make the presentation of the data clearer.
Discussion	

Comment	**Reply**
The problems with language in the way this manuscript is written are particularly pronounced in the discussion, where it is often difficult to know what is being said. This is made more difficult by the discussion not being well organised.	We appreciate the Reviewer's suggestion and decided to have the manuscript checked by an English native speaker who has experience in proofreading scientific articles. We hope that the changes made improve the readability of our manuscript
The conclusion has a number of good ideas but they are unconnected in any meaningful sense to the study findings. They are just ideas.	"This review demonstrated an association between limited health literacy and the number of conditions in patients with multimorbidity. However, across all levels of healthcare further assessment of the impact of different multimorbidity clusters on core health literacy is needed. Being able to identify whether people with limited health literacy and certain multimorbidity patterns are at greater risk of worse health outcomes can lead to the creation of specific interventions to support these patients. [26] Thus, understanding clusters is a potential path toward improving the management of multimorbidity and setting priorities. Alongside this, it is also essential to identify individuals with multimorbidity who have low health literacy. Further needed is a uniform method to classify adequacy of health literacy, taking into account the patient's skills and the complexity of information. A possible course of action for future research could involve validation of tools already widely used, like the HLS19-Q12[82], applying these in as many contexts as possible to enable more comprehensive comparison of HL levels. Additionally, research directly focusing on the health outcomes of people with limited health literacy and multimorbidity is needed, including the possibility of mediation analysis to help identify potential targets for intervention. Finally, more longitudinal studies are needed to assess the trajectory of multimorbidity and health literacy, as the chronology of multimorbidity occurrence may also be significantly related to health literacy." This change can be found in page 14, lines 44-49 of the Marked version

References

1. Simonds SK. Health Education as Social Policy. Health Education & Behavior. 1974;2:1 - 10.
2. Literacy IoMCoH. In: Nielsen-Bohlman L, Panzer AM, Kindig DA, editors. Health Literacy: A Prescription to End Confusion. Washington (DC): National Academies Press (US)

3. Urstad KH, Andersen MH, Larsen MH, Borge CR, Helseth S, Wahl AK. Definitions and measurement of health literacy in health and medicine research: a systematic review. BMJ Open. 2022;12(2):e056294.

4. Yadav UN, Lloyd J, Hosseinzadeh H, Baral KP, Dahal S, Bhatta N, et al. Facilitators and barriers to the self-management of COPD: a qualitative study from rural Nepal. BMJ Open. 2020;10(3):e035700.

5. Balakrishnan S, Karmacharya I, Ghimire S, Mistry SK, Singh DR, Yadav OP, et al. Prevalence of multimorbidity and its correlates among older adults in Eastern Nepal. BMC Geriatrics. 2022;22(1):425.

6. Yadav UN, Ghimire S, Mistry SK, Shanmuganathan S, Rawal LB, Harris M. Prevalence of non-communicable chronic conditions, multimorbidity and its correlates among older adults in rural Nepal: a cross-sectional study. BMJ Open. 2021;11(2):e041728.

7. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. J Clin Epidemiol. 2003;56(3):221-9.

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Ostini, Remo**
Affiliation Clinical School	**University of Queensland School of Medicine, Rural**
Date	**22-Dec-2023**
COI	**No competing interests**

Some brief comments on the manuscript:

Much work has gone in to the revision of this manuscript. It still needs additional work.

The writing requires further polish.

P2, ln 17: Study included 48 studies – but breakdown only adds up to 40.

The Abstract says the search period is now up to August 2023 but the Method still says the search period ended in March 2022.

It's not clear whether the definition of multimorbidity as two or more concurrent, chronic conditions is important if your search allows studies with a different definition. Studies where multimorbidity requires three or more concurrent conditions are looking at a much higher bar and conceivably, a qualitatively different group of people. Accepting both definitions in studies potentially complicates study findings.

The OR numbers for the HLS meta analysis reported in the abstract are not the same as in Figure 3. The abstract also says that the meta analysis results from both studies support the existence of an association between HL and multimorbidity – but Figure 3 shows p=0.44 for the HLS, which does not support an association.

The paper seems to alternate between health literacy affecting multimorbidity and the opposite. The nature of the associations studied does not allow directionality to be inferred – so that may explain the variation in how it is described in the manuscript. It would be better not to imply directionality at all.

Reviewer	**3**
Name	**Perna, Annalisa**
Affiliation	**Mario Negri Institute, Renal Medicine**
Date	**28-Mar-2024**
COI	**None**

Chaudan and co-workers investigated the association between health literacy and multimorbidity in 223,300 adult participants, enrolled in 48 studies. As expected, they found that people with lower health literacy levels are more likely to have multimorbidity. Although the manuscript covers an interesting topic, it appears to be incomplete, because relevant information is not provided. For this reason this manuscript should undergo a profound revision, before being suitable for publication.

More specifically the role of the following major issues appears to left unaswered:

- Level of education;

- role of culturally diverse background and linguistic culture;

- urban/rural environment;

- presence/absence of private health insurance;

- number of chronic conditions;

- Participants with lower health literacy are likely less represented, resulting in an underestimation of the problem.

A further concern is represented by the internal and external validity of study results, considering that of 48 included studies only three in figure 2 and other three in Figure 3 contributed to the quantitative analysis.

Reviewer	**4**
Name	**Hartvigsen, Jan**
Affiliation	**University of Southern Denmark**
Date	**30-Mar-2024**
COI	**I have no competing interests**

I am not sure I reviewed this paper in the first round, but I think it is very nice and the authors have done a great job in replying to the reviewers and editing the paper accordingly.

VERSION 2 - AUTHOR RESPONSE

Adrian Aldcroft, PhD

Editor-in-Chief

BMJ Open

18 July, 2024

Dear Dr. Aldcroft:

Hereby I submit our revised manuscript entitled "UNRAVELLING THE ROLE OF HEALTH LITERACY IN INDIVIDUALS WITH MULTIMORBIDITY: A SYSTEMATIC REVIEW AND META-ANALYSIS" for consideration in Open BMJ.

We appreciate the time invested by the editors and reviewers in evaluating this important work and have endeavored to incorporate all the comments and modifications as requested.

The English language editing has been thoroughly revised with the help of an expert. To ensure the internal consistency of the review and address key comments from the reviewers, particularly Reviewer 2, we invited two multimorbidity experts, Dr. Marjan Van Den Akker and Dr. Sailesh Mohan, to assist in reworking the entire manuscript.

Each author confirmed that this manuscript has not been previously published and is not currently under consideration by any other journal. Additionally, all authors approved the content of this paper and agreed to the BMJ Open submission policies.

To the best of our knowledge, the authors of this research work have no conflict of interest.

Each author has substantially contributed to conducting the underlying research and drafting this manuscript.

I kindly request you to consider our manuscript for publication in your esteemed journal if possible.

Sincerely,

Sanghamitra Pati

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Sanghamitra Pati

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Dear Editor,

Thank you for allowing us to submit a revised version of our manuscript titled “Unravelling the role of health literacy in individuals with multimorbidity: A systematic review and meta-analysis” to *BMJ Open*. We appreciate the time and effort that both the reviewers and yourself have taken to provide valuable feedback on our manuscript. Your feedback has helped to improve the quality of the article. Below you can find our replies in the following table, with the new or revised text underlined.

Kind regards,

Arohi Chauhan MD

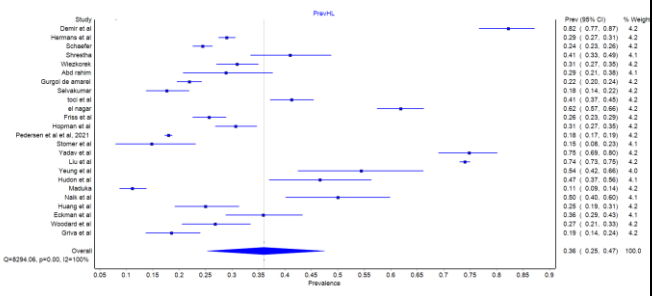
Introduction	
Comment	**Reply**
Reviewer:2	
The writing requires further polish. P2, ln 17: Study included 48 studies – but breakdown only adds up to 40.	We have revised, the entire manuscript and rewritten all the sections. Thank you for bringing this to our attention. We have revised this entire manuscript. Now the total study count includes 39, the detail breakdown is available in Table 1 on page 8-11. According, in the abstract as well as in result section, we have revised the study count. This change can be found in page 1, Abstract (result section, line 1) and page 7, para 3, line 6. Consequently, 39 studies met the inclusion criteria and were included in the review: 36 quantitative studies(1-6, 16, 20-48), 2 qualitative studies(49, 50), and 1 mixed-methods study(51).
The Abstract says the search period is now up to August 2023 but the Method still says the search period ended in March 2022.	We have revised this. We have extended the search period up to 31 October, 2023. Have updated this in abstract – method section as well as method section on page 5, para 4, line 3. The databases MEDLINE, EMBASE, CINAHL and Science Direct were searched for articles published between Jan 1st, 2000 and Oct 31, 2023 using a systematic search strategy.

It's not clear whether the definition of multimorbidity as two or more concurrent, chronic conditions is important if your search allows studies with a different definition. Studies where multimorbidity requires three or more concurrent conditions are looking at a much higher bar and conceivably, a qualitatively different group of people. Accepting both definitions in studies potentially complicates study findings.	Thank you for bringing this to our attention. We included two more experts in our review; Dr. Marjan Van Den Akker and Dr. Sailesh Mohan and based on their inputs, we agree with the reviewer's suggestion. We have included those studies in our result section based on the definition provided in the method section, i.e., two or more concurrent chronic conditions. We have excluded studies looking at three or more concurrent conditions as experts also suggested they are qualitatively different group of people and including those studies complicates study findings.
The OR numbers for the HLS meta analysis reported in the abstract are not the same as in Figure 3.	The change can be found in page 7, para 3, line 8-9. Also the same has been updated in the prisma flow, figure 1 <u>All included studies defined multimorbidity as individuals living with two or more chronic diseases.</u> Thank you for highlighting this error. We have updated the result section in abstract on page 3, result section line 3-5.
The abstract also says that the meta analysis results from both studies support the existence of an association between HL and multimorbidity – but Figure 3 shows p=0.44 for the HLS, which does not support an association.	<u>Based on our analysis of the 3 articles using the health literacy questionnaire (HLQ) tool (n = 31,228) [Pooled OR 2.88 (95%CI 1.92,4.31)] and the 3 articles using the health literacy survey questionnaire-European Union (HLS-EU) tool (n = 35,358) [OR 1.16 (95%CI 1.07]-1.25)]</u> The p value here (meta-analysis figure) represents heterogeneity, which is more than 0.05, suggesting no significant heterogeneity. The association between health literacy and

	multimorbidity is significant as denoted by the 95% CI lies, which in both HLQ-9 and HLS-EU lies above 1, implying the significance as the central line is above 1 and it does not cross the line. Therefore, we don't agree with the reviewer here.
The paper seems to alternate between health literacy affecting multimorbidity and the opposite. The nature of the associations studied does not allow directionality to be inferred – so that may explain the variation in how it is described in the manuscript. It would be better not to imply directionality at all.	Thank you for this important and valuable suggestion. The experts also agreed to this and we have removed this part from the manuscript.

Reviewer 3	
More specifically the role of the following major issues appears to left unaswered: - Level of education; - role of culturally diverse background and linguistic culture; - urban/rural environment; - presence/absence of private health insurance; - number of chronic conditions; - Participants with lower health literacy are likely less represented, resulting in an underestimation of the problem.	Thanking for this relevant comment. We agree with the reviewer and have updated the information on level of education, indigenous population, income, age, ethnicity, residence, gender, and marital status, in the review according to the availability of the data. The revision can be found in page 12 and 13, where we have provided detailed break-down of the determinants and direction. **Determinants of Health Literacy** Twelve studies reported on the determinants of health literacy among individuals with multimorbidity.(4, 6, 20, 21, 23, 26, 32, 39, 40, 47, 51, 53) Higher education and income emerged as the strongest factors of higher levels of health literacy across various settings, whether in high-income or middle-income countries. Other determinants included age (specifically, being under 65 years), residence (living in rural areas), gender, social support, and ethnicity (particularly for indigenous populations) determining higher levels of health literacy. Marital status did not appear to impact health literacy levels among these individuals. **Education** In studies using the HLQ-9 tool to assess health literacy, higher education status influenced all domains except for social support for health. These domains included: Support from healthcare providers(1, 23, 41, 51), Having sufficient health information(1, 23, 41, 51), Actively managing one's health(23, 41, 51), Critical appraisal of health information(23, 41, 51, 53), Engaging with healthcare providers, Navigating the healthcare system(23, 41, 51), Ability to find good health information(1, 23, 41, 51) and Understanding health information.(1, 23, 41, 51) Similar observations were reported in studies employing the HLS-EU and its variants, as well as those using unique health literacy

	assessment tools.(4, 6, 20, 26, 39, 40) **Income** Income was the second most consistent determinant of health literacy. Lower health literacy was observed in groups with an income of less than $240 USD in LMICs. For studies using the HLQ-9, income influenced all domains except for support from healthcare providers and actively managing one's health(21, 22, 47). Similar findings were reported in studies using unique health literacy tools.(6, 39) **Age** A study from a lower-middle-income country using the HLQ-9 suggested that being under 65 years positively influenced domains such as support from healthcare providers (22), social support for health(22), engaging with healthcare providers(21), navigating the healthcare system(21), the ability to find good health information(21), and understanding health information(21). Conversely, a study from a high-income country revealed that health literacy was influenced by being over 65 years.(26) **Residence** Living in rural areas influenced HLQ-9 domains such as support from healthcare providers (22, 51), having sufficient health information(22, 51), social support for health(22, 51), and critical appraisal of health information(51). Studies using the HLS-EU and its variants also found similar results.(20, 40) **Ethnicity and Social Support** Ethnicity was not a major determinant for most HLQ-9 domains, except for social support for health, which was influenced by being part of an indigenous or Dalit population.(1, 41) Additionally, three studies reported social support as a positive determinant of health literacy.(23, 26, 32) **Gender and Marital Status** Two studies conducted in high-income countries suggested that gender had no influence on health literacy.(22, 51)

	Contrastingly, a study from an upper-middle-income country using the HLS-EU tool found that male gender was a determinant of health literacy.(40) However, another study from a low-middle-income country reported that the HLQ-9 domains of having sufficient health information, the ability to find good health information(1), and understanding health information (1, 22, 51) were influenced by female gender, suggesting cultural factors impact health literacy levels. Regardless of settings, marital status had no influence on health literacy.(1, 22, 51)
A further concern is represented by the internal and external validity of study results, considering that of 48 included studies only three in figure 2 and other three in Figure 3 contributed to the quantitative analysis.	We thank the reviewer to bringing this to our attention. We have added the meta-analysis figure on the prevalence of limited health literacy among individuals with multimorbidity, showing data from 24 studies out of 39 studies, apart from figure 2 and 3, contributing towards the quantitative analysis according to the availability of the data. The change can be found in page 10-11 para 2-3, figure 2. 

Reviewer 4	No comments

VERSION 3 - REVIEW

Reviewer	**3**
Name	**Perna, Annalisa**
Affiliation	**Mario Negri Institute, Renal Medicine**
Date	**12-Aug-2024**
COI	**None**

The Authors addressed the previously arisen issues.