

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of multimorbidity among Bangladeshi adult population – A nationwide cross-sectional study
AUTHORS	Khan, Nusrat; Rahman, Mahfuzar; Mitra, Dipak; Afsana, Kaosar

VERSION 1 – REVIEW

REVIEWER	Carlo Eduardo Medina-Solis Academic Area of Dentistry of Health Sciences Institute at the Autonomous University of Hidalgo State. Mexico
REVIEW RETURNED	27-Apr-2019

GENERAL COMMENTS	<p>Manuscript title: Capturing the Challenge of Chronic Multimorbidity among Bangladeshi Adult Population</p> <p>The authors present results from a large cross-sectional study conducted in Bangladesh which investigated the status of multimorbidity related to diverse variables. Although the prevalence of multimorbidity and risk factors have been extensively investigated in previous studies, the location of this study makes it unique. I would like to thank the authors for choosing this topic, multimorbidity, which is very relevant nowadays. This study is interesting but requires changes prior to publication.</p> <p>Abstract 1. The conclusions are not adequately supported by the data. They seem recommendations instead of conclusions derived from the study.</p> <p>Introduction 2. Objective: Unify with the objective of the abstract. The objective is not very clear.</p> <p>Material and Methods 3. Please define the study design. 4. Please provide additional information on inclusion and exclusion criteria. 5. What was the participation rate? In general, the methodology needs to be described in greater detail to be accepted 6. It was used any adjustment for the type of sampling (stratified by conglomerates)? 7. The authors do not mention how they constructed their multivariate logistic regression model.</p>
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	<p>8. The authors do not present any global adjustment (goodness of fit) of the model.</p> <p>Results</p> <p>9. The authors mention in the results section "risk", since it is a cross-sectional study the correct thing would be to say "odds" or "possibility".</p> <p>10. The authors say: ".....people with higher economic status have access to better food and education....." Please, consider changing "better" to "more" because it would imply "good".</p> <p>Discussion</p> <p>11. The purpose of the paper is interesting, but needs to be better discussed. The authors do not argue according to the title of the work. They could mention the challenges in terms of human resources, infrastructure and costs that the health system of their country.</p> <p>Conclusion</p> <p>12. The authors say nothing about their results. Conclusions shown are not conclusions derived from their results. They just mention some suggestions. It is necessary to add conclusions based on the results of your study.</p>
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REVIEWER	Kathryn Reimer, MA, MOT. Not affiliated. Canada.
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	<p>Overall this seems like a thorough study that is very much needed. There are some grammatical concerns, and typos which need to be addressed.</p> <p>The methods/ study design section is not detailed enough. I would also recommend outlining in greater detail the measures that were taken to ensure confidential materials/data were secured. I have attached a pdf that I made some comments on. I made some notes on grammar, however they are not all encompassing and further editing is required.</p> <p>The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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REVIEWER	Ozlem Yilmaz Istanbul medical faculty, Turkey
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	<p>Major points</p> <p>1. There are written English language errors throughout the article. Therefore, English editing is absolutely necessary.</p> <p>2. Multimorbidity has been described as a chronic medical condition. However, it is understood from the article that chronic diseases exist in adults rather than medical conditions for multimorbidity. This confusion of meaning should be clarified. Multimorbidity should be better explained especially in the introduction. The article of the World Health Organization on this subject may be useful: https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf;jsessionid=7C5FAA955DCA8B176D3368A39CD95819?sequence=1</p> <p>3. Another concern is about multimorbidity: Is the situation that is referred to as multimorbidity in the studies mentioned in the introduction appropriate</p>
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	<p>with your study? This point should also be clarified and this issue should be included in the discussion if necessary.</p> <p>3. In the methodology section, on page 6, line 24, the potential risk factors for multimorbidity were selected. The authors should Explain what these risk factors are.</p> <p>4. In the methodology section, on page 6, line 29, " physical (inactivity, obesity, tobacco use, sleeping habit, and dietary diversity " 'How were asked the participants? If so, which tools were used to evaluate?</p> <p>5. In the article, the discussion section was kept short and the limitations and conclusions were written quite long. These last two sections should be shorter and the contents written in these two sections should be included in the discussion section.</p> <p>Minor points There are some spelling, grammar or language errors which should be checked</p> <ol style="list-style-type: none"> 1. Page 1 line 41: "Gender differentials for men versus women are found to be 7.7% versus 8.9%" Which variable does the percentage given in this sentence belong to? 2. Page 4 line 53: 'NCD" This abbreviation should be given in parentheses in an explicitly written form. Other abbreviations should be reviewed in this context where used for the first time. (Page 4 line 41: "UK", page 5 line 3: "CVDs", page 6 line 7: "COPD" etc) 3. Page 5 line 24: "BRAC " should be explain. 4. Page 7-10 Table 1-2-3: Decimal must be written as single digit. For example 30.1 instead of 30.14 .
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Abstract: The conclusions are not adequately supported by the data. They seem recommendations instead of conclusions derived from the study.

Response: The conclusion section in the abstract has been amended as suggested.

Conclusion

This study reported a high prevalence of multimorbidity in Bangladesh, although it explored the burden and identified risk factors considering only six major chronic diseases. Further detailed exploration through longitudinal studies that include a wider range of diseases is needed to document the actual burden and develop effective preventive measures along with clinical guidelines to improve the quality of life of the population.

2. Introduction: Objective: Unify with the objective of the abstract. The objective is not very clear.

Response: As suggested, the objective section in the introduction has been amended (Page 3)

3. Material and Methods: Please define the study design.

Response: As suggested, the study design has been defined (Page 6, 7).

Study design and population

Details about the data collection process can be found elsewhere (17). Put briefly, we collected information from 11,428 households, with a response rate of 94.9%. In the first stage of sampling,

210 Enumeration Areas (EAs) were selected randomly with probability proportional to EA size. This included 180 EAs from rural areas and 30 EAs from urban slums. An EA is a union (rural areas) or ward (urban slums) —the lowest administrative unit in Bangladesh. A union is defined as a collection of a small number of villages, whereas a ward is typically a collection of villages and/or slums. A slum is defined as a cluster of compact settlements of five or more households. A complete list of unions and wards was included in the sampling frame for the first stage of sampling, which was collected from the most recent Population and Housing Census of Bangladesh (18). In the second stage of sampling, starting from the north-west corner of an EA with a systematic random sample of five households, an average of 54 households per EA were selected to provide statistically reliable estimates for rural areas and urban slums separately. Information was collected from all the men and women aged ≥ 35 years residing in the selected households, with 80.9% complete responses (Figure 1).

4. Please provide additional information on inclusion and exclusion criteria.

Response: As suggested, additional information on inclusion and exclusion criteria have been included (page 7).

Recruitment of respondents for the study required the creation of a study base for systematic sampling based on demographic characteristics and BRAC program interventions. To recruit eligible survey respondents from the household census, eligible respondents (willing to participate, not critically ill and ≥ 35 years old) were identified.

5. What was the participation rate? In general, the methodology needs to be described in greater detail to be accepted.

Response: The participation rate is 96%. This information has been incorporated in page 6-8). Also, methodology has been thoroughly revised.

Details about the data collection process can be found elsewhere (17). Put briefly, we collected information from 11,428 households, with a response rate of 94.9%.

6. It was used any adjustment for the type of sampling (stratified by conglomerates)?

Response: As advised, type of sampling has been described (Page 6).

In the first stage of sampling, 210 Enumeration Areas (EAs) were selected randomly with probability proportional to EA size. This included 180 EAs from rural areas and 30 EAs from urban slums. An EA is a union (rural areas) or ward (urban slums) —the lowest administrative unit in Bangladesh. A union is defined as a collection of a small number of villages, whereas a ward is typically a collection of villages and/or slums. A slum is defined as a cluster of compact settlements of five or more households. A complete list of unions and wards was included in the sampling frame for the first stage of sampling, which was collected from the most recent Population and Housing Census of Bangladesh (18). In the second stage of sampling, starting from the north-west corner of an EA with a systematic random sample of five households, an average of 54 households per EA were selected to provide statistically reliable estimates for rural areas and urban slums separately. Information was collected from all the men and women aged ≥ 35 years residing in the selected households, with 80.9% complete responses (Figure 1).

7. The authors do not mention how they constructed their multivariate logistic regression model.

Response: As suggested, multivariate logistic regression model construction has been explained in the statistical analysis (Page 9).

The association between potential risk factors and multimorbidity was estimated by crude and adjusted odds ratios, using bivariate and multivariate logistic regression models respectively. The model fitness was tested using Hosmer-Lemeshow goodness-of-fit test. An association was considered significant if its p-value was <0.05 . Crude odds ratios were used to identify the association between each of the independent variables while the adjusted odds ratios (considering socio-demographic and lifestyle factors such as age, sex, BMI, physical activity, fruit, and fish and meat intake) were used to identify any association between individual factors and the outcome measurement (p-value < 0.05). The entire analysis was carried out using STATA version 12 (19).

8. The authors do not present any global adjustment (goodness of fit) of the model.

Response: The model fitness was tested using Hosmer-Lemeshow goodness-of-fit test (Page 9).

9. Results: The authors mention in the results section "risk", since it is a cross-sectional study the correct thing would be to say "odds" or "possibility".

Response: As suggested, the amendments have been done though-out text.

In table 3 we show how, within the study population, older people and females are significantly at higher odds of developing multimorbidity both in the crude and adjusted model. People belonging to the top two wealth quintiles and with higher educational status have a significantly higher probability of having developed multimorbidity than poorer and less educated respondents. Odds of multimorbidity in people with higher BMI (≥ 25) were 2.10 times the odds in people with normal BMI. The odds ratio comparing physically active people to those who are not active at all is 0.5 (95% CI: 0.2-1.3).

10. The authors say: ".....people with higher economic status have access to better food and education....." Please, consider changing "better" to "more" because it would imply "good".

Response: The following amendments have been made:

For higher educational status, aOR was 1.8 (95% CI 1.6-2.3) and for the richest wealth quintile, aOR was 2.1 (95% CI 1.6-2.7). This could owe to the fact that, being a lower-middle-income country, people with a higher economic status in Bangladesh have access to more food and education. This is consistent with findings from a recent systematic review reporting that individuals of low socioeconomic status in low and lower middle income countries are more likely to consume a less healthy diet (e.g., less fruit, vegetables, fish, and fiber, but more meat), whereas individuals of higher socioeconomic status tend to be more physically inactive, thus increasing the prevalence of non-communicable diseases (21).

11. Discussion: The purpose of the paper is interesting, but needs to be better discussed. The authors do not argue according to the title of the work. They could mention the challenges in terms of human resources, infrastructure and costs that the health system of their country.

Response: The discussion section has been thoroughly revised as suggested reads as follows (Page 15-17)

DISCUSSION

Multimorbidity is a less explored area in healthcare research compared to individual diseases, which are typically explored both clinically and epidemiologically. The recent Sustainable Development Goals suggest that the post-2015 agenda will be substantially influenced by a focus on 'health in all ages', including Target 3.8 which aims to achieve universal health coverage. The realisation of these goals and other wider development targets will require multiple morbidities to be addressed (20). Therefore, with an increasing burden of chronic diseases worldwide, individuals suffering from multiple chronic diseases are also emerging as a healthcare priority (1,11). This is the first study (to our knowledge) reporting multimorbidity burden in Bangladesh conducted both in urban and rural areas, although results cannot be compared as there has not yet been any other large-scale study amongst the general population nor any systematic review or meta-analysis on the entire South Asia reporting the pooled prevalence and risk factors. Prevalence of multimorbidity (8.4%) counted within only six diseases is quite high. We adopted the commonly used WHO definition, but the lack of data on a similar context and a similar population, as well as the absence of a consensual definition, make our findings less comparable. As we used appropriate sampling methods and/or calculation, our large population-based cross-sectional data were powerful enough to calculate the prevalence of chronic diseases and multimorbidity prevalence among the Bangladeshi population. A study such as this one contributes to generate evidence and inform healthcare policymakers for timely action and preparedness.

Several studies have been conducted on major NCD status and their risk factors, many of which are assumed to be similar to multimorbidity. Most of the previous studies in the western population have shown that low socioeconomic status and less education are positively and specifically associated with multimorbidity (2,13). Nevertheless, our study finds the opposite results, which are also statistically significant. For higher educational status, aOR was 1.8 (95% CI 1.6-2.3) and for the richest wealth quintile, aOR was 2.1 (95% CI 1.6-2.7). This could owe to the fact that, being a lower-middle-income country, people with a higher economic status in Bangladesh have access to more food and education. This is consistent with findings from a recent systematic review, reporting that individuals of low socioeconomic status in low and lower middle income countries are more likely to consume a less healthy diet (e.g., less fruit, vegetables, fish, and fiber, but more meat). Whereas, individuals of higher socioeconomic status tend to be more physically inactive, thus increasing the prevalence of non-communicable diseases (21). As we already know, lifestyle factors are closely associated with chronic diseases and multimorbidity risk. We can therefore say that, since people of higher economic status have more access to food and also traditionally live a sedentary lifestyle, this leads them to develop more NCD risk factors and ultimately multimorbidity (22). Identifying higher age and being female as a significant determinant of multimorbidity is consistent with existing literature(2,7).

On the contrary, in developed countries, epidemiological evidence is scarce. South Asians have already been characterised as a genetically high-risk group for developing cardiometabolic and other chronic diseases, resulting in a higher incidence of multimorbidity within the population (2). The risk factors of multimorbidity identified in our study are similar to the reported risk factors of individual chronic diseases in various analyses. As in many other studies, BMI showed a significant association with multimorbidity (7). Dozens of epidemiologic studies have reported findings on the association between fruit and vegetable intake on one hand, and the risk of cardiovascular disease and other NCDs on the other (22,23). Our study also corroborates that a higher intake of fish and meat is significantly associated with multimorbidity in the crude analysis, but not in the adjusted model. Increased intake of fruits and vegetables were found to be protective factors against developing multimorbidity, but after adjusting for covariates this result was not significant. Among other lifestyle factors, increased physical activity and a higher average daily sleeping time were found to be protective factors against developing multimorbidity (13,14).

Although most of the evidence on multimorbidity is limited to the elderly population globally, this study is unique in the sense that it covers a wider age range. Our study reports that the odds of developing multimorbidity are higher amongst those on the older cohort compared to the middle age group (35-40). Even in the age groups 41-50 and 51-60 the odds of developing multimorbidity are respectively

2.8 and 3.6 times higher than amongst people under 40 years of age. This suggests that people develop multimorbidity even during active and productive years of life, which can cause excess healthcare costs from earlier years in life. In a context of less developed health infrastructure and of an inadequacy of human resources, this evidence on the burden of multimorbidity in Bangladesh warrants further exploration from various perspectives, including further research as well as the development of policies to tackle the burden. Therefore, population-based data on multimorbidity is an urgent need to get the actual scenario of the burden and further develop strategies to prepare the healthcare systems. Otherwise, with the aging population and ever-rising chronic disease burden globally, healthcare systems shall not be prepared to tackle this healthcare challenge.

12. Conclusion: The authors say nothing about their results. Conclusions shown are not conclusions derived from their results. They just mention some suggestions. It is necessary to add conclusions based on the results of your study.

Response: The following amendments in the conclusion section have been made:

This study identifies the prevalence of multimorbidity amongst Bangladeshi individuals who are undergoing an epidemiological transition. It is comparable to many developing countries and thus highlights the importance of recognising associated risk factors, especially among young adults and also in the elderly. A prevalence of nearly nine percent in a nationwide sample is alarming. The lack of a consensual definition of multimorbidity may also contribute to under or overestimation. We recommend that an international clinical guideline with an approved range of diseases should be developed to serve the purpose, which would also aid in monitoring progress towards the fulfilment of the United Nations' SDGs. As for Bangladesh, there is a need for a detailed national-level exploration including the rural and urban population in a larger scale to document the current prevalence, incidence, and specific risk factors associated with multimorbidity. This would help inform policymakers and further develop preventive strategies and clinical guidelines.

Reviewer: 2

There are some grammatical concerns, and typos which need to be addressed. The methods/ study design section is not detailed enough. I would also recommend outlining in greater detail the measures that were taken to ensure confidential materials/data were secured. I have attached a pdf that I made some comments on. I made some notes on grammar, however they are not all encompassing and further editing is required.

Response: As suggested, grammatical concerns and typos has been addressed, also reviewed by a native English speaker, Roberto Zedillo Ortega, University of. Therefore, we have acknowledged him. That is highlighted throughout the revised manuscript. The methods section is further detailed. Greater detail on the measures taken to ensure confidential materials/data security is explained Page 8).

Method section has been thoroughly revised from page 6 to 8.

Reviewer: 3

Major points

1. There are written English language errors throughout the article. Therefore, English editing is absolutely necessary.

Response: As suggested, English language errors have been addressed and highlighted.

2. Multimorbidity has been described as a chronic medical condition. However, it is understood from the article that chronic diseases exist in adults rather than medical conditions for multimorbidity. This confusion of meaning should be clarified. Multimorbidity should be better explained especially in the introduction. The article of the World Health Organization on this subject may be useful: <https://apps.who.int/iris/bitstream/handle/10665/252275/9789241511650-eng.pdf;jsessionid=7C5FAA955DCA8B176D3368A39CD95819?sequence=1>

Response: As suggested, this confusion has been addressed.

Multimorbidity is becoming an emergent global health concern. It is commonly defined as the presence of two or more chronic diseases in an individual (1). Multimorbidity presents several challenges to any health care system, since most are generally focused on treating single diseases rather than multiple coexisting conditions. More common among the elderly population, the growing demand for health care needs to deal with multiple non-communicable diseases/ multimorbidity and associated polypharmacy is putting considerable strain on healthcare systems around the world (2).

3. Another concern is about multimorbidity: Is the situation that is referred to as multimorbidity in the studies mentioned in the introduction appropriate with your study? This point should also be clarified, and this issue should be included in the discussion if necessary.

Response: This has been addressed by amendments in the introduction and discussion sections.

3. In the methodology section, on page 6, line 24, the potential risk factors for multimorbidity were selected. The authors should Explain what these risk factors are.

Response: The following amendment has been made:

The list of potential risk factors of multimorbidity was based on literature about the risk factors of different chronic diseases. The assumption was that that the risk factors will be similar for multiple chronic diseases combined. These include sociodemographic characteristics (age, sex, educational status, and economic status), as well as health and lifestyle-related factors (physical (in) activity, obesity, tobacco use, sleeping habit, and dietary diversity) (7,9).

4. In the methodology section, on page 6, line 29, " physical (inactivity, obesity, tobacco use, sleeping habit, and dietary diversity " 'How were asked the participants? If so, which tools were used to evaluate?

Response: The following amendment has been made.

These data were collected through face-to-face interviews with respondents using a questionnaire. Variables BMI: underweight <18.5 kg/m², normal 18.5-24.9 kg/m², overweight 25.0-29.9 kg/m², obese ≥30.0 kg/m²; and hypertension were categorised and calculated using standardised WHO guidelines. Daily sleeping time of the participants was measured by the standard average sleeping hour of 8 hours as per participant history taking.

5. In the article, the discussion section was kept short and the limitations and conclusions were written quite long. These last two sections should be shorter and the contents written in these two sections should be included in the discussion section.

Response: As suggested, modifications in the discussion, limitation and conclusion section and highlighted.

Minor points

There are some spelling, grammar or language errors which should be checked

1. Page 1 line 41: "Gender differentials for men versus women are found to be 7.7% versus 8.9%"
Which variable does the percentage given in this sentence belong to?

Response: The following amendments have made:

The prevalence of multimorbidity was lower among males (7.7%) compared to females (8.9%).

2. Page 4 line 53: "NCD" This abbreviation should be given in parentheses in an explicitly written form. Other abbreviations should be reviewed in this context where used for the first time. (Page 4 line 41: "UK", page 5 line 3: "CVDs", page 6 line 7: "COPD" etc)

Response: As advised, all the abbreviations have been reviewed.

3. Page 5 line 24: "BRAC " should be explain.

Response: As suggested, details on BRAC have been included:

BRAC (Building Resources Across Communities), the world's no 1 non-government organization (NGO), has been a pioneer in its health initiatives since its inception. Through its flagship health intervention, health nutrition and population program (HNPP), it has come up with a comprehensive health care package to assist the vulnerable population of the country at an affordable cost.

4. Page 7-10 Table 1-2-3: Decimal must be written as single digit. For example 30.1 instead of 30.14 .

Response: As suggested, the amendments have been made and highlighted in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Carlo Medina The Autonomous University of Hidalgo State.
REVIEW RETURNED	01-Aug-2019
GENERAL COMMENTS	<ul style="list-style-type: none"> - Please copy the design from the abstract: "A cross-sectional study was conducted using a multi-stage clustered random sampling strategy." - The authors mention the overall fit of the model. But they do not present it (values) anywhere in the manuscript. - When complex sampling is performed, the analysis must be adjusted for that complexity. For example, using Stata svy module or using the "cluster" option in the analysis.

VERSION 2 – AUTHOR RESPONSE

Reviewer’s Comments to Authors:

Comment 1:

- Please copy the design from the abstract: "A cross-sectional study was conducted using a multi-stage clustered random sampling strategy."

Response: The design section from abstract is now incorporated on the Methodology section of the manuscript.

Study design and population

The cross-sectional study was conducted using a multi-stage clustered random sampling strategy. Details about the data collection process can be found elsewhere (17).

Comment 2 and 3:

- The authors mention the overall fit of the model. But they do not present it (values) anywhere in the manuscript.

- When complex sampling is performed, the analysis must be adjusted for that complexity. For example, using Stata svy module or using the "cluster" option in the analysis.

Response: As suggested, the statistical analysis section of the manuscript has been explained with details:

Statistical analysis

We first estimated the prevalence of multimorbidity in the study population using descriptive statistics. Distributions of potential risk factors were compared between respondents with and without multimorbidity using t-tests for continuous variables and chi-squared test of independence for categorical variables. The association between potential risk factors and multimorbidity was estimated by crude and adjusted odds ratios using bivariate and multivariate logistic regression models respectively. We used “robust” option to adjust for complex sampling design. An association was considered significant if P-value was <0.05. Crude odds ratio was used to identify the association of each of the independent variables while the adjusted odds ratio (adjusted for confounding considering socio-demographic and lifestyle factors such as age, sex, BMI, physical activity, fruit, and fish and meat intake) identified the association of individual factors with the outcome measurement p-value < 0.05). The fitness of the final model was tested using Hosmer-Lemeshow goodness-of-fit test (P value was not significant. All analyses were done using STATA version 12 (19).

VERSION 3 – REVIEW

REVIEWER	Carlo Eduardo Medina Soliís Academic Area of Dentistry of Health Sciences Institute at the Autonomous University of Hidalgo State. Pachuca, Mexico.
REVIEW RETURNED	25-Sep-2019

GENERAL COMMENTS	The manuscript is ready for publication.
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