

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Multimorbidity, psychoactive substance use and psychological distress among acute medically ill patients - a cross sectional study
<b>AUTHORS</b>	Kabashi, Saranda; Gamboa, Danil; Vindenes, Vigdis; Berg, Thomas; Hilberg, Thor; Jørgenrud, Benedicte; Lerdal, Anners; Bogstrand, Stig Tore

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Heyang Wang First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
<b>REVIEW RETURNED</b>	09-Jun-2021

<b>GENERAL COMMENTS</b>	The multimorbidity mentioned in this paper do not give a clear type and diagnosis, In addition, the inclusion method of sample size and the types of psychoactive drugs are unknown, so it is recommended to explain clearly.
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<b>REVIEWER</b>	Marcus Borges Universidade de Sao Paulo Hospital das Clinicas, Psychiatry
<b>REVIEW RETURNED</b>	20-Jun-2021

<b>GENERAL COMMENTS</b>	<p>Manuscript Number: 2021-052428 "Multimorbidity, psychoactive substance use and self-reported psychological distress among acute medically ill patients"</p> <p>I would like to thank the authors for the submission of their manuscript entitled: "Multimorbidity, psychoactive substance use and self-reported psychological distress among acute medically ill patients".</p> <p>This study aimed to "examine substance use patterns among acute medically ill patients, and determine the association between multimorbidity, substance use, and psychological distress."</p> <p>Clear strengths of the study are:</p> <ol style="list-style-type: none"><li>1) The authors conducted a cross-sectional analysis which was based on an observational study consisting of 2874 patients aged 18 years and over admitted to a medical emergency department in Oslo.</li><li>2) This study seems to be relevant within a field of research (on Psychiatry) and the claims are convincing;</li><li>3) The subject addressed is worthy of investigation;</li><li>4) This study is interesting and novel - the study extends previous findings.</li></ol> <p>In addition, the main finding seems to be new: "The likelihood for multimorbidity was elevated in patients with risky alcohol- and psychoactive medicinal drug use... The authors concluded that:</p>
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	<p>“Monitoring substance use among multimorbid patients is necessary to develop tailored treatments, improve health outcomes and reduce burden on the health-care system.”</p> <p>The manuscript is well written. I recommend publication of their manuscript after major revision. Below my main comments.</p> <p>Introduction section:</p> <p>1) On page 5, lines 11-13: The authors described that “Therefore, substance use as a risk factor should be addressed in both epidemiological research and in healthcare settings i.g. when developing effective interventions and adequate care for people with multimorbidity.” Should the authors have mentioned about “psychoactive substance use as a risk factor for the development of multimorbidity?” It is unclear for the readers, if previous studies have already shown that “substance use could be a predictor for multimorbidity...” or this information is new. Please, for the sake of a better understanding, clarify it. i.e. on page 5, lines 19-21: The authors reported that “A combination of alcohol, psychoactive medicinal- and illicit drugs might lead to detrimental health outcomes (7).” What are these negative outcomes (“detrimental health outcomes”)? Information is important to reinforce the main hypothesis of the study.</p> <p>2) On page 5, lines 42-44: The authors described the study aims “(2) determine the association between multimorbidity and substance use, including alcohol, illicit- and psychoactive medicinal drugs, and (3) determine the association between multimorbidity and self-reported psychological distress.” are different from Title and Abstract: “determine the association between multimorbidity, substance use, and psychological distress.” Why? Please, explain it.</p> <p>3) The research question focused on the association between multimorbidity, substance use and psychological distress. However, when the authors test all variables (i.e. substance use as a predictor for multimorbidity, so psychological distress could be a mediator or a confounder? i.e. as a confounder, psychological distress could be associated with (“lead to”) both multimorbidity and substance use?) On the other hand, when the authors cited two variables separately, the readers suppose that the relationship (association) could be unidirectional or bidirectional... regarding hypothesis testing. Please, formulate hypotheses in order to clarify and focus on the research question.</p> <p>4) On page 5, line 55: Regarding study design, the authors conducted a cross-sectional study. Were data collected from the baseline? The authors only cited “data from an observational study conducted from November 2016 to December 2017”.</p> <p>5) Why the authors did not perform a case-control study, regarding study design? Because it is ideal if the authors intended to evaluate multiple exposures (risk factors) for a single outcome (multimorbidity). I can understand that maybe it could be a selection bias (population: acute medically ill patients admitted to ED). There was no group without disease (control group). Probably, this is the main limitation to conduct a case-control study.</p> <p>6) On page 6, line 35-36: In addition, it is quite confusing for the readers, if other three variables (sociodemographic measures: “age,</p>
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	<p>sex, occupational status”) were used as covariates (other listed variables in the adjusted model). Please, clarify it.</p> <p>7) In subsection: Statistical analyses, on page 6, lines 25-27: “Differences in mean number of health conditions between men and women were analyzed using t test...” the authors did not mention “illicit drug use and psychoactive medicinal drugs and Psychological distress” in this subsection. Why? Please, explain it. On page 6, lines 28-29:” and differences across age groups, occupational status-groups were analyzed with one-way ANOVA” the authors did not cite “alcohol use patterns”. Why? Please, explain it. And p-values? Or subthreshold for the difference statistically significant (<math>p &lt; 0.005</math>)?</p> <p>8) In Results Section, on page 8, lines 20-21: “The number of disorders and the proportion of patients with multimorbidity increased significantly with age and there was no significant difference between men and women (Table 1).” However, According to Table 1, number of disorders differ significantly between sexes. Please, review this sentence, for the sake of better understanding.</p> <p>9) On page 8, lines 32-33: the authors used the term “(data not shown)”. Should the authors have shown the prevalence instead of using the term “data not shown”? Please, clarify it.</p> <p>10) On page 9 (Table 1), footnotes started with two symbols that were not seen in the Table. May the authors show the symbols into first row, Columns 3 and 4, respectively?</p> <p>11) On page 9 (Table 1), First Column, why the numbers of variables are different from the total sample (<math>n=2725</math>). The authors did not report missing data in the body of the manuscript. i.e. Sex (<math>n=2725-2707=18</math>); Age (<math>n=2725-2702=23</math>); Occupational status (<math>n=2725-2613=112</math>); Psychological distress (<math>n=2725-2513=212</math>); Alcohol use patterns by AUDIT-4 (<math>n=2725-2594=131</math>); Psychoactive medicinal drugs (<math>n=2725-2477=248</math>); illicit drugs (<math>n=2725-2477=248</math>); In addition, regarding to psychological distress and illicit drugs, it is confusing for the readers whether these variables are dichotomous (Yes/No) in the current format.</p> <p>12) On page 10, lines 13-15: “...except for the combination of illicit drugs and alcohol, which was more frequent among those without multimorbidity (53.5% vs.46.5%).” Could the authors cite the Chi-square test used to distinguish the two groups (“single-diseased patients” vs “patients with multimorbidity”? Is it statistically significant (<math>p &lt; 0.005</math>)?</p> <p>On page 10, lines 50-53: “Patients with risky alcohol use were more likely to be multimorbid compared to those with low risk drinking habits (OR: 1.53; 95% CI: 1.05 - 2.24), the same applied to abstainers (OR: 1.50; 95% CI:1.15 - 1.95)”. the authors did not cite “hazardous drinking”. Why? Please, explain it.</p> <p>13) On page 11 (Table 3) Regarding “occupational status”, the authors did not mention this variable... in the body of the manuscript.... Why?</p> <p>14) On page 11 (Table 3) Footnote started with a symbol * (an asterisk) that is related to the model after adjusting for confounders</p>
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	<p>or covariates? Why the authors used this symbol in both Columns (second and third Columns)? Please, explain it.</p> <p>15) And p-values?</p> <p>16) On page 11, lines 44-48. (Subsection: Sensitive analyses) The authors used the term “similar”? However, self-reported psychological distress did not remain statistically associated with morbidity... Please, review the first sentence of this subsection.</p> <p>17) On page 12, 3rd and 4th paragraphs (Discussion section). The authors reported in the Results section: “Prevalence of risky alcohol use was higher among patients aged 36-50 years and 51-65 years (12,7% and 12.1%) and decreased slightly for those aged 66-80 years (8.7%). Of the young multimorbid patients 14.1% used illicit drugs, 14.1% used psychoactive medicinal drugs and 31.4% reported to have psychological distress. Among multimorbid patients (age &gt; 35 years) the prevalence of psychological distress decreased compared to the the young patients (18- 35 years) while, the prevalence of psychoactive medicinal drug use increasend substantially...” Therefore, the authors could explain why there is no association between multimorbidity and psychological distress? Have younger adults shown a higher prevalence of psychological distress compared to older adults that could be associated to the use of substance (regarding illicit drugs or alcohol use)?</p> <p>18) On page 13, lines 40-60 (Subsection: Limitation) The authors should report the main limitation of a cross-sectional study, i.e. “the lack of time dimension limits the ability to make causal inference”. Temporal relationship may not be clear. So it is useful for hypotheses generating, but ability to test hypothesis will depend on the exposure.</p> <p>The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer Reports:

##### Reviewer: 1

Miss Heyang Wang, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine

##### Comments to the Author:

The multimorbidity mentioned in this paper do not give a clear type and diagnosis. In addition, the inclusion method of sample size and the types of psychoactive drugs are unknown, so it is recommended to explain clearly.

##### Response:

- The inclusion method of the sample size is further described in the methods section 2.1 Study design and participants and 2.3 Data collection, according to your comment.
- The table below describing the diagnoses the patients were assigned upon admission can be included as supplementary material if this is desirable.

Table 1. Percentage and the number of main diagnoses by ICD-10 chapters presented in our study population

ICD-10 chapters	Percentage (%)
A00-B99	5.8
C00-C97-D48	3.9
D50-D89	1.7
E00-E90	4.2
F00-F99	2.9
G00-G99	3.6
I00-I99	24.3
J00-J99	13.4
K00-K93	5.0
L00-L99	1.6
M00-M99	6.5
N00-N99	4.4
R00-R99	16.5
S00-T98	3.7
Z00-Z99	1.1
Other (H00-H59, H60-H95, Q00-Q99)	1.2

- A table describing the types of psychoactive drugs is also included below and can be added to the supplementary material if this is desirable. Also in the main document in the method section 2.4 Measures it is referred to previous paper describing the analysis of these thoroughly.

Table 2. Describes all the drugs that were included in the study

	Number of psychoactive drugs (n)	Percentage (%)
<b>Illicit</b>	167	6.4
Amphetamines	55	2.1
Amphetamine	21	0.8
Methamphetamine	45	1.7
Cocaine <sup>A</sup>	30	1.2
Benzoyllecgonine	22	0.8
Cocaine	26	1.0
Heroin	24	0.9
MDMA ecstasy	4	0.2
THC	97	3.7
<b>Medicinal</b>	843	32.3

Alprazolam	19	0.7
Buprenorphine	7	0.3
Clonazepam	98	3.8
Codeine	181	6.9
Diazepam	251	9.6
Flunitrazepam	6	0.2
Methadone	46	1.8
Morphine	107	4.1
Nitrazepam	93	3.6
Oxycodone	91	3.5
Oxazepam	215	8.2
Tramadol	121	4.6
Zolpidem	32	1.2
Zopiclone	139	5.3

**Reviewer: 2**

Dr. Marcus Borges, Universidade de Sao Paulo Hospital das Clinicas

## Introduction section:

1) On page 5, lines 11-13: The authors described that “Therefore, substance use as a risk factor should be addressed in both epidemiological research and in healthcare settings i.g. when developing effective interventions and adequate care for people with multimorbidity.” Should the authors have mentioned about “psychoactive substance use as a risk factor for the development of multimorbidity? It is unclear for the readers, if previous studies have already shown that “substance use could be a predictor for multimorbidity...” or this information is new. Please, for the sake of a better understanding, clarify it.

**Response:**

We agree on your comment and have added a paragraph elaborating this (the paragraph just ahead of study aims) in the Introduction section. For the sake of precision we also deleted the term ‘risk-factor’ on page 5 Introduction section and in the Conclusion section, since it appears as a rather conclusive term.

i.e. on page 5, lines 19-21: The authors reported that “A combination of alcohol, psychoactive medicinal- and illicit drugs might lead to detrimental health outcomes (7).” What are these negative outcomes (“detrimental health outcomes”)? Information is important to reinforce the main hypothesis of the study.

**Response:**

We agree and this is further elaborated with examples in the Introduction section.

2) On page 5, lines 42-44: The authors described the study aims “(2) determine the association between multimorbidity and substance use, including alcohol, illicit- and psychoactive medicinal drugs, and (3) determine the association between multimorbidity and self-reported psychological distress.” are different from Title and Abstract: “determine the association between multimorbidity, substance use, and psychological distress.” Why? Please, explain it.

**Response:**

This is corrected in the abstract to be the same as in the body of the paper, according to your comment.

3) The research question focused on the association between multimorbidity, substance use and psychological distress. However, when the authors test all variables (i.e. substance use as a predictor for multimorbidity, so psychological distress could be a mediator or a confounder? i.e. as a confounder, psychological distress could be associated with (“lead to”) both multimorbidity and substance use?) On the other hand, when the authors cited two variables separately, the readers suppose that the relationship (association) could be unidirectional or bidirectional... regarding hypothesis testing. Please, formulate hypotheses in order to clarify and focus on the research question.

**Response:**

We agree on your important comment about the hypothesis and have formulated the hypothesis/aims according to your comment, where we test the bidirectional relationship/association between multimorbidity and substance use, and psychological distress.

4) On page 5, line 55: Regarding study design, the authors conducted a cross-sectional study. Were data collected from the baseline? The authors only cited “data from an observational study conducted from November 2016 to December 2017”.

**Response:**

The data were collected from baseline and this is further elaborated in the section 2.1 Study design and participants and in section 2.3 Data collection.

5) Why the authors did not perform a case-control study, regarding study design? Because it is ideal if the authors intended to evaluate multiple exposures (risk factors) for a single outcome (multimorbidity). I can understand that maybe it could be a selection bias (population: acute medically ill patients admitted to ED). There was no group without disease (control group). Probably, this is the main limitation to conduct a case-control study.

**Response:**

Thank you for this valuable idea. Unfortunately, we do not have population data on multimorbidity from the general population to be used as controls, so the current study had to be performed in a cross sectional manner.

6) On page 6, line 35-36: In addition, it is quite confusing for the readers, if other three variables (sociodemographic measures: "age, sex, occupational status") were used as covariates (other listed variables in the adjusted model). Please, clarify it.

**Response:**

Sociodemographic measures were included in the analysis mainly as covariates for adjustment in the model, since our aim was to examine the association between multimorbidity and psychoactive substance use and psychological distress. However, we included all variables in the same model as depicted in the second column of table 2 as predictors for multimorbidity, e.g. since our patient population comes from socio-economically deprived areas of Oslo, we were interested to know the magnitude of the association between multimorbidity and increasing age. Practically speaking, all variables are used to adjust for each other, as is stated underneath the table.

7) In subsection: Statistical analyses, on page 6, lines 25-27: "Differences in mean number of health conditions between men and women were analyzed using t test..." the authors did not mention "illicit drug use and psychoactive medicinal drugs and Psychological distress" in this subsection. Why? Please, explain it.

On page 6, lines 28-29:" and differences across age groups, occupational status-groups were analyzed with one-way ANOVA" the authors did not cite "alcohol use patterns". Why? Please, explain it.

**Response:**

This was a mistake and is now corrected thanks to your attentive remark.

And p-values? Or subthreshold for the difference statistically significant ( $p < 0.005$ )?

**Response:**

The p-value threshold in our analyses is now cited with a sentence on section 2.5 Statistical analysis.

8) In Results Section, on page 8, lines 20-21: "The number of disorders and the proportion of patients with multimorbidity increased significantly with age and there was no significant difference between men and women (Table 1)." However, According to Table 1, number of disorders differ significantly between sexes. Please, review this sentence, for the sake of better understanding.

**Response:**

Thanks to your attentive remark, this has been corrected in the text in section 3. Results to be the same as table 1 indicates, namely that there is a significant difference in the mean number of disorders between women and men.

9) On page 8, lines 32-33: the authors used the term "(data not shown)". Should the authors have shown the prevalence instead of using the term "data not shown"? Please, clarify it «Among multimorbid patients by the age of  $\geq 35$  the prevalence of psychological distress decreased compared to the young patients (18-35), while the prevalence of psychoactive medicinal drug use increased substantially (data not shown). Illicit drugs were most prevalent among those aged 36-65 years (data not shown).»

**Response:**

These prevalences are now included in the text, as you are suggesting.

10) On page 9 (Table 1), footnotes started with two symbols that were not seen in the Table. May the authors show the symbols into first row, Columns 3 and 4, respectively?

**Response:**

According to your comment, the symbols are added to the table as well.

11) On page 9 (Table 1), First Column, why the numbers of variables are different from the total sample (n=2725). The authors did not report missing data in the body of the manuscript. i.e. Sex (n=2725-2707=18); Age (n=2725-2702=23); Occupational status (n=2725-2613=112); Psychological distress (n= 2725-2513=212); Alcohol use patterns by AUDIT-4 (n=2725-2594=131); Psychoactive medicinal drugs (n= 2725-2477=248); illicit drugs (n= 2725-2477=248);

**Response:**

The missing data presented in table 1 are all excluded from the main analysis and this is stated with a sentence in section 2.5 Statistical analyses, as well as in the third sentence in the section 3.Results.

In addition, regarding to psychological distress and illicit drugs, it is confusing for the readers whether these variables are dichotomous (Yes/No) in the current format.

**Response:**

These variables are dichotomous (Yes/No). For SCL-5 questionnaire the positive outcome (Yes) was a scoring of >2 and the negative outcome (No) was a scoring of < 2. For illicit/medicinal drugs the positive outcome (Yes): at least one illicit/medicinal drugs detected and the negative outcome (No): zero illicit/medicinal drug detected in blood. This is described in the text of the section 2.4 Measures for both illicit drugs and psychological distress.

12) On page 10, lines 13-15: "...except for the combination of illicit drugs and alcohol, which was more frequent among those without multimorbidity (53.5% vs.46.5%)."

Could the authors cite the Chi-square test used to distinguish the two groups ("single-diseased patients" vs "patients with multimorbidity"? Is it statistically significant (p<0.005)?

**Response:**

The two groups differed significantly, the combination of illicit drugs and alcohol was significantly more frequent among those without multimorbidity.

A chi-square test showed that there were significant differences in the prevalence of psychoactive substance use and combination of substances between single-diseased patients and those with multimorbidity. The p-value was the same and below 0.001 for all of them and hence we cited the p-value below the table.

On page 10, lines 50-53: "Patients with risky alcohol use were more likely to be multimorbid compared to those with low risk drinking habits (OR: 1.53; 95% CI: 1.05 - 2.24), the same applied to abstainers (OR: 1.50; 95% CI:1.15 - 1.95)". the authors did not cite "hazardous drinking". Why? Please, explain it.

**Response:**

According to your suggestion hazardous drinking is also included in the body of the text in section 3.Results.

13) On page 11 (Table 3) Regarding "occupational status", the authors did not mention this variable... in the body of the manuscript.... Why?

**Response:**

According to your comment this information is now included in the manuscript in the description of the results depicted in table 1, in section 3.Results.

14) On page 11 (Table 3) Footnote started with a symbol \* (an asterisk) that is related to the model after adjusting for confounders or covariates? Why the authors used this symbol in both Columns (second and third Columns)? Please, explain it.

**Response:**

That was a mistake and the asterisk remains now only on the second column where the adjusted ORs are presented.

15) And p-values?

**Response:**

Since the majority of p-values were almost the same and either below 0.005 or 0.001, we did not dedicate an own column depicting the same p-value but rather indicated the p-value below the table 1 and table 3. While in table 2 the Confidence intervals (CI) show if the associations are significant e.g. Confidence Intervals that cross number 1 are non-significant such as low-drinking or hazardous drinking, or illicit drugs in our study:

Alcohol use in excess of low-risk guidelines (scores 4-6)	0.71 (0.59 - 0.87)	0.96 ( <b>0.76 - 1.21</b> )
Hazardous drinking (scores 7-8)	0.74 ( <b>0.54 - 1.02</b> )	1.18 ( <b>0.81 - 1.71</b> )

16) On page 11, lines 44-48. (Subsection: Sensitive analyses) The authors used the term “similar”? However, self-reported psychological distress did not remain statistically associated with morbidity... Please, review the first sentence of this subsection.

**Response:**

This sentence is now corrected to state that self-reported psychological distress did not remain statistically associated.

17) On page 12, 3rd and 4th paragraphs (Discussion section). The authors reported in the Results section: “Prevalence of risky alcohol use was higher among patients aged 36-50 years and 51-65 years (12,7% and 12.1%) and decreased slightly for those aged 66-80 years (8.7%). Of the young multimorbid patients 14.1% used illicit drugs, 14.1% used psychoactive medicinal drugs and 31.4% reported to have psychological distress. Among multimorbid patients (age > 35 years) the prevalence of psychological distress decreased compared to the the young patients (18- 35 years) while, the prevalence of psychoactive medicinal drug use incresead substantially...” Therefore, the authors could explain why there is no association between multimorbidity and psychological distress? Have younger adults shown a higher prevalence of psychological distress compared to older adults that could be associated to the use of substance (regarding illicit drugs or alcohol use)?

**Response**

Thank you for this good argument, this might be the reason to it, however the decrease in the prevalence of psychological distress with age was not that drastic (this was not shown in this draft but is included now, see the paragraph underneath). Similar scenario was observed for risky alcohol use as well with the young patients (18-34years: 8.9%) having as low alcohol consumption as those aged 65-79 years (8.7%) and prevalence of risky alcohol use was the highest among patients aged 35-49 years and 50-64 years (12.7% and 12.1%). Now that we have added all the prevalences to the text we hope to have elucidated this better.

The paragraph added to the section 3.Results is altered to include all prevalences as you suggest on your comment number 9):

“Of the young patients (18-34 years) 35.0% were multimorbid (Table 1). Of these, 40.3% used alcohol above the recommended guidelines, 12.6% used it hazardously and 8.9% in a risky manner. Prevalence of risky alcohol use was higher among patients aged 35-49 years and 50-64 years (12.7% and 12.1%) and decreased slightly for those aged 65-79 years (8.7%). Of the young multimorbid patients (18-34 years) 14.1% used illicit drugs, 14.1% used psychoactive medicinal drugs and 31.4% reported to have psychological distress. Among multimorbid patients by the age of ≥ 35 the prevalence of psychological distress decreased (For those aged 35-49 years the prevalence was 30.2%; for those 50-64 years it was 26.3%; 65-79 years 23.9% and for those > 80 years it was

13.8%), while the prevalence of psychoactive medicinal drug use increased substantially (For those aged 35-49 years the prevalence was 32.6%; for those 50-64 years it was 45.4%; 65-79 years 43.8% and for those > 80 years it was 41.2%). Illicit drugs were most prevalent among those aged 35-64 years (16.9%) and decreased substantially for the older patients (for those 50-64 years it was 10.7%; 65-79 years 1.3% and for those > 80 years it was 0.8%).”

This is also further elaborated with a new paragraph on alcohol use and adverse events with psychoactive medicinal substances among the elderly in the Discussion section.

18) On page 13, lines 40-60 (Subsection: Limitation) The authors should report the main limitation of a cross-sectional study, i.e. “the lack of time dimension limits the ability to make causal inference”. Temporal relationship may not be clear. So it is useful for hypotheses generating, but ability to test hypothesis will depend on the exposure.

**Response:**

We agree on your comment and have added this to the limitation section as you suggest.

**Other changes:**

- 1) The age categories were slightly corrected without any impact on the percentages or anything else, as follows:

Originally, in the first draft they were depicted as follows in Table 1 and Table 2, and in the body of the manuscript:

18-35
36-50
51-65
66-80
> 80

They were corrected to:

18-34
35-49
50-64
65-79
≥ 80

These corrections were made in the body of the manuscript as well, where the age groups were mentioned in section 3. Results.

- 2) The first paragraph of section 4.Discussion was slightly modified to include the association between multimorbidity and psychological distress found in our main analysis. The Conclusion paragraph in the abstract was slightly modified as well, in the same manner.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Marcus Borges Universidade de Sao Paulo Hospital das Clinicas, Psychiatry
<b>REVIEW RETURNED</b>	19-Oct-2021
<b>GENERAL COMMENTS</b>	The authors have addressed all my comments. Therefore, I recommend their manuscript for publication (Accept).