PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of combined exercise in people with type 2 diabetes and concurrent overweight/ obesity: a systematic review and meta-analysis
AUTHORS	Zhao, Xiaoyan ; He, Qianyu; Zeng, Yongmei; Cheng, Li

VERSION 1 – REVIEW

REVIEWER	Joseph, Nitha University of Texas Health Science Center at Houston
REVIEW RETURNED	04-Dec-2020

GENERAL COMMENTS	Very well written manuscript. Abstract : More information on methods can be included. Methods: For the systematic review to be according to the Cochrane Handbook, at least one gray literature source need to be searched. Did you use the Cochrane Handbook - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedures for the reporting purpose in method section ?

REVIEWER	Sigal, Ronald Ottawa Hospital
REVIEW RETURNED	18-Jan-2021

GENERAL COMMENTS	GENERAL COMMENTS This is a systematic review of randomized controlled trials evaluating effects of combined aerobic and resistance exercise. Because the authors stipulated (as far as I can tell) that body mass index needed to be above ethnicity-specific cutpoints for all participants for a study to be included, two of the largest, most important and most-cited trials evaluating combined exercise in type 2 diabetes were excluded (Church TS, JAMA 2010 and Sigal RJ, Ann Intern Med 2007), even though the vast majority of participants in both of these trials met criteria for overweight or obesity. While I understand that authors should not retroactively change inclusion/exclusion criteria for a systematic review, I think it would be very desirable for the authors to do a sensitivity analysis including these two trials. These two key trials, and how they would have influenced results if included, should also be mentioned in the discussion. I acknowledge my potential conflict of interest as the lead author of one of these trials.

	There are numerous errors in English usage reflecting a need for review and proofreading of the article by a native English speaker; this should ideally have been done prior to submission. SPECIFIC COMMENTS 1. On the first page of the pdf (title page with “BMJ Open” at the top, the first and last names of the first author should be capitalized. 2. I suggest changing the title to “Effects of combined exercise in people with type 2 diabetes and overweight or obesity: a systematic review and meta-analysis”. The phrase “overweight or obese type 2 diabetes” is not correct English. 3. Major professional associations and patient groups prefer that people with high BMI be described as “people with obesity” rather than “obese people”. This applies throughout the paper. 4. Page 3 line 27-28: delete “the concentration of” before HbA1c; it should read “…significantly reduced hemoglobin A1c”. 5. Page 3, lines 50-53 “To our knowledge, this is the first systematic review and meta-analysis of RCTs investigating the effects of combined exercise on overweight/obese patients with T2D.” I would not consider this much of an advance; there have been several high-quality meta-analyses including the effects of combined exercise on the same outcomes examined here, and the great majority of participants in all the studies included in these earlier meta-analyses met criteria for overweight or obesity. 6. Page 4, lines 22-28 “Although we performed subgroup analyses, the subgroup of <150 min/week in exercise duration and the subgroups of 3 weeks and 52 weeks in exercise intervention time were addressed in only one study, which may have caused the deviation of results.” I found this sentence very difficult to follow. Please reword it with greater clarity. 7. Page 4 lines 50-54 “Furthermore, obesity accounts for 50.9–98.6% of adults with T2D in Europe and 56.1% in Asia.” What do you mean by this? Do you mean that obesity causes these percentages of type 2 diabetes, or that these are the percentages of people with T2D who meet criteria for overweight or obesity? 8. Page 5 line 11-12 “…not many options are available for those with T2D and overweight/obesity”. What do you mean by this? There are numerous types of physical activity, numerous dietary approaches and numerous classes of medications that are suitable for people with type 2 diabetes who are above their ideal weight. 9. Page 6, lines 30-33 “Resistance exercise can enhance muscle strength, which in turn improves insulin sensitivity”. I know of no evidence of a causal relationship between muscle strength per se and insulin sensitivity. It is more likely that resistance exercise increases strength and also increases insulin sensitivity, without strength being in the causal pathway. 10. Page 7, lines 24-28 “(2) overweight or obesity was indicated by body mass index (BMI≥25 kg/m2 for Caucasians…or BMI≥25 kg/m2 for Asian subjects”. Does this mean that every single participant in all included studies met these criteria? 11. Page 7 lines 32-38: Please provide definitions of aerobic exercise and resistance exercise. Currently you provide examples but not definitions. 12. Page 9, last line: change “random effect” to “random effects”.

	13. ¬Page 13 line 51: change “the value of serum insulin” to “serum insulin” or “serum insulin level”. 14. Page 14 line 43: change “BMI concentration” to “BMI”. There is no such thing as a concentration of BMI. 15. Page 17, line 42 “exercise achieved a pronounced decrease in BMI”. I’m not sure that a BMI decrease of about 1 kg/m2 qualifies as “pronounced” even though it is statistically and clinically significant. 16. Page 18 line 34 “…overweight/obesity were more likely to have poor BP and lipid control”. If this is the case, one would expect to see a greater effect of the intervention, not a lesser one. 17. Page 19, lines 31-34: What do you mean by making exercise more “efficient”? 18. Page 20 lines 39-45 “According to the features of effective exercise interventions on glycemic and weight control among included studies, most researches performed center-based exercise with supervision.” I find this sentence difficult to understand; please reword it for greater clarity. By “researches” I think you mean “research studies”. 19. Page 19, lines 47-50 “Objective measures such as pedometers and accelerometers”. These methods are unsuitable for assessing resistance exercise. 20. Pages 30-33: These show raw RevMan output, and the font is too small to be readable easily.

REVIEWER	Montazeri, Ali Iranian Institute for Health Sciences Research, ACECR, Mental Health
REVIEW RETURNED	23-Feb-2021

GENERAL COMMENTS	This is an interesting review and meta-analysis of the literature on the effectiveness of combined exercise on overweight or obese type 2 diabetes. In all 10 randomized trials were included and the results were reported accordingly. Overall the review and the analysis are well done and it merits publication. My only comment relates to sub-group analysis. As the authors indicated since the number of studies is not enough, I recommend removing sub-analysis for exercise duration and intervention time.

REVIEWER	Zsakai, Annamaria Eotvos Lorand Univ
REVIEW RETURNED	20-Mar-2021

GENERAL COMMENTS	General remarks The paper represents an effort to analyse the effect of combined exercise intervention on BMI and T2D parameters. The topic of the manuscript is of high importance, since the prevalence of T2D is still increasing both in adults and subadults. The aim of the study was clearly defined and the data were analysed according to the research purposes. I recommend to accept this paper for publication in BMJ Open after a minor revision. Only the structure of the manuscript should be changed a bit (too long Discussion and too short Results section, results are introduced in the Discussion section).

	I list my minor comment in the order of the sections of the manuscript. Minor remarks and suggestions Material and methods M1: „comparison groups included placebo, any format of exercise intervention, or usual care." – please make it clear what kind of placebo effect could appear in control groups (if they did not use any exercise intervention) M2: please make it clear what primary and what secondary outcomes mean in this context – why HbA1c was considered a primary, and why for example HDL-C was considered a secondary outcome? Results R1: "the mean (SD) HbA1c ranged from 6.44 (0.33) to 9.50 (0.90); and the mean (SD) BMI ranged from 28.15 (3.72) to 39.9 (7.3) kg/m2." – these are the baseline data? Please indicate that these values were estimated for the beginning point of the interventions. R2: "subgroup of <150 min/week favored the intervention group with a lower BMI concentration than the control group …" – please correct this sentence, concentration is not the right expression here. R3: the same sentence: this sentence should be revised to help its understanding R4: "Subgroup analysis (exercise frequency)" – why not mention the subgroup with more than 3 active days a week from this aspect? How can we explain the lack of influence of intervention? R5: "Subgroup analysis (exercise intervention time)" – why only one subgroup is mentioned again? I see, it could not be described effect of intervention on the studied parameters in the other subgroups, but why not mention these data? I know that these subgroups are mentioned in the Discussion section, but the Readers would like to see the evaluation of results together in the Results section. Discussion D1: The Discussion section is too long, some parts (evaluation of effect of intervention in subgroups) should be moved to Results, see RR4 and R5 comments.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Nitha Joseph, University of Texas Health Science Center at Houston

Abstract: More information on methods can be included.
Response: Thank you for your kind comments. We now have included the bias assessment, search dates and databases in the abstract.

Methods: For the systematic review to be according to the Cochrane Handbook, at least one gray literature source need to be searched.
Response: Thank you very much for pointing it out. We now have searched ClinicalTrials.gov and OpenGrey for unpublished studies, 113 and 130 records were identified, respectively. But none of these studies fulfilled the eligibility criteria and was included in our meta-analysis. 'Search strategy' in the methods section, 'Search outcome' in the results section, and Figure 1- 'Flow chart for study selection according to PRISMA Declaration 2009' were also revised accordingly to reflect the integration of searching in grey literature databases.

Did you use the Cochrane Handbook - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedures for the reporting purpose in method section?
Response: Yes, the PRISMA procedures was used in the methods section, we have also added a sentence "This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement" in the method section (see P6L14-17). And the updated PRISMA 2020 checklist was added as a supplementary file in our revised manuscript, the relevant information can be found in the PRISMA 2020 checklist.

Reviewer: 2
Dr. Ronald Sigal, Ottawa Hospital

Response: Thank you very much for your comments. The authors agree that some important RCTs were excluded due to our strict inclusion criteria. The authors fully respect your opinions, and we have considered your suggestion carefully, we now have added related content about Sigal RJ, Ann Intern Med 2007 in the discussion section (see P17L6-18) as following:
…The pooled effect of combined exercise in patients with T2D and concurrent overweight/obesity, however, seems to be much lower than that reported in the first adequately powered RCT that examined the effects of aerobic, resistance, and combined exercise in people with T2D. Sigal and colleagues found a pronounced reduction (0.9%) in HbA1c with combined exercise. Such discrepancy might be attributed to the long exercise duration (210−270 min/week) of the combined exercise program, in which participants performed intensive aerobic training program (75−135min/week) as well as resistance training program (135min/week).

We have also added the limitation section and stated the weakness that some well conducted and important RCTs were excluded owing to our strict inclusion criteria. Some important RCTs that determining the effect of combined exercise in people with T2D but did not focus on obesity (Church TS, JAMA 2010, ect.) have been cited in this area.

However, since the two articles you mentioned above did not make it clear the T2D patients were overweight/obese or not, which did not meet our inclusion criteria, we cannot include these articles in our meta-analysis although they are most-cited RCTs in this area. And the central notion of sensitivity analysis is excluding influential studies and outliers instead of including other similar studies. We have also searched all meta-analyses published in BMJ Open, there is no sensitivity analysis including other studies, so we are sorry we did not do the sensitivity analysis in the manuscript. But we did the analyses on primary outcomes by including the two trials in this reply. The results did not change the significance, indicating that the results were robust. Detailed results are as following:

Variables Study included Number of

included studies Sample size (EX) Sample size (CON) Mean Difference (95% CI) P I2
HbA1c the original meta-analysis 9 457 424 -0.16(-0.28, -0.05) 0.006 28%
Church 2010 10 533 498 -0.36(-0.40, -0.33) <0.001 61%
Sigal 2007 10 515 516 -0.20(-0.31, -0.08) <0.001 52%
BMI the original meta-analysis 8 445 413 -0.98(-1.41, -0.56) <0.001 0%
Sigal 2007 9 509 508 -0.98(-1.40, -0.56) <0.001 0%

There are numerous errors in English usage reflecting a need for review and proofreading of the article by a native English speaker; this should ideally have been done prior to submission.
Response: Thank you for pointing it out. We have sought for English editing service to improve the readability of the article.

SPECIFIC COMMENTS
1. On the first page of the pdf (title page with “BMJ Open” at the top, the first and last names of the first author should be capitalized.
Response: Done accordingly.

2. I suggest changing the title to “Effects of combined exercise in people with type 2 diabetes and overweight or obesity: a systematic review and meta-analysis”. The phrase “overweight or obese type 2 diabetes” is not correct English.
Response: Thank you for your suggestion. We have revised the title to “Effectiveness of combined exercise in people with type 2 diabetes and concurrent overweight/ obesity: a systematic review and meta-analysis”.

3. Major professional associations and patient groups prefer that people with high BMI be described as “people with obesity” rather than “obese people”. This applies throughout the paper.
Response: Done accordingly throughout the paper.

4. Page 3 line 27-28: delete “the concentration of” before HbA1c; it should read “…significantly reduced hemoglobin A1c”.
Response: The word has been deleted accordingly.

5. Page 3, lines 50-53 “To our knowledge, this is the first systematic review and meta-analysis of RCTs investigating the effects of combined exercise on overweight/obese patients with T2D.” I would not consider this much of an advance; there have been several high-quality meta-analyses including the effects of combined exercise on the same outcomes examined here, and the great majority of participants in all the studies included in these earlier meta-analyses met criteria for overweight or obesity.
Response: Thank you for your comments. We have deleted this sentence.

6. Page 4, lines 22-28 “Although we performed subgroup analyses, the subgroup of <150 min/week in exercise duration and the subgroups of 3 weeks and 52 weeks in exercise intervention time were addressed in only one study, which may have caused the deviation of results.” I found this sentence very difficult to follow. Please reword it with greater clarity.
Response: We are sorry we did not make this sentence clear. What we meant is—in subgroup analysis of exercise duration, the subgroup of <150 min/week only had one study; in subgroup analysis of exercise intervention time, the subgroups of 3 weeks and 52 weeks only had one study, respectively. This situation

may cause the deviation of results. One of the reviewers also pointed this problem, and recommended that we deleted these subgroup analyses, so we now have removed sub-analyses for exercise duration and intervention time after discussion on team members. This sentence has also been deleted.

7. Page 4 lines 50-54 “Furthermore, obesity accounts for 50.9–98.6% of adults with T2D in Europe and 56.1% in Asia.” What do you mean by this? Do you mean that obesity causes these percentages of type 2 diabetes, or that these are the percentages of people with T2D who meet criteria for overweight or obesity?
Response: Yes, these are the percentages of people with T2D who meet criteria for overweight or obesity according to data from WHO. The purpose of this sentence here is to highlight that the proportion of obesity is relatively high in T2D patients, and the coexistence of obesity and diabetes put pressure on individuals and healthcare system, so this group of people needs more attention, this is also the reason why we focus on this group of people.

8. Page 5 line 11-12 “…not many options are available for those with T2D and overweight/obesity”. What do you mean by this? There are numerous types of physical activity, numerous dietary approaches and numerous classes of medications that are suitable for people with type 2 diabetes who are above their ideal weight.
Response: Thank you for pointing it out. We apologize for this statement, what we meant is- although there are guideline recommendation and exercise options for people T2D or excess weight, people with T2D and concurrent overweight/obesity received little attention. We have revised this sentence to “Although various exercise options are available for individuals with either T2D or excess weight, individuals with T2D and concurrent overweight/obesity receive little attention.”.

9. Page 6, lines 30-33 “Resistance exercise can enhance muscle strength, which in turn improves insulin sensitivity”. I know of no evidence of a causal relationship between muscle strength per se and insulin sensitivity. It is more likely that resistance exercise increases strength and also increases insulin sensitivity, without strength being in the causal pathway.
Response: Thank you for your comments. We now have revised this sentence to “Resistance exercise can enhance muscle strength, insulin sensitivity and muscle rehabilitation”.

10. Page 7, lines 24-28 “(2) overweight or obesity was indicated by body mass index (BMI≥25 kg/m2 for Caucasians…or BMI≥25 kg/m2 for Asian subjects”. Does this mean that every single participant in all included studies met these criteria?
Response: Yes, the authors in these studies had included BMI as their inclusion criteria, every single subject in all included studies was overweight/obese, so the participants also met the inclusion criteria in our meta-analysis.

11. Page 7 lines 32-38: Please provide definitions of aerobic exercise and resistance exercise. Currently you provide examples but not definitions.
Response: Thank you for your comments. We have added the definition of combined exercise, aerobic exercise, and resistance exercise in the introduction section (P5L17-25): Combined exercise involves aerobic exercise (repeated and continuous movement of large muscle groups when oxygen supply is sufficient) and resistance exercise (a strength-training workout that uses some form of resistance or tension) performed within the same or separate exercise sessions of a training program.

12. Page 9, last line: change “random effect” to “random effects”.
Response: Done accordingly.

13. ¬Page 13 line 51: change “the value of serum insulin” to “serum insulin” or “serum insulin level”.
Response: This word has been changed to “serum insulin”.

14. Page 14 line 43: change “BMI concentration” to “BMI”. There is no such thing as a concentration of BMI.
Response: Done accordingly.

15. Page 17, line 42 “exercise achieved a pronounced decrease in BMI”. I’m not sure that a BMI decrease of about 1 kg/m2 qualifies as “pronounced” even though it is statistically and clinically significant.
Response: We have revised this sentence to “…combined exercise achieved a statistically and clinically significant decrease in BMI…”.

16. Page 18 line 34 “…overweight/obesity were more likely to have poor BP and lipid control”. If this is the case, one would expect to see a greater effect of the intervention, not a lesser one.
Response: Thank you for your comments. The main purpose of this sentence here is to explain the difference between the result of Albalawi, Bersaoui, and our study. We apologize for the inaccurate statement. This sentence now has been revised to “…combined exercise may have limited effect on BP and lipid control in people with T2D and concurrent overweight/obesity”. We have also added the statement “…Low-grade metabolic inflammation in this group of people can induce changes in the neural mechanisms (e.g., hypothalamic-pituitary-adrenal axis), which in turn damage the cognitive function of individuals. Cognitive impairments further attenuate individuals’ motivation and ability to engage in self-management activities and maintain therapeutic lifestyles...” to further explain the different result. (see P18L42-58)

17. Page 19, lines 31-34: What do you mean by making exercise more “efficient”?
Response: Sorry for the inaccurate statement. What we meant is—the effect of exercise intervention might be amplified with additional interventions (physical activity counseling and diet adherence). This sentence now has been revised to “…Additionally, Balducci even implemented diet management in addition to physical activity counseling. Thus, the results of subgroup analysis should be interpreted with caution.”. The structure of this paragraph has also been adjusted to make it more organized. (see P19)

18. Page 20 lines 39-45 “According to the features of effective exercise interventions on glycemic and weight control among included studies, most researches performed center-based exercise with supervision.” I find this sentence difficult to understand; please reword it for greater clarity. By “researches” I think you mean “research studies”.
Response: Thank you for your comments. This sentence has been revised to “According to the features of effective exercise interventions among the included studies, most research studies performed center-based exercise with supervision.”

19. Page 19, lines 47-50 “Objective measures such as pedometers and accelerometers”. These methods are unsuitable for assessing resistance exercise.
Response: Thank you for your comments. This sentence has been deleted.

20. Pages 30-33: These show raw RevMan output, and the font is too small to be readable easily.
Response: Thank you for your comments. We have reedited these pictures to be more readable.

Reviewer: 3
Prof. Ali Montazeri, Iranian Institute for Health Sciences Research, ACECR

Response: Thank you for your kind comments. Indeed, the number of studies is insufficient to undertake some types of subgroup analyses, which might cause the deviation of the results. We now have removed sub-analyses for exercise duration and intervention time accordingly. The related information in the methods, results and discuss section has also been deleted.

Reviewer: 4
Dr. Annamaria Zsakai, Eotvos Lorand Univ

Minor remarks and suggestions

Material and methods
M1: „comparison groups included placebo, any format of exercise intervention, or usual care." – please make it clear what kind of placebo effect could appear in control groups (if they did not use any exercise intervention)
Response: Thank you very much for your comments. We now have revised this sentence to "potential comparison groups included any format of exercise intervention, general health counseling, or usual care." (see P6L46-48)

M2: please make it clear what primary and what secondary outcomes mean in this context – why HbA1c was considered a primary, and why for example HDL-C was considered a secondary outcome?
Response: Thank you for your comments. In this study, patients with T2D and concurrent overweight/obesity are our research subjects. We pay more attention to the effect of combined exercise on glycemic control and weight loss, we have also indicated this objective in the introduction section (P5L4-6,L46-50). thus, primary outcomes in our study are HbA1c and BMI, and other clinical indicators are secondary outcomes.
Moreover, HbA1c is widely recognized as the golden standard in the assessment of diabetes treatments and interventions. we have also added the statement "It is important to mention that a 1% absolute reduction in HbA1c is associated with a 21% reduction in the risk of any end point or death related to diabetes" in the discussion section to show the importance of HbA1c and indicate it is a primary outcome. As for BMI, it has been widely used due to its convenience, safety, and minimal cost. Many associations (e.g., WHO, CDC, IOTF) defines obesity by BMI. Therefore, we used HbA1c and BMI as primary outcomes.

Results
R1: "the mean (SD) HbA1c ranged from 6.44 (0.33) to 9.50 (0.90); and the mean (SD) BMI ranged from 28.15 (3.72) to 39.9 (7.3) kg/m2." – these are the baseline data? Please indicate that these values were estimated for the beginning point of the interventions.
Response: Yes, these are baseline data. We now have revised this sentence to "the baseline mean (SD) HbA1c ranged from 6.44 (0.33) to 9.50 (0.90); and the baseline mean (SD) BMI ranged from 28.15 (3.72) to 39.9 (7.3) kg/m2".

R2: "subgroup of <150 min/week favored the intervention group with a lower BMI concentration than the control group …" – please correct this sentence, concentration is not the right expression here.

Response: We apologize for the wrong expression. Due to only one study was included in the subgroup with exercise duration <150 min/week, one of the reviewers recommended us to delete the subgroup analysis of exercise duration, this sentence has been deleted.

R3: the same sentence: this sentence should be revised to help its understanding
Response: Thank you for your comments. Due to the insufficient number of study (only one) in subgroup of <150 min/week, the subgroup analysis (exercise duration) has been deleted, and this sentence has also been removed.

R4: “Subgroup analysis (exercise frequency)” – why not mention the subgroup with more than 3 active days a week from this aspect? How can we explain the lack of influence of intervention?
Response: Thank you for pointing it out. We now have added the result of subgroup with more than 3 active days a week in subgroup analysis (exercise frequency)—'while combined exercise with frequency ≥3 days/week had no effect on HbA1c (MD=0.03%, 95%CI: -0.45 to 0.51, P=0.90) and BMI (MD=0.18 kg/m2, 95%CI: -1.34 to 1.71, P=0.81)’. We have explained such results in the discussion section (see P19L18-42): …subjects in the studies with exercise frequency more than 3 days/week tended to perform short-duration exercise (3 weeks, 12 weeks), which was likely not enough to make a difference in outcomes. While subjects in the study with exercise frequency less than 3 days/week had been offered with long-term (48 weeks) exercise under supervision. Long-term exercise sessions and professional supervision were identified as important factors associated with prominent improvement of glycemic and weight control…

R5: “Subgroup analysis (exercise intervention time)” – why only one subgroup is mentioned again? I see, it could not be described effect of intervention on the studied parameters in the other subgroups, but why not mention these data? I know that these subgroups are mentioned in the Discussion section, but the Readers would like to see the evaluation of results together in the Results section.
Response: Thank you for your comments. The authors agree that all subgroups should be mentioned. In the original manuscript, we considered that the results section might be too long if we presented all the positive and negative results, so we only presented the result in subgroup of 48 weeks.
Because the subgroups of 3 weeks, and 52 weeks in exercise intervention time only included one study, which might cause the deviation of the results, and one of the reviewers recommended us to delete the subgroup analysis of exercise intervention time, we now have deleted the subgroup analyses of exercise intervention time after discussion on team members. The related information in the results and discuss section has also been deleted.

Discussion
D1: The Discussion section is too long, some parts (evaluation of effect of intervention in subgroups) should be moved to Results, see RR4 and R5 comments.
Response: Thank you for your comments. Due to the insufficient number of studies in some subgroups, we now have deleted the subgroup analyses of exercise duration and exercise intervention time according to suggestion of reviewer 3# and team discussion, the related information in the results and discuss section has also been deleted. As for subgroup analysis of exercise frequency, we have added the result of subgroup with ≥3 days/week in the results section. We have also revised some parts of the discussion to be more organized. Now the discussion section has become more concise.

VERSION 2 – REVIEW

REVIEWER	Sigal, Ronald Ottawa Hospital
REVIEW RETURNED	07-Jun-2021

GENERAL COMMENTS	I am satisfied with the authors' responses to reviewers' comments and with the revised manuscript. The manuscript is now far better-written than it was originally; it has benefitted from good editing.

REVIEWER	Montazeri, Ali Iranian Institute for Health Sciences Research, ACECR, Mental Health
REVIEW RETURNED	12-Jun-2021

GENERAL COMMENTS	My comments were attended. No further comments.

REVIEWER	Zsakai, Annamaria Eotvos Lorand Univ
REVIEW RETURNED	29-May-2021

GENERAL COMMENTS	I have read the revised manuscript, thank you, all my requests were done. I suggest accepting the revised manuscript for publication in BMJ Open.