PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between Dyslipidemia and Risk of Type 2 Diabetes Mellitus in Middle-aged and Older Chinese Adults: a Secondary Analysis of a Nationwide Cohort
AUTHORS	Peng, Jieru; Zhao, Fei; Yang, Xue; Pan, Xiongfei; Xin, Jue; Wu, Mengjun; Peng, Yong G

VERSION 1 – REVIEW

REVIEWER	Vasilios ATHYROS Aristotle University, Thessaliniki, GREECE
REVIEW RETURNED	29-Aug-2020

GENERAL COMMENTS	The original research paper bmjopen-2020-042821 entitled "Association between Dyslipidemia and Risk of Type 2 Diabetes Mellitus in Middle-aged and Older Chinese adults: A Retrospective Cohort Study" has relevance to the scope and the audience of bmj. This paper aimed to evaluate the type 2 diabetes mellitus (T2DM) risk of individuals with different types of dyslipidemia and compare the predictive value of distinct lipid parameters in predicting T2DM. The authors suggest that middle-aged and elderly adults with hypertriglyceridemia, hypercholesterolemia and low HDL-C were at higher risk for developing diabetes, also non-HDL-C, TG, TC/HDL and TG/HDL have greater performance than other lipid parameters in predicting T2DM incidence. Major comments for the authors 1. The text, the tables, the supplementary staff and the figures are of appropriate length and informative. 2. The paper is well written. 3. References are up to date. 4. The results of the paper has practical implications.

REVIEWER	Aleksandra Klisic Primary Health Care Center, Podgorica, Montenegro
REVIEW RETURNED	22-Sep-2020

GENERAL COMMENTS	# Review In the present study the Authors aimed to evaluate the type 2 diabetes mellitus (T2DM) risk of individuals with different types of

	dyslipidemia and compare the predictive value of distinct lipid parameters in predicting T2DM. This is the important topic and can add significant contribution to other researches in this field. The manuscript is well written and the data justify the conclusions. Minor corrections: - Some minor typographical and grammatical errors need correction. - The units for blood pressure in supplemental figures are missing.

REVIEWER	Richard Stevens University of Oxford
REVIEW RETURNED	07-Dec-2020

GENERAL COMMENTS	The title is not quite right: this is not a retrospective cohort study. This is a prospective study. Exposures were measured prospectively, before follow-up. Acronyms such as TG, LDL-C etc. should be defined at their first use in the text. In section 2.3, there is mention that “investigators would confirm the [diagnosis of diabetes] in the next interview”. How is this used? In particular, what happened if a study participant said yes at one interview, but no at the next interview? Be aware that stepwise variable selection is no longer favoured, because it is associated with bias (see for example “Regression modelling strategies” by Frank Harrell Jr). Protocol-specified adjustment strategies are preferred. However, this is not likely to seriously affect the conclusions of the paper. Page 10: “The statistically significant association between LDL-C and T2DM did not observed in our study (p=0.396)”. But according to Table 3, LDL-C is predictive (AUC significantly above 0.5). In Table 1, consider using median and quartiles instead of mean (SD), especially for variables such as triglycerides that are usually skewed. For the t-tests in Table 1, skewed variables such as triglycerides should be log-transformed. In Table 2, it is sufficient to give hazard ratios to two decimal places e.g. 1.33 (1.08 to 1.65). On page 23, lines 6-8, the recommendation “lipids control should be considered as an effective strategy for primary prevention of diabetes” is not justified. This observational analysis cannot prove that risk factor modification is an effective strategy. In fact, in statin trials, lipid control with statins causes increased risk of diabetes: see Sattar et al., Lancet 2010. The last sentence of the Discussion is a problem for the same reason. Regarding the remark “Blood lipid profiles are important indexes in predicting risk of T2DM”: is this remark justified? In particular, do the modest AUC values in this study justify the word “important”? Next remark, about “the predictive power of lipid panels combined with conventional T2DM risk factors have not been compared.” Is that true? I am surprised to find that the authors of QDScore did not even consider cholesterol; but what about the authors of other scores for diabetes such as FINDRISC etc? See https://bmjopen.bmj.com/content/5/7/e007195. If it is true that none of the well-known scores for diabetes considered inclusion of lipids, then that is worth saying. The Discussion needs to be completely re-written, because at the moment the sentences claiming novelty (e.g. “this current study was the first to compare the predictive power of different lipid profiles”, “the predictive power of lipid panels combined with

	conventional T2DM risk factors have not been compared") seem to contradict other sentences such as "The important role of non-HDL-C in predicting T2DM was also emphasized by recently other studies" and so on. Similarly, the Introduction needs to be completely re-written to avoid apparent contradictions between sentences claiming novelty (e.g. "Overall, the risk of diabetes in people with dyslipidemia has not been clearly elucidated") and sentences claiming what is already known (e.g. "Dyslipidemia have recently been recognised as a risk factor for T2DM", and many other remarks.

VERSION 1 – AUTHOR RESPONSE

Comments of reviewer: 1
Dr. Vasilios Athyros, Aristotle University of Thessaloniki
The original research paper bmjopen-2020-042821 entitled "Association between Dyslipidemia and Risk of Type 2 Diabetes Mellitus in Middle-aged and Older Chinese adults: A Retrospective Cohort Study" has relevance to the scope and the audience of bmj.
This paper aimed to evaluate the type 2 diabetes mellitus (T2DM) risk of individuals with different types of dyslipidemia and compare the predictive value of distinct lipid parameters in predicting T2DM.
The authors suggest that middle-aged and elderly adults with hypertriglyceridemia, hypercholesterolemia and low HDL-C were at higher risk for developing diabetes, also non-HDL-C, TG, TC/HDL and TG/HDL have greater performance than other lipid parameters in predicting T2DM incidence.
Major comments for the authors
1. The text, the tables, the supplementary staff and the figures are of appropriate length and informative.
2. The paper is well written.
3. References are up to date.
4. The results of the paper has practical implications.
Response: Sincerely thank the reviewer for the positive comments concerning our article and hard work.

Comments of reviewer: 2
Dr. Aleksandra Klisic, Primary Health Care Center, Podgorica, Montenegro
Review
In the present study the Authors aimed to evaluate the type 2 diabetes mellitus (T2DM) risk of individuals with different types of dyslipidemia and compare the predictive value of distinct lipid parameters in predicting T2DM.
This is the important topic and can add significant contribution to other researches in this field. The manuscript is well written and the data justify the conclusions.
Minor corrections:
- Some minor typographical and grammatical errors need correction.
Response: Thanks for reviewer's suggestion. We carefully reexamined the full text of our paper and corrected typographical and grammatical errors. We hope that the correction will meet with approval.
- The units for blood pressure in supplemental figures are missing.
Response: We added the units for blood pressure into the supplemental figures. And the revised figures have been uploaded again in the attachment.

Comments of review: 3
Dr. Richard Stevens, University of Oxford
1.The title is not quite right: this is not a retrospective cohort study. This is a prospective study. Exposures were measured prospectively, before follow-up.
Response: Thank the reviewer for the helpful comments. As reviewer suggested, we corrected the title of our study as a prospective cohort study. We confused retrospective cohort study with prospective cohort study in our previous manuscript. Actually, in a retrospective cohort study, the grouping of the research subjects is based on the historical materials about the exposure status of the subjects at a certain point in the past. But the exposures in our study, namely, concentrations of four classical serum lipid indices, were tested from blood samples stored in the freezer after the China Health and Retirement Longitudinal Study (CHARLS) commenced. So the design of our study should be a prospective study.

2.Acronyms such as TG, LDL-C etc. should be defined at their first use in the text.
Response: Thanks for the reviewer's reminder. The definitions of acronyms were added into the revised manuscript when they firstly occurred in the paper, including total cholesterol (TC) on page 6, line 40; triglyceride (TG) on page 6, line 40; low density lipoprotein cholesterol (LDL-C) on page 6, line 46; high density lipoprotein cholesterol (HDL-C) on page 6, line 46 and body mass index (BMI) on page 9, line 33.

3.In section 2.3, there is mention that "investigators would confirm the [diagnosis of diabetes] in the next interview". How is this used? In particular, what happened if a study participant said yes at one interview, but no at the next interview?
Response: If a participant said he or she had diabetes in the first interview but denied in the second interview, the participant was not considered as T2DM patient. We had to admit that one of our study's limitations was that case of diabetes was defined by interviewee's self-report , lacking of clinical evaluation may lead to discrepancy with the actual situation. So we used the second confirmation to ensure the authenticity of their health status as far as possible.

4.Be aware that stepwise variable selection is no longer favoured, because it is associated with bias (see for example "Regression modelling strategies" by Frank Harrell Jr). Protocol-specified adjustment strategies are preferred. However, this is not likely to seriously affect the conclusions of the paper.
Response: Thanks for reviewer's professional advice. We did not notice the limitation of stepwise regression during the analysis, and we will be careful about this in other research.

5.Page 10: "The statistically significant association between LDL-C and T2DM did not observed in our study (p=0.396)". But according to Table 3, LDL-C is predictive (AUC significantly above 0.5).
Response: In page 10, we described "The statistically significant association between LDL-C and T2DM did not observed in our study (p=0.396)". The P value indicate that the coefficient of LDL-C (1.27×10-3 ,95CI% -1.66×10-3—4.19×10-3) in the full adjusted model (model 3) is not significant. In table 3, the AUC of LDL-C represented the prediction value of the full adjusted model which contained LDL-C, not for LDL-C only. The AUC significantly above 0.5 mainly attributed to the effect of other risk factors included in the full adjusted model. Other risk factors contained age, gender, waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, C reactive protein, plasma glucose, cigarette smoking, and alcohol drinking.

6.In Table 1, consider using median and quartiles instead of mean (SD), especially for variables such as triglycerides that are usually skewed. For the t-tests in Table 1, skewed variables such as triglycerides should be log-transformed.
Response: As reviewer suggested, we replaced mean (standard deviation) with median (interquartile

range) if variables were non-normal distribution and the skewed variables were compared after logarithmic transformation. The reanalyzed results are shown in Table 1. We previously thought that skewed variables can be approximately regarded as normal distribution since the sample size is large enough, but this viewpoint seemed unreasonable. So we adjusted the analysis method of skew distribution data.

7.In Table 2, it is sufficient to give hazard ratios to two decimal places e.g. 1.33 (1.08 to 1.65).
Response: The hazard ratios and interval confidences were accurate to two decimal places.

8.On page 23, lines 6-8, the recommendation “lipids control should be considered as an effective strategy for primary prevention of diabetes” is not justified. This observational analysis cannot prove that risk factor modification is an effective strategy. In fact, in statin trials, lipid control with statins causes increased risk of diabetes: see Sattar et al., Lancet 2010. The last sentence of the Discussion is a problem for the same reason.
Response: Thanks for reviewer’s suggestion, we had re-written these two sentences. The sentence on page 23, lines 6-8, "lipids control should be considered as an effective strategy for primary prevention of diabetes" was corrected as " dyslipidemia may be a risk factor for T2DM ."
The sentence on page 25, lines 36-39,"These findings emphasize a strategic approach for continuing efforts to control cholesterol level in middle-aged and elderly adults in prevention of development of T2DM" was corrected as "These findings provide more data for the future effective prevention of T2DM to support. "

9.Regarding the remark “Blood lipid profiles are important indexes in predicting risk of T2DM”: is this remark justified? In particular, do the modest AUC values in this study justify the word “important”?
Response: We agreed with review’s suggestion, so we deleted the word "important" since the modest AUC values in this study could not justify the word "important".

10.Next remark, about “the predictive power of lipid panels combined with conventional T2DM risk factors have not been compared.” Is that true? I am surprised to find that the authors of QDScore did not even consider cholesterol; but what about the authors of other scores for diabetes such as FINDRISC etc? See https://bmjopen.bmj.com/content/5/7/e007195. If it is true that none of the well-known scores for diabetes considered inclusion of lipids, then that is worth saying.
Response: Thanks for the reviewer's suggestion, we consulted other literature on scores for diabetes and found that the predictive role of lipids was rarely mentioned. For instance, in FINDRISC, scores for diabetes included age, BMI, waist circumference, family history of diabetes, use of blood pressure medication, history of elevated blood glucose, daily physical activity, and daily consumption of vegetables, fruit, and berries. This FINDRISC research did not mention blood lipids.

11.The Discussion needs to be completely re-written, because at the moment the sentences claiming novelty (e.g. “this current study was the first to compare the predictive power of different lipid profiles”, “the predictive power of lipid panels combined with conventional T2DM risk factors have not been compared”) seem to contradict other sentences such as “The important role of non-HDL-C in predicting T2DM was also emphasized by recently other studies” and so on.
Similarly, the Introduction needs to be completely re-written to avoid apparent contradictions between sentences claiming novelty (e.g. “Overall, the risk of diabetes in people with dyslipidemia has not been clearly elucidated”) and sentences claiming what is already known (e.g. “Dyslipidemia have recently been recognised as a risk factor for T2DM”, and many other remarks.
Response: Thanks the reviewer’s suggestion, we had re-written this two part on the last paragraph of introduction and conclusion. And here we did not list the re-written parts but marked in red in revised paper.

We tried our best to improve the manuscript and made some changes in the manuscript. These

changes will not influence the content and framework of the paper. And here we did not list all of the changes but marked in red in revised paper.
We appreciate for editors and reviewers' warm work earnestly, and hope that the correction will meet with approval. Please do not hesitate to contact with me if you have any questions. Once again, thank you very much for your comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Stevens, Richard University of Oxford, Nuffield Dept Primary Care Health Sciences
REVIEW RETURNED	23-Feb-2021

GENERAL COMMENTS	Thank you for clarifying several points.