

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Glycaemic control in type 2 diabetes patients and its predictors: a retrospective database study at a tertiary care Diabetes Centre in Ningbo, China
AUTHORS	Li, Jialin; Chattopadhyay, Kaushik; Xu, Miao; Chen, Yanshu; Hu, Fangfang; Chu, Jianping; li, li

VERSION 1 – REVIEW

REVIEWER	Yoke Mun Chan University Putra Malaysia
REVIEW RETURNED	19-Oct-2017

GENERAL COMMENTS	the paper should be accompanied with the consort diagram
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REVIEWER	Franco Cavalot San Luigi Gonzaga University Hospital Orbassano (Turin) Italy
REVIEW RETURNED	25-Oct-2017

GENERAL COMMENTS	<p>In their study Li J et al have examined the characteristics of the population of patients affected by type 2 diabetes (T2D) and followed-up at their tertiary diabetes center and have tried to determine the factors that affect the degree of metabolic control. The Authors have recovered data from electronic records. The study is overall well performed, the statistical evaluation appropriately conducted and the manuscript is clearly written.</p> <p>Comments:</p> <ul style="list-style-type: none">- That approximately 50% of patients affected by T2D have HbA1c <50% is not a really bad score. However, one missing point is how these patients are referred to the tertiary care diabetes centre rather than being followed in a different way. Which are alternative follow-up options for patients? Are there any criteria for referral to tertiary care? Which are they? The population shows some characteristics that make them not so similar to an average western population of patients with T2D: they are relatively young and have a relatively short diabetes duration compared to the more typical western countries T2D patients' population.- The percentage of patients on insulin therapy is rather high, despite the relatively short diabetes duration. This aspect would point to prevalent insulin deficiency in the pathogenesis of type 2 diabetes in Chinese population. Have the Authors any evidence that this is the case, beside insulin dependency?
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	<p>- On average T2D is a progressive disease; however, from everyday experience it emerges that some patients maintain stable therapy and metabolic control for lifetime, while other patients are not able to maintain good metabolic control with time and need to intensify treatment. Do the Authors have any evidence of these two different kinds of behaviour?</p> <p>Abstract Page 2, line 19: 'The study included adult T2DM patients, registered and received treatment..' should be 'The study included adult T2DM patients, registered and receiving treatment..'. Page 2, line 21: the phrase 'Those diagnosed ...from the study', can be removed from the abstract.</p>
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REVIEWER	Dr Elisabeth Svensson Department of Epidemiology and Biostatistics, The Danish Clinical Registries, Aarhus, Denmark
REVIEW RETURNED	13-Nov-2017

GENERAL COMMENTS	<p>This study was a retrospective cross-section study, which aimed to assess glycemic control in T2DM patients, and to determine factors that independently predicted their glycemic control.</p> <p>The main objectives/comments are:</p> <ul style="list-style-type: none"> - I am surprised at the low number of patients included in the study. In a large hospital with 2 million visits - who are referred for diabetes treatment? I am missing some information about who does treat diabetes in China? Do you have a primary care sector, w.e local doctors/general practitioners? - It is not clear when the HbA1c and the other predictors are measured - are they measured at first visit - or after 6 months? - Medication in China, is this entirely paid by the patient himself? Is payment an issue? - Please define tertiary care hospital, vs secondary and primary care hospital. <p>Minor comments</p> <p>Introduction</p> <ul style="list-style-type: none"> - I have not looked into all references, but especially reference 1 and 2 can be updated <p>Material and methods</p> <ul style="list-style-type: none"> - I am lacking the information about why all patients who have less than 6 months of treatment are excluded? Why not include all patients referred for diabetes treatment? - A possible extension to the study is to look at HbA1c at entry to the Clinic - and then observe the HbA1c after 6 months of treatment (but that is another study), and easily describe predictors. Is that what was done? - in some patients, there might be a justification for an HbA1c over 7%, for example old and frail. How many are old and frail? - I would suggest to classify duration of T2DM categorically - less than one year, 1-2 years, 3-4 years, over 5 years. - Suggest to categorize age as well - Look again at the analyses concerning therapeutic regimen - the conclusion from those findings are not correct - that diet and physical activity are predictors of poor glycemic control. Suggest to put diet-physical activities - and OHA's as reference - as this is the largest Group. The finding suggest higher levels of poor glycemic
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	<p>control in the Groups with medication. This is also what others find, as one would treat medically those with the poorest glycaemic control</p> <p>- Comorbidities is defined as overview of obese only, I would not call this comorbidities, but Obesity.</p> <p>-</p> <p>Results</p> <p>- focus on effect sizes, not p-values. The effect size convey much more information than a simple p-value.</p> <p>Discussion</p> <p>- "Some of the data were self-reported and this could have been an issue." - please be more specific. How could this be an issue - how did the influence the results?</p>
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REVIEWER	Shaun Lee Monash University Malaysia
REVIEW RETURNED	14-Nov-2017

GENERAL COMMENTS	<p>Overall the authors examined reasons for poor glycaemic controls among Chinese with type 2 diabetes in China. They sought to examine some potential reasons and associations for poor and worse glycaemic controls among these group and found duration of diabetes, use of diet and those living in urban areas had worse control. Some potential reasons were given but I feel these lack depth and insight which could be used to impact practice in the future. In addition, the authors only sought to state OHA but did not describe what these were. As we know, the use of multiple OHAs would be better and use of insulin would even provide better control. Had these been examined? Also , other potential facotrs such as duration of exercise , type of diet were not described.</p> <p>I think this would need substantial work and reanalysis before this can be considered.</p>
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REVIEWER	Richard Stevens University of Oxford, UK
REVIEW RETURNED	24-Nov-2017

GENERAL COMMENTS	<p>This is a perfectly good paper, well-executed and well-reported, but it is not clear that it has sufficient novelty, or international relevance, to interest a non-specialist audience outside China.</p> <p>The rationale for the outcome (HbA1c\geq7%) is not stated; in some settings HbA1c\geq7.5% would be more relevant, so please state why 7% is relevant in your setting.</p> <p>Views differ on the merits of backward stepwise regression, and whether there is any value to pre-screening variables for significance in univariate regression (see Harrell, "Regression Modelling Strategies", Springer-Verlag). However, that is unlikely to materially affect the conclusions here.</p>
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VERSION 1 – AUTHOR RESPONSE

Editorial Requests:

- Is it possible to include the relevant Odds Ratios and 95% CIs in the abstract >> results section?

Answer: As suggested, we have included the ORs and 95% CIs.

- Please revise your data sharing statement on page 11 ("The study is part of a bigger project and further publications are expected from the dataset which prevents us from making it public right now.") At a minimum we would expect your dataset to be available upon request (e.g. from the corresponding author) unless there are legal or ethical reasons for not doing so.

Answer: As suggested, we have amended the data sharing statement.

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Yoke Mun Chan

Institution and Country: University Putra Malaysia

Competing Interests: None declared

The paper should be accompanied with the consort diagram.

Answer: Thank you for your suggestion. As CONSORT (Consolidated Standards of Reporting Trials) flowchart is used in randomised controlled trials and our study is an observational study (cross-sectional study using routinely collected data), so we have not included a CONSORT flowchart.

Reviewer: 2

Reviewer Name: Franco Cavalot

Institution and Country: San Luigi Gonzaga University Hospital Orbassano (Turin), Italy

Competing Interests: None declared

Thank you for your suggestions and appreciating our hard work.

In their study Li J et al have examined the characteristics of the population of patients affected by type 2 diabetes (T2D) and followed-up at their tertiary diabetes center and have tried to determine the factors that affect the degree of metabolic control. The Authors have recovered data from electronic records. The study is overall well performed, the statistical evaluation appropriately conducted and the manuscript is clearly written.

Comments:

- That approximately 50% of patients affected by T2D have HbA1c <50% is not a really bad score. However, one missing point is how these patients are referred to the tertiary care diabetes centre rather than being followed in a different way. Which are alternative follow-up options for patients? Are there any criteria for referral to tertiary care? Which are they? The population shows some characteristics that make them not so similar to an average western population of patients with T2D: they are relatively young and have a relatively short diabetes duration compared to the more typical western countries T2D patients' population.

Answer: In China, people (including T2DM patients) can attend any hospital of their choice. In other words, it is not based on any referral system by the community hospital with general practitioners. This has been included in the manuscript.

We agree that the prevalence of poor glycaemic control in our study (based at a tertiary care hospital) was not bad enough as compared to some other studies conducted in China (which included different types of hospitals/patients). In terms of glycaemic control in T2DM patients, tertiary care hospitals usually perform better as compared to primary or secondary care hospitals. However, the prevalence was high in our study as compared to studies conducted in various developed countries. All these points have already been mentioned in the manuscript (in the discussion section). In addition, we have now included this sentence: It should be noted that Chinese people are more susceptible to T2DM as compared to Whites (e.g., they develop T2DM at a much younger age).

- The percentage of patients on insulin therapy is rather high, despite the relatively short diabetes duration. This aspect would point to prevalent insulin deficiency in the pathogenesis of type 2 diabetes in Chinese population. Have the Authors any evidence that this is the case, beside insulin dependency?

Answer: We agree with your point that the percentage of patients on insulin therapy (alone or in combination with OHD) was high (612 (44.1%)), despite the relatively short duration of T2DM. This finding was consistent with other studies conducted in China (e.g., Clin Ther. 2010; 32(5):973-83). The current guideline for the prevention and management of T2DM in China recommends that insulin should be started in patients when:

- 1) HbA1c is more than 9% or FBG is more than 11.1 mmol/L in a newly diagnosed case or
- 2) HbA1c is $\geq 7\%$ or FBG is more than 7.0 mmol/L even after treating with two or more OHDs.

This could be a reason behind such a high percentage of patients on insulin therapy. However, it was not possible to determine insulin deficiency or dependency in the pathogenesis of T2DM in this population, which was beyond the scope of this study. However, based on previous studies, we have added this sentence to the manuscript- "...in Chinese T2DM patients, the defects in β -cells function are more pronounced than decreased insulin sensitivity".

- On average T2D is a progressive disease; however, from everyday experience it emerges that some patients maintain stable therapy and metabolic control for lifetime, while other patients are not able to maintain good metabolic control with time and need to intensify treatment. Do the Authors have any evidence of these two different kinds of behaviour?

Answer: We agree with your point, which needs a much longer time period. The focus of our study (cross-sectional) was at 6 months of registration and treatment/management, which is not long enough to explore these two types of patient groups.

Abstract

Page 2, line 19: 'The study included adult T2DM patients, registered and received treatment..' should be 'The study included adult T2DM patients, registered and receiving treatment..'.
Page 2, line 21: the phrase 'Those diagnosed ...from the study', can be removed from the abstract.

Answer: As suggested, these two sentences have been amended.

Reviewer: 3

Reviewer Name: Dr Elisabeth Svensson

Institution and Country: Department of Epidemiology and Biostatistics, The Danish Clinical Registries, Aarhus, Denmark

Competing Interests: none declared

Thank you for reviewing our manuscript.

This study was a retrospective cross-section study, which aimed to assess glycemic control in T2DM patients, and to determine factors that independently predicted their glycemic control.

The main objectives/comments are:

- I am surprised at the low number of patients included in the study. In a large hospital with 2 million visits - who are referred for diabetes treatment? I am missing some information about who does treat diabetes in China? Do you have a primary care sector, w.e local doctors/general practitioners?

Answer: We have amended the manuscript to enhance the readability:

“In China, people (including T2DM patients) can attend any hospital of their choice. In other words, it is not based on any referral system by the community hospital with general practitioners.

.... There are 152 community hospitals with general practitioners, 22 secondary hospitals and 21 tertiary care hospitals in the city. Ningbo First Hospital, with 1600 beds, is a tertiary care hospital. The hospital’s Diabetes Centre has a team of qualified and experienced diabetes experts.”

The Diabetes Centre is only one of the several existing departments at this hospital. From 1st July 2012 to 30 June 2017, there were 6699 patients in the Diabetes Centre database. The study inclusion criteria were satisfied by only 1387 patients.

- It is not clear when the HbA1c and the other predictors are measured - are they measured at first visit - or after 6 months?

Answer: This study specifically includes variables which were measured after 6 months. This statement has been included in the manuscript.

-Medication in China, is this entirely paid by the patient himself? Is payment an issue?

Answer: In China, the majority of people have a health insurance, which covers their medication. In our study, we included the variable ‘health insurance’. However, it was not a predictor of poor glycaemic control.

- Please define tertiary care hospital, vs secondary and primary care hospital.

Answer: This information has been included in the manuscript. In China, hospitals are categorised into three: primary care, secondary care and tertiary care. A primary care hospital (community hospital with general practitioners) usually has less than 100 beds, and are mainly responsible for providing preventive care and minimal health services. A secondary care hospital usually has 100 to 500 beds, and are mainly responsible for providing health services and for performing a role in medical education and research. A tertiary care hospital usually has more than 500 beds, and are mainly responsible for providing specialist health services and for performing a bigger role in medical education and research. In China, people (including T2DM patients) can attend any hospital of their choice. In other words, it is not based on any referral system by the community hospital with general practitioners.

Minor comments

Introduction

- I have not looked into all references, but especially reference 1 and 2 can be updated.

Answer: Majority of our references are from the last decade. However, as suggested, we have updated reference 1 and 2.

Material and methods

- I am lacking the information about why all patients who have less than 6 months of treatment are excluded? Why not include all patients referred for diabetes treatment?

Answer: In China, people (including T2DM patients) can attend any hospital of their choice. In other words, it is not based on any referral system by the community hospital with general practitioners. In China, T2DM patients are usually given at least six months' time to adjust to their T2DM therapeutic regimen and control their blood glucose levels. Thus, the study included T2DM patients who registered and received treatment at the Diabetes Centre for at least six consecutive months. We have added these sentences to the manuscript.

- A possible extension to the study is to look at HbA1c at entry to the Clinic - and then observe the HbA1c after 6 months of treatment (but that is another study), and easily describe predictors. Is that what was done?

Answer: Yes, variables (including Hba1c and FBG) were measured at 6 months of treatment/management at the Centre – a cross-sectional study was conducted.

- in some patients, there might be a justification for an HbA1c over 7%, for example old and frail. How many are old and frail?

Answer: We agree with your point and have included this in the discussion section. "It should also be noted that blood glucose levels of some patients could be relaxed, especially those who are old and frail. However, for the purpose of analysis, the glycaemic control was categorised into poor and good, based on the current guideline for the prevention and management of T2DM in China." Using ≥ 60 years as old age, there were 525 (37.9%) patients in the study. However, there is no information in the database on patients who were frail.

- I would suggest to classify duration of T2DM categorically - less than one year, 1-2 years, 3-4 years, over 5 years.

Answer: We have categorised this variable, as suggested: ≤ 1 year, >1 to 2 years, >2 to 4 years, or >4 years.

- Suggest to categorize age as well

Answer: We have categorised this variable, as suggested: 18-39 years, 40-59 years and ≥ 60 years.

- Look again at the analyses concerning therapeutic regimen - the conclusion from those findings are not correct - that diet and physical activity are predictors of poor glycaemic control. Suggest to put diet-physical activities - and OHA's as reference - as this is the largest Group. The finding suggest higher levels of poor glycaemic control in the Groups with medication. This is also what others find, as one would treat medically those with the poorest glycaemic control.

Answer: We have already mentioned in the manuscript that the odds of poor glycaemic control were lower in patients only on diet and physical activity as part of their T2DM therapeutic regimen. However, as suggested, we have re-analysed the data using diet and physical activity and OHD as the reference and found the same result. In addition, in terms of HbA1c, the odds of poor glycaemic control were higher in patients on diet, physical activity, OHD and insulin as part of their T2DM therapeutic regimen.

- Comorbidities is defined as overview of obese only, I would not call this comorbidities, but Obesity.

Answer: We have included three conditions as comorbidities: overweight/obese, hypertension and hyperlipidaemia. We have highlighted this sentence in the manuscript.

Results

- focus on effect sizes, not p-values. The effect size convey much more information than a simple p-value.

Answer: As suggested, we have amended the results section and have included effect sizes.

Discussion

- "Some of the data were self-reported and this could have been an issue." - please be more specific. How could this be an issue - how did the influence the results?

Answer: As suggested, this sentence has been amended. Some of the data were self-reported (e.g., duration of T2DM), and recall error could have been a problem. This inaccurate measurement of the variable could mean that individuals were assigned to the wrong category, and then resulted in an incorrect estimation of the association between duration of T2DM and poor glycaemic control.

Reviewer: 4

Reviewer Name: Shaun Lee

Institution and Country: Monash University Malaysia

Competing Interests: None declared

Thank you very much for your comments.

Overall the authors examined reasons for poor glycaemic controls among Chinese with type 2 diabetes in China. They sought to examine some potential reasons and associations for poor and worse glycaemic controls among these groups and found duration of diabetes, use of diet and those living in urban areas had worse control. Some potential reasons were given but I feel these lack depth and insight which could be used to impact practice in the future. In addition, the authors only sought to state OHA but did not describe what these were. As we know, the use of multiple OHAs would be better and use of insulin would even provide better control. Had these been examined? Also, other potential factors such as duration of exercise, type of diet were not described.

I think this would need substantial work and reanalysis before this can be considered.

Answer: In this study, we have used an existing database (routinely collected data). We have extracted a range of variables from the database, based on our clinical knowledge in this area and relevant previous research studies. We feel that our study results have an adequate value to impact practice, as mentioned in the manuscript. In addition, we have amended the manuscript based on the comments of the editor and the reviewers.

We have already mentioned the types of OHD included in this study (under study variables, in the methods section). We have highlighted the sentence.

Under T2DM therapeutic regimen, we have included 4 categories (based on the current guideline for the prevention and management of T2DM in China):

- 1) Diet+Physical activity
- 2) Diet+Physical activity+OHD
- 3) Diet+Physical activity+Insulin
- 4) Diet+Physical activity+OHD+Insulin

As suggested by reviewer 3, we have re-analysed the data using diet and physical activity and OHD as the reference. In terms of HbA1c and FBG, the odds of poor glycaemic control were lower in

patients only on diet and physical activity as part of their T2DM therapeutic regimen. In terms of HbA1c, the odds of poor glycaemic control were higher in patients on diet, physical activity, OHD and insulin as part of their T2DM therapeutic regimen.

Regarding diet and physical activity, we have included these as part of the T2DM therapeutic regimen (as prescribed by the doctor). In the database, data were available on prescription but not on uptake and adherence. We have already mentioned this point in the discussion section. We have highlighted these sentences.

Reviewer: 5

Reviewer Name: Richard Stevens

Institution and Country: University of Oxford, UK

Competing Interests: None

Thank you very much for appreciating our hard work.

This is a perfectly good paper, well-executed and well-reported, but it is not clear that it has sufficient novelty, or international relevance, to interest a non-specialist audience outside China.

Answer: The health issues in any particular population or setting could be different from others, and this needs exploration and reporting. China has the world's largest T2DM epidemic and its healthcare system is different from many other countries, as mentioned in the introduction section. One of the most important strengths of our study is - this is the first study to explore glycaemic control in T2DM patients at the tertiary care Diabetes Centre in Ningbo, China and, as far as we are aware, in the Zhejiang province of China. We have also compared our study findings with studies conducted in various other countries. The study findings could be taken into consideration in future interventional studies aimed at improving glycaemic control in these patients, and either Chinese experts or international experts or both (collaboration) can undertake this work.

The rationale for the outcome ($HbA1c \geq 7\%$) is not stated; in some settings $HbA1c \geq 7.5\%$ would be more relevant, so please state why 7% is relevant in your setting.

Answer: We have already included a reference for this – the poor and good glycaemic control cut-off point is recommended in the current guideline for the prevention and management of T2DM in China. We have amended the sentence, as requested.

Views differ on the merits of backward stepwise regression, and whether there is any value to pre-screening variables for significance in univariate regression (see Harrell, "Regression Modelling Strategies", Springer-Verlag). However, that is unlikely to materially affect the conclusions here.

Answer: Thanks for your comment. We agree that experts have different views on the type of analysis to be conducted and which is the best/most appropriate one. This is the reason we conducted two types of analysis: backward stepwise regression analysis and sensitivity analysis (only those variables with a P value of ≤ 0.20 in simple logistic regressions were included in multiple logistic regression models). Similar results were found in the sensitivity analyses except for the association between glycaemic control (in terms of FBG) and hypertension.

VERSION 2 – REVIEW

REVIEWER	Shaun lee Monash University Malaysia Malaysia
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REVIEW RETURNED	13-Dec-2017
GENERAL COMMENTS	The authors have done a great job addressing the comments and it is very well defined and written
REVIEWER	Franco Cavalot AOU San Luigi Gonzaga di Orbassano (TO) - ITALY
REVIEW RETURNED	25-Dec-2017
GENERAL COMMENTS	<p>BMJOpen manuscript 2017-019697 Revision 2 of manuscript by Li J et al.</p> <ul style="list-style-type: none"> - the Authors have modified the manuscript according to most observations raised in the first revision, particularly concerning the referral mode to the tertiary care center. It appears that the access to the center is on individual basis and note to a particularly specialized care. Thus, these subjects appear to be similar to patients followed in primary and secondary care. The organization of care could be an interesting issue to improve health care delivery for type 2 diabetic patients. It is impressive the high percentage (41%) of type 2 diabetic patients among people over 40 years of age. - Further comments: <ul style="list-style-type: none"> o concerning diabetes therapy, The Authors have chosen the category of subjects on oral drugs as the reference category; it should be better to choose diet and physical activity as the reference. Otherwise an explanation for this should be given. o Page 5: '...and registered and received treatment ...' should be "...and registered and receiving treatment at the Diabetes Centre...' o Page 5, Study Variables: '..were extracted from the database: age (18-39 years, 40-59 years, or ≥60 years), sex (male or female), education (university/college, class 7 to 12, class 1 to 6, or no qualifications), occupation ...' etc, should be modified like this: "...were extracted from the database: age (18-39 years, 40-59 years, or ≥60 years); sex; education (university/college, class 7 to 12, class 1 to 6, or no qualifications); occupation: manual workers (i.e., more physical than mental work), non-manual workers (i.e., more mental than physical work) or never worked/retired); marital status (married or single/divorced/widowed); residence: urban or rural based on the "hukou" system (i.e., residence registration system in China) [15]; health insurance; smoking (current status); alcohol drinking (current status); family history of T2DM (any parent or sibling); duration of T2DM (≤1 year, >1 to 2 years, >2 to 4 years, or >4 years); number of visits to the Diabetes Centre for T2DM since registration; T2DM therapeutic regimen: only diet and physical activity, diet and physical activity and oral hypoglycaemic drug (OHD - metformin, acarbose, sulfonylureas, meglitinides and/or thiazo-lidinediones), diet and physical activity and insulin (long-term insulin, intermediate insulin, rapid-acting insulin and/or premix insulin); or diet and physical activity, OHD and insulin[16]; comorbidities: overweight or obesity (diagnosis based on body mass index (BMI) ≥24 kg/m2) [17]; hypertension (diagnosis based on blood pressure ≥140/90 mm Hg); hyperlipidaemia (diagnosis based on serum lipids- total cholesterol ≥4.5 mmol/L or triglycerides ≥1.7 mmol/L)); and blood glucose levels. o Page 5, Study Variables: among comorbidities, BMI has been categorized with only one cut-off. It could be useful to evaluate if different degrees of obesity impact on the blood glucose control. o Page 7, Results: 'In terms of HbA1c and FBG...' should be

	<p>'In terms of HbA1c, the odds of poor glycaemic control...'</p> <ul style="list-style-type: none"> o Page 7 and Page 8, Results: Data reported in the Tables should not be reported also in the text of the Results. o Page 8, Discussion, last 3 lines: In spite of the availability of diabetes experts at this tertiary care Diabetes Centre and of effective and safe glucose-lowering therapies, the prevalence of poor glycaemic control in, etc. Data from great clinical trials (ACCORD, VADT, ADVANCE) have shown that the drugs that are used in China are not so safe. A sentence acknowledging that the impossibility to use the new drugs may limit the therapeutic chances of improvement in this population. o Page 9, Discussion: The addition 'In terms of HbA1c and FBG, the odds of poor ...' should be deleted until the sentence 'Similar results were found in the sensitivity analyses except for the association between glycaemic control (in terms of FBG) and hypertension.', since this is only a repetition of what has already been described in the 'Results'. o Page 11, Discussion: the sentence '... and may have benefits in terms of their long-term glycaemic control.' should be deleted. Actually, statins have been shown to increase (slightly, but they increase) the risk of diabetes, thus may worsen, not ameliorate diabetes control, even though the benefit/risk ratio is in favour of benefit.
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VERSION 2 – AUTHOR RESPONSE

Reviewer's Comments to Author:

Reviewer: 2

Reviewer Name: Franco Cavalot

Institution and Country: AOU San Luigi Gonzaga di Orbassano (TO) - ITALY

Competing Interests: None declared

The Authors have modified the manuscript according to most observations raised in the first revision, particularly concerning the referral mode to the tertiary care center. It appears that the access to the center is on individual basis and note to a particularly specialized care. Thus, these subjects appear to be similar to patients followed in primary and secondary care. The organization of care could be an interesting issue to improve health care delivery for type 2 diabetic patients. It is impressive the high percentage (41%) of type 2 diabetic patients among people over 40 years of age.

Thank you for your suggestions and appreciating our hard work.

Further comments:

- Concerning diabetes therapy, The Authors have chosen the category of subjects on oral drugs as the reference category; it should be better to choose diet and physical activity as the reference. Otherwise an explanation for this should be given.

Answer: We agree that diet and physical activity should be the reference category and we have reanalysed the data, as suggested.

- Page 5: '...and registered and received treatment ...' should be "...and registered and receiving treatment at the Diabetes Centre...'

Answer: As suggested, this sentence has been amended.

- Page 5, Study Variables: ‘..were extracted from the database: age (18-39 years, 40-59 years, or ≥60 years), sex (male or female), education (university/college, class 7 to 12, class 1 to 6, or no qualifications), occupation ...’ etc, should be modified like this: “..were extracted from the database: age (18-39 years, 40-59 years, or ≥60 years); sex; education (university/college, class 7 to 12, class 1 to 6, or no qualifications); occupation: manual workers (i.e., more physical than mental work), non-manual workers (i.e., more mental than physical work) or never worked/retired); marital status (married or single/divorced/widowed); residence: urban or rural based on the “hukou” system (i.e., residence registration system in China) [15]; health insurance; smoking (current status); alcohol drinking (current status); family history of T2DM (any parent or sibling); duration of T2DM (≤1 year, >1 to 2 years, >2 to 4 years, or >4 years); number of visits to the Diabetes Centre for T2DM since registration; T2DM therapeutic regimen: only diet and physical activity, diet and physical activity and oral hypoglycaemic drug (OHD - metformin, acarbose, sulfonylureas, meglitinides and/or thiazolidinediones), diet and physical activity and insulin (long-term insulin, intermediate insulin, rapid-acting insulin and/or premix insulin); or diet and physical activity, OHD and insulin[16]; comorbidities: overweight or obesity (diagnosis based on body mass index (BMI) ≥24 kg/m²) [17]; hypertension (diagnosis based on blood pressure ≥140/90 mm Hg); hyperlipidaemia (diagnosis based on serum lipids- total cholesterol ≥4.5 mmol/L or triglycerides ≥1.7 mmol/L)); and blood glucose levels.

Answer: As suggested, these sentences have been amended.

- Page 5, Study Variables: among comorbidities, BMI has been categorized with only one cut-off. It could be useful to evaluate if different degrees of obesity impact on the blood glucose control.

Answer: As suggested, we have reanalysed the data using 4 BMI categories: under, normal, overweight, obese.

- Page 7, Results: ‘In terms of HbA1c and FBG...’ should be ‘In terms of HbA1c, the odds of poor glycaemic control...’

Answer: We have amended the results section, based on the following comment.

- Page 7 and Page 8, Results: Data reported in the Tables should not be reported also in the text of the Results.

Answer: As suggested, the results section has been amended. We have deleted the odds ratios, 95% confidence intervals and p values from the results section as they have been already reported in the tables.

- Page 8, Discussion, last 3 lines: In spite of the availability of diabetes experts at this tertiary care Diabetes Centre and of effective and safe glucose-lowering therapies, the prevalence of poor glycaemic control in, etc. Data from great clinical trials (ACCORD, VADT, ADVANCE) have shown that the drugs that are used in China are not so safe. A sentence acknowledging that the impossibility to use the new drugs may limit the therapeutic chances of improvement in this population.

Answer: As suggested, these sentences have been amended.

“In spite of the availability of diabetes experts at this tertiary care Diabetes Centre, the prevalence of poor glycaemic control in T2DM patients was high in our study as compared to other studies conducted in various developed countries [10,11]. Some of the reasons could be non-usage of new hypoglycaemic drugs (such as DPP-IV inhibitors and GLP-1 receptor agonists) and inadequate self-management of T2DM in this population. This indicates that there is still a room for improvement at this Diabetes Centre.”

- Page 9, Discussion: The addition 'In terms of HbA1c and FBG, the odds of poor ...' should be deleted until the sentence 'Similar results were found in the sensitivity analyses except for the association between glycaemic control (in terms of FBG) and hypertension.', since this is only a repetition of what has already been described in the 'Results'.

Answer: As suggested, these sentences have been deleted.

- Page 11, Discussion: the sentence '... and may have benefits in terms of their long-term glycaemic control.' should be deleted. Actually, statins have been shown to increase (slightly, but they increase) the risk of diabetes, thus may worsen, not ameliorate diabetes control, even though the benefit/risk ratio is in favour of benefit.

Answer: As suggested, this sentence has been amended.

Reviewer: 4

Reviewer Name: Shaun lee

Institution and Country: Monash University Malaysia, Malaysia

Competing Interests: None declared

The authors have done a great job addressing the comments and it is very well defined and written.

Thank you very much for appreciating our work.

VERSION 3 – REVIEW

REVIEWER	Franco Cavalot San Luigi Gonzaga University Hospital Italy
REVIEW RETURNED	12-Feb-2018
GENERAL COMMENTS	No further comments.