PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of ADA HbA1c Criteria in the Diagnosis of Pre-diabetes and Diabetes in a Population of Chinese Adolescents and Young Adults at High Risk for Diabetes: a Cross-sectional Study
AUTHORS	Li, Ming; Li, Ge; Han, Lanwen; Wang, Yonghui; Zhao, Yanglu; Li, Yu; Fu, Junling; Gao, Shan; Willi, Steven

VERSION 1 – REVIEW

REVIEWER	Julia Townson Cardiff University, UK
REVIEW RETURNED	13-Dec-2017

GENERAL COMMENTS	I think the authors need to explore the potential limitation that a subset of the original population took part in this particular study. Did this introduce any bias? Or the potential for bias? I cannot see where the study was registered. Could the authors provide a potential explanation as to why their results differed from previous studies? The conclusions arrived at should be more measured to reflect the small numbers involved.

REVIEWER	Christine L. Chan Christine L. Chan MD, Assistant Professor of Pediatrics, University of Colorado Anschutz Medical Center, USA
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	Summary: This paper assesses the performance characteristics of HbA1c for diagnosing prediabetes and diabetes as defined by the OGTT in a large population of Chinese youth and young adults. Additionally, the authors group the participants by ADA A1c categories vs their A1c cutpoints after ROC curve analysis and compare the differences in metabolic syndrome characteristics as well as OGTT estimates of beta cell function and insulin resistance. Although similar findings have been described in obese youth in other countries, they do a very nice job characterizing a population of young adults in China that has not previously been characterized in this much detail. Comments: Methods/subjects - The cohort from, and time line over, which the participants for this study were recruited was not entirely clear. The baseline recruitment criteria for high-risk BCAMS youth were described and presumably, these participants were recruited from this cohort during a follow up period. Although the intro sets us up for a pediatric study, with discussions on childhood obesity as well as the lack of diabetes studies in pediatric Chinese populations, the

age group of the cohort is actually a bit older with a mean age of 20+/-2.7 years. Therefore I am assuming recruitment occurred as part of the follow up study 8 years later (although why there are still 14 yr olds as well as individuals up to 28 yrs old is unclear).

Results:
Most prior studies of high risk adolescents include obesity as an inclusion criteria. Interestingly, other metabolic syndrome criteria were also used in this paper, and only 1/3 of the population was obese. It would be interesting to compare the anthropomorphics and metabolic phenotype of the young adults diagnosed with diabetes to those that have been well-characterized in other countries such as US.

Although only 7/10 with A1c >6.4% had an OGTT diagnosis of diabetes, this would imply that 2 were diagnosed with diabetes by A1c >6.4% that did not have an OGTT in the diabetes range. Although OGTT has traditionally been considered the gold-standard test for diagnosing diabetes, this has been controversial and at least one paper assessing the relationships of OGTT and A1c to glycemic abnormalities defined by CGM found that both performed similarly yet appeared to show pattern differences in the strengths of their individual correlations to different CGM variables (Chan et al, doi: 10.1210/jc.2014-3612). Therefore, the two tests may reflect different components of glycemia, and should not be considered interchangeable. Would consider referencing above paper which also found that FPG performed poorly compared to A1c and OGTT and does not appear to have added value beyond A1c.

If adolescents were included, was there any measure of tanner staging/puberty and consideration given to the insulin resistance of puberty as a contributor to dysglycemia and metabolic outcomes? If framing as a study in youth, this is an important demographic variable to at least mention. Otherwise, might consider framing as a study in late adolescents/young adults.

General - recommend English Grammatical editing (verb tenses in particularly) need editing. Examples:
Intro -
Line 4 "With increasing obesity,…"
Line 5 "(WHO) data demonstrate that… In China,…"
Line 7 "have emerged"
Line 9 "obese youth are at risk for long-term"
Last sentence 1st paragraph of Intro seems incomplete

other examples: Table 1 - in title, HbA1c is misspelled, and 2nd line of table, r=0.718 (not 718)

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:
REVIEWER 1:
Reviewer Name: Julia Townson
Institution and Country: Cardiff University, UK
Competing Interests: None declared
Comments:

1. I think the authors need to explore the potential limitation that a subset of the original population took part in this particular study. Did this introduce any bias? Or the potential for bias?
Response: Many thanks for the comments. We have compared the baseline characteristics of subjects with and without follow-up (Page 7, Line 12-15). At baseline, those lost to follow-up were relatively younger and thinner than those available for follow-up. Nonetheless, there were no significant differences in gender, pubertal status, blood pressure, fasting lipids or fasting blood glucose levels (P > 0.05). Mainly due to great migration to other parts of the country or to other countries as those school-aged children growing up with the rapid development of society and economy in Beijing, the sample size at 9–year follow-up is relatively small, compared with our original population at baseline (n=3514). Although there were no significant difference in the major demographic and clinical characteristics between those followed-up and those lost to follow-up, there is still a potential for bias. Therefore, further large studies in Chinese population will be needed to validate our findings. We have added this as a possible limitation in the 'Strengths and Limitations' summary on Page 3 (Line 13-14) and the Discussion section (Page 16, Line 21-23; Page 17, Line 1).

2. I cannot see where the study was registered.
Response: The BCAMS study has been registered at www. clinicaltrials.gov (NCT03421444) (Page 7, Line 17).

3. Could the authors provide a potential explanation as to why their results differed from previous studies?
Response: We thank the reviewer for this suggestion. These discrepancies between previous studies and ours might due to different age ranges, races and territory. We have added a potential explanation to the manuscript (Page 14, Line 22-23).

4. The conclusions arrived at should be more measured to reflect the small numbers involved.
Response: We are in full agreement with this excellent suggestion. We have identified this limitation and added that further large studies in the Chinese population are needed to validate our findings in the Discussion section (Page 16, Line 17).

Reviewer: 2
Reviewer Name: Christine L. Chan
Institution and Country: Christine L. Chan MD, Assistant Professor of Pediatrics, University of Colorado Anschutz Medical Center, USA
Competing Interests: None declared

Summary: This paper assesses the performance characteristics of HbA1c for diagnosing prediabetes and diabetes as defined by the OGTT in a large population of Chinese youth and young adults. Additionally, the authors group the participants by ADA A1c categories vs their A1c cutpoints after ROC curve analysis and compare the differences in metabolic syndrome characteristics as well as OGTT estimates of beta cell function and insulin resistance. Although similar findings have been described in obese youth in other countries, they do a very nice job characterizing a population of young adults in China that has not previously been characterized in this much detail.

Comments:
Methods/subjects
1. The cohort from, and time line over, which the participants for this study were recruited was not entirely clear. The baseline recruitment criteria for high-risk BCAMS youth were described and presumably, these participants were recruited from this cohort during a follow up period. Although the intro sets us up for a pediatric study, with discussions on childhood obesity as well as the lack of diabetes studies in pediatric Chinese populations, the age group of the cohort is actually a bit older with a mean age of 20+/-2.7 years. Therefore I am assuming recruitment occurred as part of the

follow up study 8 years later (although why there are still 14 yr olds as well as individuals up to 28 yrs old is unclear).

Response: Many thanks for these comments. The BCAMS study is a longitudinal cohort study of cardiovascular risk factors beginning in childhood. The baseline survey was conducted in school children (aged 6-18 years) beginning in 2004. The follow-up study of this cohort was carried out in 2012-2014. The follow-up time ranged 8-10 years, with a mean of 9.1 ± 1.2 years. Thus the age range for participants in follow-up was 14 to 28 years old. Although we focused on diabetes in youths, actually, as you indicated, the children recruited from our cohort at the follow–up period became adolescents and young adults, with mean ages of 20±2.7 years.

Results:

2. Most prior studies of high risk adolescents include obesity as an inclusion criteria. Interestingly, other metabolic syndrome criteria were also used in this paper, and only 1/3 of the population was obese. It would be interesting to compare the anthropomorphics and metabolic phenotype of the young adults diagnosed with diabetes to those that have been well-characterized in other countries such as US.

Response: Thanks for this suggestion. Given that East or South Asians who are at high risk for cardiometabolic abnormalities, even at relatively low levels of body mass index (BMI) (1,2), as the reviewer suggested, it would be interesting to compare the anthropomorphics and metabolic phenotype of youths diagnosed with diabetes in our cohort to those that have been well-characterized in other countries. However, due to the lack of study in youths, we found 2 studies in US (see Ref. 25, 26 in the article) and compared the clinical features. As showing in below table1, compared with subjects in the US study, the Chinese subjects in our study tend to have lower levels of BMI and waist circumference, but appear to have higher levels of glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, despite that our subjects were a little older than those in other studies (see Table 1 below).

Reference:

1. Razak F, Anand SS, Shannon H, Vuksan V, Davis B, Jacobs R, et al. Defining obesity cut points in a multiethnic population. Circulation. 2007;115:2111-8.

2. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnicspecific BMI cutoff points for assessing diabetes risk. Diabetes Care. 2011;34:1741-8.

Table 1. Clinical features of youths with HbA1c% more than 6.4 in different studies.

Study	BCAMS @	Study in Colorado reported by Chan et al *	Yale Pathophysiology of Type 2 Diabetes in Obese Youth Study #
HbA1c %	> 6.4	> 6.4	> 6.4
N	9	3	16
Country	China	USA	USA
Age (years)	22.11(0.86)	14.1 (10.6–14.4)	13.5 (2.33)
Sex (M/F)	6/3	1/2	4/12
BMI (kg/m2)	28.73 (2.82)	42.8 (38.3–47.3)	38.98 (35.73–42.23)
WC (cm)	97.7 (7.8)	124.0 (108.0–138.0)	/
SBP (mmHg)	127.5(3.6)	129 (115–135)	/
DBP (mmHg)	81.7(2.9)	75 (59–86)	/
FBG (mg/dL)	166.32 (4.14)	103 (80–130)	106.64 (102.03–111.47)
2h-BG (mg/dL)	295.74 (9.18)	249 (223–276)	188.09 (170.61–207.36)
INS (mIU/L)	14.01 (12.30)	/	41.81 (32.77–53.34)
LDL-C (mg/dL)	134.15 (9.28)	99 (83–112)	91.83 (78.36–107.62)
HDL-C (mg/dL)	52.19 (3.87)	28 (26–39)	38.08 (33.76–42.97)
TC (mg/dL)	214.62 (12.76)	165 (148–175)	156.36 (141.00–173.38)
TG (mg/dL)	198.34 (23.02)	223 (195–332)	88.96 (65.41–120.98)

Abbreviations: BMI: Body mass index; WC: Waist circumference; FBG: Fasting blood glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; INS: insulin.
@ our study. Data were showed as geometric means (SD).
* study from reference 26 in our article. Data were showed as median (min–max).
# study from reference 25 in our article. Data were showed as geometric mean and 95% CI.

3. Although only 7/10 with A1c > 6.4% had an OGTT diagnosis of diabetes, this would imply that 2 were diagnosed with diabetes by A1c > 6.4% that did not have an OGTT in the diabetes range. Although OGTT has traditionally been considered the gold-standard test for diagnosing diabetes, this has been controversial and at least one paper assessing the relationships of OGTT and A1c to glycemic abnormalities defined by CGM found that both performed similarly yet appeared to show pattern differences in the strengths of their individual correlations to different CGM variables (Chan et al, doi: 10.1210/jc.2014-3612). Therefore, the two tests may reflect different components of glycemia, and should not be considered interchangeable. Would consider referencing above paper which also found that FPG performed poorly compared to A1c and OGTT and does not appear to have added value beyond A1c.
Response: We thank the reviewer for providing us the reference. We learned a lot from this paper and cited it in Page 15, Line 7-9 as Reference 26 in our article.

4. If adolescents were included, was there any measure of tanner staging/puberty and consideration given to the insulin resistance of puberty as a contributor to dysglycemia and metabolic outcomes? If framing as a study in youth, this is an important demographic variable to at least mention. Otherwise, might consider framing as a study in late adolescents/young adults.
Response: Thank you for this comment. As you indicated, pubertal stage has been recognized as a contributor to insulin resistance and metabolic outcomes. As such, we measured tanner stages in all subjects at baseline in BCAMS (see ref 13-15 in article). However, at the follow-up assessment 9 years later, the vast majority of the subjects would were over 16 years old, and at Tanner stage 5. So, we didn't evaluate pubertal stage in the follow-up study. Nonetheless, since puberty is associated with age, and we have included age as a covariate when comparing the clinical features of the study population according to HbA1c categories, we feel that this is likely to adjust the effect of pubertal stage to some degree. In addition, we have added this as a possible limitation in the Discussion section (Page 16, Line 17-21).
Reference in article:
13. Li M, Fisette A, Zhao XY, et al. Serum resistin correlates with central obesity but weakly with insulin resistance in Chinese children and adolescents. International journal of obesity 2009;33(4):424-39.
14. Li L, Yin J, Cheng H, et al. Identification of Genetic and Environmental Factors Predicting Metabolically Healthy Obesity in Children: Data From the BCAMS Study. The Journal of clinical endocrinology and metabolism 2016;101(4):1816-25.

5. General - recommend English Grammatical editing (verb tenses in particularly) need editing.
Response: We thank the reviewer for these suggestions. We have thoroughly edited the manuscript.
Examples:
Intro -
Line 4 "With increasing obesity,…"
Response: We have modified the manuscript accordingly (Page 5, Line 5-6).
Line 5 "(WHO) data demonstrate that… In China,…"
Response: We have modified the manuscript accordingly (Page 5, Line 7-8).
Line 7 "have emerged"
Response: We have modified the manuscript accordingly (Page 5, Line 10).
Line 9 "obese youth are at risk for long-term"

Response: We have modified the manuscript accordingly (Page 5, Line 12-14).

Last sentence 1st paragraph of Intro seems incomplete

Response: We have modified the manuscript accordingly (Page 5, Line 23; Page 6, Line 1).

other examples: Table 1 - in title, HbA1c is misspelled, and 2nd line of table, r=0.718 (not 718)

Response: We have modified the manuscript accordingly (Page 23, Table 1).

VERSION 2 – REVIEW

REVIEWER	Julia Townson Cardiff University, UK
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	The authors have taken on board some of the comments that were made at the initial review. However, I am finding the level of written English poor, indeed in some places worse than before. This makes reviewing the document very difficult. In addition, I have a specific comment on the patient and public involvement (PPI) section. As there was no PPI in the study, I suggest that a sentence, stating "Patients or public representatives were not involved at any stage of this study", is more appropriate. I am afraid that I cannot effectively review the document again at this stage, due to the number of errors, typos, and poor English within the manuscript.

REVIEWER	Christine L. Chan University of Colorado Anschutz Medical Center, United States
REVIEW RETURNED	11-Apr-2018

GENERAL COMMENTS	Would recommend editing by a native English speaker - particularly the Discussion section. Otherwise, concerns addressed satisfactorily.

VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Julia Townson

Institution and Country: Cardiff University, UK

Competing Interests: None declared

The authors have taken on board some of the comments that were made at the initial review. However, I am finding the level of written English poor, indeed in some places worse than before. This makes reviewing the document very difficult.

In addition, I have a specific comment on the patient and public involvement (PPI) section. As there was no PPI in the study, I suggest that a sentence, stating "Patients or public representatives were not involved at any stage of this study", is more appropriate.

I am afraid that I cannot effectively review the document again at this stage, due to the number of errors, typos, and poor English within the manuscript.

Response: Thank you for the comments. We have thoroughly modified the manuscript. We hope this modification improves understanding.

In addition, in accordance with the requirement of BMJ open, we need to provide responses to all the questions below in patient and public involvement (PPI) section:

How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?

How did you involve patients in the design of this study?

Were patients involved in the recruitment to and conduct of the study?

How will the results be disseminated to study participants?

Reviewer: 2

Reviewer Name: Christine L. Chan

Institution and Country: University of Colorado Anschutz Medical Center, United States

Competing Interests: None declared

Would recommend editing by a native English speaker - particularly the Discussion section. Otherwise, concerns addressed satisfactorily.

Response: Thank you for the comments. We have thoroughly copy-edited the manuscript, particularly the Discussion section.

VERSION 3 – REVIEW

REVIEWER	Julia Townson Cardiff University, UK
REVIEW RETURNED	31-May-2018

GENERAL COMMENTS	The written English within the manuscript has been significantly improved, which now makes it comprehensible. The PPI section now reflects that the public were not involved in the study. No other changes required.