PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Validation of the Framingham General Cardiovascular Risk Score in a multi-ethnic Asian Population– a retrospective cohort study
AUTHORS	Ching, Siew Mooi; Chia, Yook Chin; Gray, Sarah Yu Weng; Lim, Hooi Min; Karuthan, Chinna

VERSION 1 - REVIEW

REVIEWER	Cheong Lieng Teng International Medical University, Seremban, Malaysia
REVIEW RETURNED	09-Jan-2015

GENERAL COMMENTS	Overall a well written manuscript. Page 9, Line 8, one percentage is missing? Page 14, Line 46-48, "Our study showed that the Framingham general CVD risk score tool has moderate discrimination and good calibration in an Asian population." "moderate" and "good" not defined in the Methods. Page 15, Line 25-27, "This is because the prediction is accurate for both men and women with low risk and for men with high risk." The prediction for men with high risk in this cohort varied from that of Framingham by 6%. The authors did not explain how much of discrepancy is considered acceptable. Page 16, Line 12-14, "To the best of our knowledge, this is the first study that examines the validity and applicability of the Framingham general CVD risk tool for primary care." There may be some publications that need to be looked at, see below: (i) Liu J, Hong Y, D'Agostino RB Sr, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004; 291(21):2591-9. (ii) Khalili D, Hadaegh F, Soori H, et al. Clinical usefulness of the Framingham cardiovascular risk profile beyond its statistical performance: the Tehran Lipid and Glucose Study. Am J Epidemiol. 2012;176(3): 177-86. (iii) Al-Lawati JA, Barakat MN, Al-Lawati NA, et al. Cardiovascular risk assessment in diabetes mellitus: comparison of the general Framingham risk profile versus the World Health Organization/International Society of Hypertension risk prediction charts in Arabs--clinical implications. Angiology. 2013;64(5): 336-42. Ref 19: author's name incorrect?

REVIEWER	Dr Gil-Guillén Miguel Hernández University, Spain
REVIEW RETURNED	13-Jan-2015

GENERAL COMMENTS	Introduction: 1) Please, avoid the use of the abbreviation “CV”. 2) Indicate if the Framingham General Risk Score has been validated in other regions. 3) Taking into account that your population is multi-ethnic, please indicate some information about this in the introduction of the manuscript. Material and Methods: 1) Please use a subsection entitled “design”. 2) I think you could use time-to-CVD data; therefore you will not have losses in your study. This is the methodology of the Framingham Heart Study. MAJOR COMMENT. 3) Did you calculate confidence intervals? 4) Once you calculate time-to-event, you have to perform a Cox model with the Framingham Score. The c-index of this model is the best value you have to use. MAJOR COMMENT. Results, Discussion and Conclusion: please, use my recommendations about the statistical methods and then update these sections.

REVIEWER	Jennifer Salinas University of Texas Health Science Center Houston School of Public Health Epidemiology, Human Genetics and Environmental Sciences El Paso Regional Campus
REVIEW RETURNED	03-Feb-2015

GENERAL COMMENTS	Overall this is a well-written manuscript addressing the applicability of the FRS in the Asian population. This work is important, since the index was created based on a non-Hispanic white population living in the United States. Determining its usefulness in other race/ethnic groups and countries is an important step. Moreover testing its utility in a clinic-setting is novel. The justification is acceptable and methods are appropriate. My only real comment to the authors is that there are some grammatical issues throughout the paper that should be addressed prior to publication

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Cheong Lieng Teng
Thank you very much for all your pertinent comments. We have made the revisions as below.

Reviewer’s comment:
1. Page 9, Line 8, one percentage is missing?

Answer:
We have now added 46.3% into the sentence to read as “Inspite of the increase in the prevalence of diabetes from 43.3% to 46.3%, HbA1c control actually improved from a mean of 7.8% to 7.5%.”

2. Page 14, Line 46-48, "Our study showed that the Framingham general CVD risk score tool has moderate discrimination and good calibration in an Asian population." "moderate" and "good" not defined in the Methods.-add in
Answer:

We have now added the definition on moderate and good discrimination in the materials and methods section and have referenced this definition as reference number 22 (title of Contrasting two frameworks for ROC analysis of ordinal ratings.)
Under discrimination subheading last paragraph, we have added as below

A value of 0.75 is considered as good discrimination. Value between 0.51-0.74 is considered moderate and ≤0.5 as poor [22].

3. Page 15, Line 25-27, "This is because the prediction is accurate for both men and women with low risk and for men with high risk." The prediction for men with high risk in this cohort varied from that of Framingham by 6%. The authors did not explain how much of discrepancy is considered acceptable.

Answer:
We made this statement because while the predicted absolute risk (28.7%) varied by 6% compared with the observed risk (22.8%) both risks scores still fall within the same category of risk i.e. predicted risk is high risk, observed risk is still high risk. Similarly for the low risk group for men and women, their predicted risks and the observed risk still remain in the same low risk category. So we are now expanded the sentence to read as
In-spite of the Framingham risk score seemingly over-predicting CVD risk to some extent, we feel that it is appropriate for use in our cohort. This is because the prediction is accurate for both men and women with low risk and for men with high risk in that the predicted and the observed risk score belong to the same category of risk i.e when

4. Page 16, Line 12-14, "To the best of our knowledge, this is the first study that examines the validity and applicability of the Framingham general CVD risk tool for primary care." There may be some publications that need to be looked at, see below:
(i) Liu J, Hong Y, D'Agostino RB Sr, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA. 2004; 291(21):2591-9.
(ii) Khalili D, Hadaegh F, Soori H, et al. Clinical usefulness of the Framingham cardiovascular risk profile beyond its statistical performance: the Tehran Lipid and Glucose Study. Am J Epidemiol. 2012;176(3): 177-86.
(iii) Al-Lawati JA, Barakat MN, Al-Lawati NA, et al. Cardiovascular risk assessment in diabetes mellitus: comparison of the general Framingham risk profile versus the World Health Organization/International Society of Hypertension risk prediction charts in Arabs--clinical implications. Angiology. 2013;64(5): 336-42.
Answer:
Thank you for your pertinent comment. We were actually referring more to a multi-ethnic population rather than just a primary care setting and we inadvertently left out the word of multi-ethnic. We have now removed the word " first study" and have included the word " multi-ethnic" which is reflected our results.
We have addressed the above by deleting the sentence with the word "first study" and replaced in our manuscript for it to read as

Another strength of this study is that it examines the validity and applicability of the Framingham general CVD risk tool in a multi-ethnic primary care population.

5. Ref 19: author's name incorrect?
Answer:
Thank you for your accurate observation. The citation is correct as appears in the journal and in Pubmed. The authors had asked for a correction but it was not carried out. Hence the citation remains as it is.

Reviewer Name Dr Gil-Guillén
Thank you very much for all your pertinent comments. We have made the revisions as below.
1.Introduction:
1.1) Please, avoid the use of the abbreviation “CV”.
Answer:
We have replaces CV with the word “cardiovascular” in the manuscript.

1.2) Indicate if the Framingham General Risk Score has been validated in other regions.
Answer:
We addressed the above in our manuscript under discussion of this study, first paragraph last three sentences to read as:-
A very recent study validated the Framingham cardiovascular risk score in Tehran , a Middle Eastern population and found it to work very well [24].

1.3) Taking into account that your population is multi-ethnic, please indicate some information about this in the introduction of the manuscript.
Answer:
We added this statement under Introduction to read as:-
Malaysia is a multi-ethnic country with a population of 30 million. The major ethnic group is the Malay (50.4%) lowed by Chinese (26%), Indians (7.1%) and others (21.5%) [19].

2. Material and Methods:
2.1) Please use a subsection entitled “design”.
Answer:
We added this subsection entitled design under Material and Methods to read as:-
Design
This sample was randomly selected using a computer generated number based on the patient’s unique registration number with the clinic. All patient records were in paper form.

2.2) I think you could use time-to-CVD data; therefore you will not have losses in your study. This is the methodology of the Framingham Heart Study. (MAJOR COMMENT)
Answer:
We acknowledge that time to event is very important. However the time to event was not captured. Hence we are unable to do time-to-CVD data.

2.3) Did you calculate confidence intervals? (FRS)
Answer:
Yes , we calculated the confidence interval from SPSS program.
The median Framingham risk score is 21.1% (95% confidence interval is 19.9% to 21.1%).
We added the confidence interval into Framingham CVD risk scores under Result to read as:-

The median Framingham general CVD risk score for the study population was 21.1% (IQR 1.2-30.0%) with a 95% confidence interval (CI) of 19.9% to 21.1%. The actual number of CVD events that occurred in the 10 years was 127 (13.1%) while the predicted was 204(21.1%). In male, their median risk score was 30.0% (95% CI 24.9%, 26.4%) while the events that occur was 62 (19%). In female, their median risk score was 18.5% (95% CI 24.9%, 26.4%) while the event that occur was 65 (10.2%).

2.4) Once you calculate time-to-event, you have to perform a Cox model with the Framingham Score. The c-index of this model is the best value you have to use.(MAJOR COMMENT)
Answer:
Since we did not have the data on the time to event . Hence we are unable to do cox model.

3. Results, Discussion and Conclusion: please, use my recommendations about the statistical methods and then update these sections.
Answer:
Thank you for your very pertinent comment.
We acknowledge and know that time to event is very important. Unfortunately we did not capture the time to event and hence we are unable to do time to CVD event or cox model and update accordingly.

Reviewer Name Jennifer Salinas

Overall this is a well-written manuscript addressing the applicability of the FRS in the Asian population. This work is important, since the index was created based on a non-Hispanic white population living in the United States. Determining its usefulness in other race/ethnic groups and countries is an important step. Moreover testing its utility in a clinic-setting is novel. The justification is acceptable and methods are appropriate. My only real comment to the authors is that there are some grammatical issues throughout the paper that should be addressed prior to publication
Answer:
We had addressed this issue by sending the article for proof reading.

VERSION 2 – REVIEW

REVIEWER	Dr Gil-Guillén Miguel Hernández University, Spain.
REVIEW RETURNED	03-Mar-2015

GENERAL COMMENTS	All the comments have been assessed correctly.