PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Distribution of 10-Year and Lifetime Predicted Risk for Cardiovascular Disease in the Indian Sentinel Surveillance Study Population (Cross-sectional survey results)
AUTHORS	Jeemon, P; Prabhakaran, D; Huffman, M; Ramakrishnan, L; Goenka, S; Thankappan, KR; Mohan, V; Joshi, PP; Mohan, BVM; Ahmed, F; Ramanathan, M; Ahuja, R; Chaturvedi, V; Lloyd-Jones, DM; Reddy, KS

VERSION 1 - REVIEW

REVIEWER	***Danish Saleheen*** ***Center for Non-Communicable Diseases, Pakistan*** ***I dont have any competing interests with the work under review.***
REVIEW RETURNED	16-Feb-2011

THE STUDY	The investigators have used western tools (ATP III) criteria to calculate short term and life long risk of CHD in a population living in India. There are various limitations in both the design and the statistical analyses of the study which are outline below: (I) The ATP III risk assessment tool is known to have even limitations in the western populations. Other risk scores such as Q-risk which allows recognition of certain ethnicities (eg, South Asians) could have been better suited for this particular study; (II) The investigators have used blood pressure and total cholesterol as categorical variables whereas they could have used them as linear variables given that both of these variables are continuously associated with the risk of CHD.
REPORTING & ETHICS	No details on the research ethics have been provided.

REVIEWER	***Richard W Morris*** ***Professor of Medical Statistics & Epidemiology*** ***University College London, UK***
REVIEW RETURNED	24-Feb-2011

THE STUDY	The chief "outcome" in the paper is the categorisation of risk for each subject, whether low short-term, low lifetime risk, low short-term/ high lifetime risk, or high short-term risk. While these definitions can be understood by reading some of the author's references (notably 13 and 21), they were not at all clear in the present manuscript. The chief limitation of the work, not mentioned in the manuscript, is that the participants range from ages 20-69, yet the concept of high

	lifetime risk is taken from risk factor data among participants of the Framingham study when they reached the age of 50. Thus no account can be taken of the participants' varying ages. Even if the age-adjusted lifetime risk of CVD for the Indian population were the same as for the Framingham population, the classification in the present study would be flawed. Arguably high lifetime risk has been underestimated for those under 50, and overestimated for those over 50. Comparisons by age are therefore of doubtful validity. Similarly, other comparisons involving socio-demographic variables possibly related to age (such as educational group) will also be biased. Even the overall estimate may be affected: since the mean age for study population was 40.8, the main result "2 in 3 men and 1 in 2 women had high lifetime risk" may be an underestimate. The problem outlined might be fixed by adjusting all risk factor levels observed in the present study to their expected levels at age 50, achieved by a series of regression analyses of each risk factor on age. Thus for example a 20 year-old participant's blood pressure would be adjusted upwards, and a 69 year old participant's blood pressure would be adjusted downwards. This would probably lead to a higher estimate of lifetime risk for younger participants and lower estimate for older participants. It would assume the younger individuals will all survive to age 50 without dying from CVD, and in this sense the adjustment will not quite go far enough. Some reporting of p-values seems inappropriate in the manuscript (see below)
RESULTS & CONCLUSIONS	Many of the p-values in Table 2 are inevitably low because of the definitions of risk groups being compared. The null hypothesis is inevitably false when comparing distributions of variables which from part of the risk group definition (e.g. age, SBP, DBP, TC, tobacco use, diabetes etc). I suggest all p-values be omitted from Table 2, which stands as a very useful descriptive Table. The p-values in Table 3 are invalid for age (as explained above) and possibly for "Location" and "Education" which may well be related to age. The p-value for Total (top row) appears meaningless. Adjusted estimates as suggested above may be useful. Much of the text in the results section would need to be rewritten.
GENERAL COMMENTS	I note that the authors quote Marma et al (2010). Having looked at Marma et al's paper, I see they follow exactly the same methodology as in the present manuscript, applying Framingham lifetime risk to the NHANES data. I still maintain however that the differential biases with age will apply. Please note that Marma et al do not make the mistake of carrying out significance tests to compare risk factors across risk groups. I wish however to say that the description of risk factor data from such a major study in India are very worthy of placing in the public domain and I should be keen to see the data published. I would just ask the authors to consider a further analysis along the lines suggested.

VERSION 1 – AUTHOR RESPONSE

Please see below our response to reviewers comments.

Reviewer 1: (I) The ATP III risk assessment tool is known to have even limitations in the western populations. Other risk scores such as Q-risk which allows recognition of certain ethnicities (eg, South Asians) could have been better suited for this particular study.

Our response: We agree with the reviewer that the ATP III 10-year risk assessment tool has limitations in using in the Indian population. However, Chow et al (2009) performed a recalibration of Framingham short-term risk score using prospective data from the South Indian population. No significant difference in risk prediction using the original risk score vs. locally calibrated version was observed (10 year probability is men was 10.4% vs. 10.7% and in women it was 5.3% vs. 4.2%).

The risk factor-disease lifetime risk relationship in Framingham lifetime CVD risk score is further strengthened with the evaluation of markers of preclinical atherosclerosis (Berry, et al 2009): younger individuals with higher risk factor burdens (the low short-term/high lifetime risk group) have a thicker CIMT and higher CAC scores than individuals with lower risk factor burdens (low short-term/low lifetime risk group).

The QRISK lifetime CVD risk score developed by Hippisley-Cox, et al (2010) includes additional variables on deprivation score, chronic kidney disease and atrial fibrillation. We did not measure these variables in our population and the deprivation score is not applicable to Indians living in India. Furthermore, similar to the Framingham Risk Score, the QRISK score is not validated in Indians living in India. It is important to note that the risk factor profile of Indian migrants in UK and non-migrants in India vary significantly.

We believe that Framingham risk score is much simpler and useful in the general population. We have also explained the limitations of using this risk assessment in our manuscript in the discussion section.

Reviewer 1: (2) The investigators have used blood pressure and total cholesterol as categorical variables whereas they could have used them as linear variables given that both of these variables are continuously associated with the risk of CHD.

We agree with the reviewer. However, the lifetime risk assessment tool uses categorical variables and follows a risk factor counting strategy to calculate lifetime CVD risk. We therefore used this model in our analysis.

Reviewer 1: (3) No details on the research ethics have been provided.

The study protocol was approved by the institutional review boards of all participating institutes and written informed consent was obtained from all participants. We have added this statement in the text.

Reviewer 2: (21) The chief "outcome" in the paper is the categorisation of risk for each subject, whether low short-term, low lifetime risk, low short-term/ high lifetime risk, or high short-term risk. While these definitions can be understood by reading some of the author's references (notably 13 and 21), they were not at all clear in the present manuscript.

Our response: We thank the reviewer for his comments and understand that it will be difficult for a general reader to check the references to comprehend the concept. We have now added the following statement in the introduction section to provide clarity: Lifetime CVD risk estimation, which measures the cumulative risk of developing the disease during the remainder of an individual’s lifespan, may provide a more appropriate assessment on future CVD risk than short-term (typically 10-year) risk estimates, especially in younger individuals in whom short-term risks are low. Furthermore, we explain the lifetime risk stratification in detail in Table 1.

Reviewer 2: (2) The chief limitation of the work, not mentioned in the manuscript, is that the participants range from ages 20-69, yet the concept of high lifetime risk is taken from risk factor data among participants of the Framingham study when they reached the age of 50. Thus no account can be taken of the participants' varying ages. Even if the age-adjusted lifetime risk of CVD for the Indian population were the same as for the Framingham population, the classification in the present study would be flawed. Arguably high lifetime risk has been underestimated for those under 50, and overestimated for those over 50. Comparisons by age are therefore of doubtful validity. Similarly, other comparisons involving socio-demographic variables possibly related to age (such as educational group) will also be biased. Even the overall estimate may be affected: since the mean age for study population was 40.8, the main result "2 in 3 men and 1 in 2 women had high lifetime risk" may be an underestimate.

Our response: A forthcoming paper by co-author Dr. Donald Lloyd-Jones (first author: Jarett Berry) using data from the Lifetime Risk Pooling Project (second review, New England Journal of Medicine) describes the fidelity of the risk factor/disease relationships across various cohorts, age groups, and risk factor combinations, without requiring adjustments as suggested by the reviewer. The risk factor-disease lifetime risk relationship is further strengthened with the evaluation of markers of preclinical atherosclerosis (Berry JD, et al. Circulation 2009; 119: 382-9): younger individuals with higher risk factor burdens (the low short-term/high lifetime risk group) have a thicker CIMT and higher CAC scores than individuals with lower risk factor burdens (low short-term/low lifetime risk group). Given the strength of these relationships, over- and underestimates appear minimal. We have added this as a potential limitation in the manuscript.

Reviewer 2: (3) The problem outlined might be fixed by adjusting all risk factor levels observed in the present study to their expected levels at age 50, achieved by a series of regression analyses of each risk factor on age. Thus for example a 20 year-old participant's blood pressure would be adjusted upwards, and a 69 year old participant's blood pressure would be adjusted downwards. This would probably lead to a higher estimate of lifetime risk for younger participants and lower estimate for older participants. It would assume the younger individuals will all survive to age 50 without dying from CVD, and in this sense the adjustment will not quite go far enough.

Our response: We have adjusted all risk factors levels observed in the present study to their expected levels at age 50 years, as suggested by the reviewer. We have then calculated the lifetime CVD risk based on the adjusted risk factor variables and data are presented in a separate figure (Figure 3). We prefer to keep this figure as an additional figure as it may not be appropriate to estimate the risk factor levels at age 50 years based on the current risk factor status and their relationship with age.

Reviewer 2: (3) Many of the p-values in Table 2 are inevitably low because of the definitions of risk groups being compared. The null hypothesis is inevitably false when comparing distributions of variables which from part of the risk group definition (e.g. age, SBP, DBP, TC, tobacco use, diabetes etc). I suggest all p-values be omitted from Table 2, which stands as a very useful descriptive Table.

Our response: We agree with the reviewer and we have removed all 'p' values.

Reviewer 2: (4) The p-values in Table 3 are invalid for age (as explained above) and possibly for "Location" and "Education" which may well be related to age. The p-value for Total (top row) appears meaningless.

Our response: We have removed the 'p' values for age. However, the 'p' values for 'location' and 'education' are adjusted for age.

Reviewer 2: (5) I note that the authors quote Marma et al (2010). Having looked at Marma et al's paper, I see they follow exactly the same methodology as in the present manuscript, applying Framingham lifetime risk to the NHANES data. I still maintain however that the differential biases with age will apply.

We have addressed this concern in our previous comments (Reviewer 2: (2) and Reviewer 2: (3))

Reviewer 2: (6) I wish however to say that the description of risk factor data from such a major study in India are very worthy of placing in the public domain and I should be keen to see the data published. I would just ask the authors to consider a further analysis along the lines suggested.

Our Response: We agree with the reviewer that it is important to publish this data in the public domain. To the best of our knowledge lifetime CVD risk estimate among Indians are not available in the public domain. We have done our best to address all the concerns raised by the reviewer and modified the manuscript by incorporating new analysis and omitting redundant text.

VERSION 2 - REVIEW

REVIEWER	***Richard W Morris***
REVIEW RETURNED	22-Mar-2011

GENERAL COMMENTS	Reviewer completed checklist only. No further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author: None

Comments from the managing editor, BMJ Open:

Please expand the 'Strengths of this study' section to read 'Strengths and limitations of this study' and incorporate a brief overview of the study's limitations, as discussed later in your paper.

Our response: We have expanded the section to include the limitations of the study as well and added the following bullet point;

- Our simple cardiovascular risk factor counting strategy provides good discrimination for identifying individuals at high and low lifetime risk for CVD, but the lifetime CVD risk prediction model has not been validated nor calibrated in India.

Please also check the ICMJE criteria for authorship: http://www.icmje.org/ethical_1author.html. At present it is not clear that all authors meet all three criteria - for example, which authors approved the final version? Also, authors Goenka and Chaturvedi did not appear to have any involvement in the writing/revising of the manuscript and therefore would not qualify as authors.

Our response: We apologize for the oversight. Drs Goenka, Chaturvedi and all other authors revised the draft manuscript and approved the final version. We have revised the authorship statement to incorporate these changes.