Author's response to reviews

Title: Younger Age of Escalation of Cardiovascular Risk Factors in Asian Indian Subjects

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Version: 2 **Date:** 19 April 2009

Author's response to reviews: see over

Manuscript No. MS: 1897871095245849

Steep Age-Associated Escalation of Multiple Cardiovascular Risk Factors in Young Asian Indian Subjects

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We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.
Please also address the following:
- Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'.
A: Enclosed

- Please include an Authors' contributions section before the Acknowledgements and Reference list.
A: Enclosed

- Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study.
A: Enclosed

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.
A: Not relevant.

First Reviewer's report
Reviewer: Jeetesh Patel
Reviewer's report:

This is an interesting and topical article about the accelerated advance of cardiovascular risk amongst people living in India. The data underlines a rapid growth in the prevalence of risk factors – a conundrum for any primary prevention strategies.
A: Thanks

- Major Compulsory Revisions
1. My main concern is statistical. The authors use ANOVA and chi square tests to test for the significance of trends. However, fundamentally, these test should be used to signify differences between groups. In this context, these tests should only be used to underline secular differences – not trends. Rather, I would propose that ordinal regression (PLUM on packages such as SPSS) be employed to look at the magnitude of such trends. Ordinal regression can be used to identify whether there is a significant ordinal trend, and one may also calculate a pseudo R square to determine the strength of such a trend. Given that the basis for this work is developed around trends in risk factors, I also propose that attention is given to an ad hoc power calculation based on the identification of trends / association in this manner.

A: This issue has been discussed with the statistics expert in the group and other statistical consultants. Ordinal regression is useful when there are more than two outcome groups and the consensus was that this is not an appropriate test. .
For Table 2, we have now analysed the data using regression analyses using SPSS program. The details have been added to the methods section and results have been

modified. Regression coefficients, standardised beta (alike correlation coefficient) and p values have been calculated.

For Table 3, trend calculations using ordinal regression outcomes was possible if there were more than 2 outcome groups. Chi-square for trends was considered better option.

2. Cross sectionally, age is an established risk factor (albeit elsewhere) for all of the CVD risk factors that have been listed in this paper. However, the authors use linear regression and logistic regression in a cross sectional manner to profess the 'age associated escalation of risk factors'. This is not appropriate and while data here supports the view that age is related to CVD risk factors, it does not support an acceleration of these risk factors. What is needed is an analysis of the change in risk factors (vector rather than scalar approach – cf. an analysis of acceleration rather than velocity). This is likely to involve a far more complex analysis of the data, likely to be beyond the scope for this work. Nonetheless, terms such as 'age associated escalation' should be removed. The authors have sufficient evidence to describe the nature with which CVD risk changes in a secular sense within this group, and are ill advised to discuss the determinants of such an advance.
A: We agree. This has been added to the discussion and study limitations section.

3. The conclusion does not include any details relating to the implications of such findings.
A: Added.

- Minor Essential Revisions
The introduction is far to verbose and reads as a review of the topic rather than an intro. Much of the text can be moved to the discussion (eg. Tuzcu et al reported that coronary atherosclerosis as determined by intravascular ultrasound in asymptomatic subjects started early and was significant by the age of 30-39 years in a Caucasian population. 18 Framingham study has reported that risk factor burden starts early in life and by 50 years of age was 51.7% for men and 39.2% for women. 19)
A: Introduction section has been shortened accordingly.

Rather, what is needed is a clear explanation of the clinical utility of such work and its context. The authors should also consider how similar studies (eg. Secular trends in CVD risk factors for African Americans in the US; stroke risk factors for ethnic minorities in the UK) have been important in identifying the epidemiology of disease within populations.
A: Added to introduction and discussion sections.

The methods are lacking details as to how the work was carried out. Further information is needed on anthropometric methods (definition of waist and hip), the equipments used and their standardization between the two studies. Also, biochemical descriptions of tests are inadequate. For example, if one fasting blood sample was taken, was it a fluoride oxalate tube? How was cholesterol, glucose etc measured on the same sample? What equipment was used and how were the tests standardized. These may questions may appear to be an over complication of details – but the study is based on the evaluation of secular changes in these aforementioned risk factors - as such, the reader needs to be confident that the measurements taken were standardized.
A: More details of methodology for anthropometeric measurements and biochemical estimations have been added.

- Discretionary Revisions
The results section in the abstract is difficult to read. It would be easier to see the data presented in a fashion that allows the reader to appreciate the magnitude of change in these risk factors. For example, I would quote the prevalence of risk factors in the young, but then follow this with 95% CI changes in risk factors for

subsequent groups.
A: Changed accordingly.

Remove the term and data for metabolic syndrome in the abstract as the clustering of risk factors does not add to the value of this abstract – the data on individual risk factors are far more interesting.
A: Changed.

In the introduction, references to studies of CVD in young and adolescents that have been carried out in India should be included - this includes references from the authors themselves as well as authors such as S Dwivedi – who has looked at early CAD in India.
A: Agreed.

Second Reviewer's report
Reviewer: kiran patel
Reviewer's report:

Discretionary:
1.The title could be more crisp to identify ' Increasing prevalence of cardiovascular risk factors with Age in Indians'
A: Title changed accordingly.

2. Is there data on socioeconomic migration as individuals age - i.e. is there a difference in the extent of CV risk factor accumulation for those who increase social standing vs those who do not? If possible, it would be useful to have this data to strengthen this data. If not, this may form the basis of an excellent follow on paper.
A: Unfortunately no such data are available. Thanks for the suggestion.

Overall, this is a valuable paper and identifies the need for targeting primary prevention in Indians at a young age.
A: Thanks.

Third Reviewer's report
Reviewer: Ashan Gunarathne
Reviewer's report:

The objective of this manuscript was to determine the age-associated escalation of Multiple Cardiovascular Risk Factors in young South Asian population. Overall this paper appears well constructed and the methods suitably performed but there is a scope for improvement in scientific writing and results presentation.
A: Presentation improved as above.

I have some serious concerns with the main study hypothesis and the derived conclusions. The research hypothesis which is being tested is not clear and apparent. In keeping with the given study hypothesis, this is not a novel study and has been carried out in many previous studies in India as well as in migrant South Asian populations living in the developed world. Increase prevalence of CVD risk factors with age has been repeatedly reported in many cross sectional as well as few longitudinal studies, even looking at impact of migration, life style etc. Therefore the presented finding don't add any new knowledge to the current understanding of conventional CVD risk characteristics amongst this higher risk South Asian population.(Please see recent publications by JV Patel & GYH Lip etc.. below). However one suggestion would be to present the current findings in a different angle including CVD risk scores, and compare these with other South Asian and European Caucasian population. Moreover then the authors have the valuable opportunity to follow this cohort over a period of time to observe their actual CVD /CHD risk and validate or propose a more ethnicity

sensitive risk score for South Asians as majority of the current risk score under estimate CVD risk amongst higher risk young South Asians.

A: Thanks for the suggestions. The focus of the article is identification of age at which escalation of cardiovascular risk factors start. This is important for planning of suitable intervention and prevention strategies. We feel that the revised version of the article now provides this clear message.

Chaturvedi N. Ethnic differences in cardiovascular disease. Heart. 2003;89:681-6
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3 Gunarathne A, Patel JV, Potluri R, Gill PS, Hughes EA, Lip GY.Secular trends in the cardiovascular risk profile and mortality of stroke admissions in an inner city, multiethnic population in the United Kingdom (1997-2005). J Hum Hypertens 2008;22:18-23