

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)	Additive influence of genetic predisposition and conventional risk factors in the incidence of coronary heart disease: a population-based study in Greece
AUTHORS	Yiannakouris, N.; Katsoulis, Michail; Trichopoulou, Antonia; Ordovas, Jose; Trichopoulos, Dimitrios

VERSION 1 - REVIEW

REVIEWER	Carlo La Vecchia University of Milan
REVIEW RETURNED	30-Nov-2013

GENERAL COMMENTS	<p>This is a well written report from an original and interesting dataset.</p> <p>I have only two minor suggestions open to the authors' consideration:</p> <ol style="list-style-type: none">1. The association between smoking and myocardial infarction in intrinsically underestimated in cohort studies, since a proportion of smokers stop after data collection, and the RR falls rapidly after stopping. This can be further discussed.2. Before the up to date approach to define genetics of CHD in this paper, there were works based simply on family history as an indicator of genetic risk, such as the one quoted below. This work can be mentioned, if useful, in the Discussion. <p>Influence of selected lifestyle factors on risk of acute myocardial infarction in subjects with familial predisposition for the disease</p> <p>Tavani A, Augustin L, Bosetti C, Giordano L, Gallus S, Jenkins D J A, La Vecchia C Prev Med 2004 ; 38 : 468-472</p>
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REVIEWER	Dr. Jayashree Shanker Thrombosis Research Institute India
REVIEW RETURNED	08-Dec-2013

GENERAL COMMENTS	It is recommended that the authors include the information on diabetes to the conventional risk factors and calculate RERI.
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

This is a well written, interesting paper from a well recognised group, which is likely to be widely quoted. This is a well written report from an original and interesting dataset.

We appreciate the statement of the Reviewer that our paper is well written and interesting. Thank you.

I have only two minor suggestions open to the authors' consideration:

1. The association between smoking and myocardial infarction is intrinsically underestimated in cohort studies, since a proportion of smokers stop after data collection, and the RR falls rapidly after stopping. This can be further discussed.

We thank the reviewer for this comment, and have added the following lines to the Discussion section.

Page 12, lines 9-15

Nevertheless, the use of single baseline measurements of ConvRFs can lead to underestimation of associations with CHD risk (through regression dilution bias). [42] For example, the association between smoking and cardiovascular disease is intrinsically underestimated in cohort studies, since a proportion of smokers stop after data collection, and the relative risk falls rapidly after stopping. Correcting for within-person variation in lifestyle factors over time may result in more informative estimates of CHD risk associated with these factors, particularly for the risks associated with continued smoking and the benefits of regular physical activity,[43], and therefore, future studies should take these influences into account.

2. Before the up to date approach to define genetics of CHD in this paper, there were works based simply on family history as an indicator of genetic risk, such as the one quoted below. This work can be mentioned, if useful, in the Discussion.

Tavani A, Augustin L, Bosetti C, Giordano L, Gallus S, Jenkins D J A, La Vecchia C Influence of selected lifestyle factors on risk of acute myocardial infarction in subjects with familial predisposition for the disease. *Prev Med* 2004; 38: 468-472.

We thank the reviewer his comment. The following lines have been added to the Discussion section quoting also the indicated reference (ref. 39 of the revised manuscript).

Page 11, lines 20-24

In this respect, Tavani et al.[39] have previously examined the joint effect of a family history of heart disease, taken as a proxy for genetically determined predisposition to the disease, and selected adult life risk factors on the risk of the disease and have shown that a substantial increase in heart disease is evident when both a family history and the environmental risk factors are present.

Reviewer #2

It is recommended that the authors include the information on diabetes to the conventional risk factors and calculate RERI.

According to the reviewers' comment we have included the information on diabetes in all Tables (Tables 1-4) and calculated RERI.