PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Famine in childhood and post-menopausal coronary artery calcification
AUTHORS	Idris, Nikmah; Uiterwaal, Cuno; van der Schouw, Yvonne; van Abeelen, Annet; Roseboom, Tessa; de Jong, Pim; Rutten, Annemarieke; Grobbee, Diederick; Elias, Sjoerd

VERSION 1 - REVIEW

REVIEWER	STEFANO CIANFARANI Tor Vergata University, Rome, Italy
REVIEW RETURNED	24-Sep-2013

GENERAL COMMENTS	The aim of this study was to investigate the association between the exposure to famine during childhood and the development of coronary calcium deposition and its effect on cardiac valve and aortic calcifications in late adulthood. This was a retrospective cohort study on 286 postmenopausal women exposed to famine during World Was II in the Netherlands. The main finding was that severe famine exposure during adolescence was related to a 3.5 fold higher risk (OR 3.47, 95% CI 1.00-12.07) for a high coronary calcium score than unexposed women, also after confounder adjustment. No association with extra-coronary calcifications was observed. Coronary artery calcifications were evaluated by CT scan. The degree of exposure to famine was assessed by questionnaires. This study was conceived on the basis of the programming concept proposed to link early life events with cardiometabolic risk in adulthood. The reported data suggest that the critical time window for programming extends well beyond intrauterine and early extrauterine life, involving childhood and adolescence. The aim of the study is certainly worthwhile but hardly achievable. Indeed, this study suffers from a number of weaknesses. The responses to the questionnaires after so many years can be affected by multiple factors as honestly recognized by the Authors. Association does not necessarily mean causation. For instance, the stress related to the exposure to famine as well as diet and life style in later years, diseases and therapies, and genetic susceptibility could account for the findings and were not extensively investigated. In the Discussion, the Authors try to conceptualize their results but the comparison with patients with end-stage renal disease looks stilted. The sentence “that maintaining a balanced life, including a balanced nutrition, is important throughout growth and development” looks trivial. The Authors do not provide an explanation for the absence of detrimental effect of undernutrition on extra-coronary calcifications. Finally, the cohort sizes in the different subgroups (139 vs 103 vs 44) appears too small to draw convincing conclusions on this delicate and intriguing issue.

REVIEWER	Caroline Fall University of Southampton, UK
REVIEW RETURNED	25-Sep-2013

GENERAL COMMENTS	This study tests whether exposure to famine in childhood and/or adolescence is associated with increased coronary artery calcification detected on CT scans (CT-CAC, an indicator of coronary artery disease) in post-menopausal women. Valvular calcification and thoracic aorta calcification were additional outcomes. It was an 'opportunistic' study, taking advantage of the fact that CAC measurements were made as part of another study in individuals exposed to famine in early life. Data were obtained by questionnaire to assess self-reported famine exposure. The opportunistic nature of the study probably explains the small sample size (see below). The definition of 'scan positive' was appropriate and scan quality as judged by reproducibility was good; scans were reported blind to famine exposure. The study found an association between severe famine exposure during adolescence and increased CT-CAC. There were no associations between famine exposure and valvular calcification of aortic calcification. It is an important question whether exposure to under-nutrition in utero predisposes to adult coronary heart disease (CHD). This question has mainly been studied using less specific methods to assess the outcome of CHD (either mortality, or events or ECG changes). As far as I know, this is the first study to examine CT-CAC in relation to early life under-nutrition. The results are consistent with other data from this group, other Dutch Famine groups, and the Leningrad famine group, showing an increased risk of diabetes, CVD and/or greater CVD mortality in people exposed to famine in adolescence. The study is interesting a) for its use of CT-CAC scores, b) for also studying calcification in heart valves and aorta, which may have a different aetiology from CAC, and c) in identifying adolescence as a potentially critical period for under-nutrition to programme the development of atherosclerotic disease. The results were appropriately analysed, clearly described, and in general well discussed. The main criticism of the study is its small sample size and consequent lack of power. It is possible that the study missed effects that would have been seen in a larger study. The authors should acknowledge the fact that the study is under-powered more than they do, and suggest that further evidence is needed. None the less, as an opportunistic study, in which the results are consistent with the starting hypothesis, these novel findings deserve publication. I think the important section in the Discussion, dealing with why there may be different findings for CAC compared with valvular and aortic calcification, was inadequately referenced – there needs to be better support for the proposition that there are differing aetiologies for calcification at these sites. Minor point: In my print copy, many of the references (eg 9, 12, 24, 46, 47) contained typos due to missing letters – this needs to be

	checked out by the authors.

VERSION 1 – AUTHOR RESPONSE

Response to to Stefano Cianfarani's comments:

We thank the reviewer for his valuable comments. Herewith you find our response to his queries:

In terms of concerns related to famine exposure measurement, we have acknowledged that our measurement may be prone to misclassification. However, as has been mentioned in the discussion section (paragraph 6), our exposure data reflects the historical facts of calorie rationing practice at that time that it can be considered a validation for our data quality. The reviewer will agree that our acute famine exposure data, although indeed not perfect, is quite rare (worldwide) and that it is impossible to improve it to date. We believe that it is currently the best estimate of famine exposure. Notably, famine exposure questions were asked without any reference to the research question addressed here, and therefore misclassification/measurement error in famine exposure cannot have been selective in the sense of having been related to CT scan findings. Moreover, if misclassification did occur, we believe that it had occurred at random and will only have resulted in underestimation of the observed effects.

We respectfully disagree that we have not extensively investigated other factors that may influence our findings. Although we did not directly adjust our analysis for diet, lifestyles, or co-morbidities, we did account for body mass index and waist-to-hip ratio, which are largely reflective for those factors and which are direct risk factors for vascular changes that we describe. We do not find it easy to understand how genetic susceptibility could confound our finding. We can conceive of such susceptibility being related to calcification but we cannot understand how it could be related to whether one is exposed to famine or not. The reviewer is correct in that the effects of famine and war related stress can not fully be distinguished.

We do agree that at first glance it may seem somewhat irrelevant to compare our findings to patients with end-stage renal disease, but we used this comparison because as far as we know it is the only known human model for the association of malnutrition and vascular or valve calcification.

We have explained in the discussion section that the absence of a detrimental effect on extra-coronary calcification may be caused by different biological mechanisms of coronary versus extra-coronary calcification.

In concurrence with the other reviewer, we do agree with this reviewer’s remark that our study has small sample size. Our study is indeed ‘opportunistic’ in the sense that it uses the rare combination of famine data in youth and CT scan data in later adulthood. The size of this study was therefore largely beyond our control. The reviewer rightfully indicates that we could have missed the effects of famine on valvular or aortic calcification, simply for reasons of lack of statistical power. Nevertheless, with this relatively small number of subjects, we have been able to show an association between famine in adolescence and coronary artery calcification. We do, for now, consider this finding a relevant confirmation of our earlier finding about such famine exposure being associated with clinical cardiovascular disease. To address the size issue, we have revised the corresponding paragraph (paragraph 2) in the discussion section, in which we further acknowledge this lack of statistical power. Obviously, we do consider our finding one of a hypothesis generating nature that hopefully stimulates further research in this area.

VERSION 2 – REVIEW

REVIEWER	Stefano Cianfarani Tor Vergata University, Rome, Italy
REVIEW RETURNED	12-Oct-2013

GENERAL COMMENTS	Although the data are undoubtedly intriguing, unfortunately this reviewer is not yet convinced about the robustness of the provided evidence. The Authors' rebuttals have not fully addressed and solved the weaknesses of the study.

REVIEWER	Caroline Fall MRC Lifecourse Epidemiology Unit, University of Southampton
REVIEW RETURNED	24-Oct-2013

- The reviewer completed the checklist but made no further comments.