

Oct-2015

Dear Prof. Jousilahti

Manuscript ID BMJ.2015.027895.R1 entitled "Forty-year change in coronary heart disease mortality among working aged men and women in Eastern Finland: the role of primary prevention and risk factor reduction" which you submitted to BMJ,

Thank you for sending us your paper, manuscript. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Jose Merino
jmerino@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=de55da439cbc4a82b846f6436daa0c3d

****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Gary Collins (statistician), Wim Weber, Alison Tonks, Tiago Villanueva, Rubin Minhas, Jessamy Bagenal, José Merino

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- We see the clinical and historical value of this study. This is a major effort and the findings from the 40-year analysis will be very useful to clinicians and researchers.

-We need more information about the participants. How many patients were enrolled and followed each year (n per year)? Did the characteristics of the enrolled patients change over time?

- Please provide additional details about the models. How were the four predictors (age, smoking status, cholesterol level, BP) chosen? Were any other predictors examined and not included? The authors looked at both diastolic and systolic and in 'stepwise' analyses but DBP was dropped. Why? We need more information on these models and the steps taken to derive them, as well as some indication on their performance (model fit) as the analysis is underpinned by these models.

- The authors used data between 1972 and 1997 – why? This is not stated.

- Please clarify how the confidence interval around the predicted mortality change was derived.

- Presumably the figures in brackets in Table 2 represent the CI but this is not stated. Please clarify.

- Emphasize, if appropriate, the role of competing risk factors over time.

- Raw data numbers in the abstract will be important to ensure the paper is read and referenced. Please modify.

- You will notice that the three patient reviewers made several valuable comments. When preparing your response, please take these comments into account as their suggestions may improve the reporting and analysis. If you disagree with some comments or conclusions, please justify your thought process. We are not persuaded that the findings do not translate to other settings.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

**** Comments from the external peer reviewers****

Reviewer: 1

Comments:

This paper reports the 40-year trends in coronary heart disease mortality in the working-age population of Finnish men and women and relates these trends to changes in risk factors. Given the duration of the study and the fact that the risk factor collection protocols were both carefully constructed and the observations were carefully recorded, this study is unique. It demonstrates that very large changes in CHD mortality rates can be achieved through concerted action.

I do have some issues with some of the wording. In the abstract, line 31, for example, I would prefer a word other than "remarkably", but that is a minor point.

Regarding the conclusion, I think it is more accurate to write, "Large declines in disease burden and mortality due to CHD can be achieved through population-based primary prevention programs. Secondary prevention among high risk individuals confers additional benefit." I think that this is what the study adds (page 3, line20)--a very important observation for world-wide efforts to control chronic diseases.

Articles like "the" are frequently missing in the text, perhaps because Finnish doesn't use them. This is an easy fix for the editors.

Page 8, line 51 has a colloquialism "...way to go." A more formal text might be, "Thus, a population-based strategy to move the whole cholesterol distribution downward would be the most effective."

I don't find that the paragraph on trends in other countries (page 10 starting on line 42) adds to the discussion. It could be deleted if space is tight.

To sum up, this paper is a unique resource for individuals and organizations that are developing plans to address the burden of coronary heart disease. The methods are clearly described and the discussion clearly describes the changes in each of the risk factors and the extent to which they contributed to the very large decline in coronary heart disease mortality rates.

Additional Questions:

Please enter your name: Thomas Kottke

Job Title: Medical Director for Population Health

Institution: HealthPartners

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here:

Reviewer: 2

Comments:

The research team present a high quality study on trends in contributions of risk factors to CHD mortality in Finland over four decades. The data are from a unique and valuable source of information CVD epidemiology—population surveillance data from Finland, and in this case, Eastern Finland, the site of the landmark North Karelia study. Not only were the society-wide CVD prevention strategies of the North Karelia study revolutionary for their time, but the idea of measuring the results of these interventions has proved valuable as a proof of the value of primary CVD prevention. Less appreciated is the importance of Finland's use standard CVD case and cause of death definitions over decades, which avoids the vulnerability to changing case and cause of death definitions other surveillance studies face.

*** Originality**

Conceptually, this study is not unique or novel. A number of modeling and regression studies (including the IMPACT studies cited by the authors) have used modeling methods to distinguish the contributions of CVD primary versus secondary prevention/acute care. The liability of these studies is that they often pull data on risk factor exposures, treatment use, mortality, and relative risks from diverse sources (derived from samples or populations that differ from the population of interest). The contribution of this study is that it studies long term trends in major risk factors and their association with mortality in the same population, using logistic regression and standard risk factor and mortality metrics over time. The finding that the contributions of smoking, cholesterol, and high blood pressure have diminished over time is provocative, and the authors propose some possible explanations, but none of these is backed with any evidence and these explanations remain conjectural in the end.

*** Importance of work to general readers**

As stated above, this study deals with the leading cause of death in Finland and worldwide. An important question is whether CHD is becoming an epidemic of the 20th century or if obesity, sedentarism, diabetes, and nontraditional risk factors will lead to a new wave of higher CHD burden. This analysis partially, but not completely answers the question. Certainly there is no evidence that CHD mortality is returning to the rates seen in 1970's Finland. The authors clearly demonstrate that the

contribution of smoking/cholesterol/blood pressure have diminished. But the question of whether different risk factors and secondary prevention treatments have become more important drivers of CHD death rates than tobacco/cholesterol/blood pressure is not clearly demonstrated in the paper.

* Scientific reliability

Yes, the research question is clearly defined.

Overall design of study - adequate ?

Yes.

Participants studied

Yes.

Methods

Really Finland is the gold standard for population surveillance of CVD. The authors provide a full accounting of their methods in the STROBE statement attached with the paper.

The authors report that ethical standards were followed and informed consent was obtained from participants.

Statistical methods were appropriate, standard and clearly stated.

The study would be improved if average #cigarettes/day is substituted for active smoking in a sensitivity analysis (this would investigate possible confounding by lighter smoking over time). Please add medication use to models of cholesterol and blood pressure if possible.

The Methods could be improved by providing a rationale for the selection of tobacco, cholesterol, and blood pressure alone. Because they were the only ones measured consistently? Because they account for by far the greatest disease burden?

Results

Research question is clear and well presented.

Tabular and graphical presentation of the data is excellent.

Interpretation and conclusions

The interpretation and conclusions are warranted by the data, but limited and tentative. I believe the authors could draw strengthen the paper's assertions in the following ways:

1) The authors fail to account for the possible effects of medication treatments. Statins and antihypertensive drugs may lower population mean cholesterol and blood pressure, but not fully reverse the atherosclerotic impact of years of prior exposure. This would bias the estimation of % contribution of these risk factors.

2) Similarly, did the authors consider estimating the tobacco contribution using number of cigarettes per day? If smokers are smoking less on average recently, this will also bias the estimate.

3) Please report on simultaneous trends in overweight, obesity, and diabetes at least for the years in which they were measured.

4) CHD death rates are much more affected by acute care procedure availability than are ischemic stroke death rates. The authors would do well to include an analysis of ischemic stroke mortality trends, using a similar method. It may be very instructive. At the least, the authors should report on the trend in ischemic stroke mortality over the same period.

5) Page 11: The trend in coronary catheterizations and percutaneous interventions in the United States does not parallel the rate of acute MIs. This is because much of the PCI trend was driven by elective procedures in patients with stable coronary disease. The author's contention that PCI rate increases represent an improvement in acute care is not necessarily true. Additional information is needed in order to establish that clinical practice in Finland is such that the observed increase in PCIs represents an increase in acute coronary interventions (in the setting of MI or unstable angina), not elective, sometimes unnecessary procedures.

6) As far as alternate drivers of CHD mortality, along with the possibilities the authors list, the following should be mentioned: binge alcohol drinking, depression, and social deprivation.

References -

References are good.

Abstract/summary/key messages/What this paper adds -

The key messages text is well stated

See above for my opinion on the limitations of the paper's conclusions

If the paper is a randomised controlled trial we will have asked the authors to provide the protocol and a CONSORT checklist. Other research designs should have the relevant checklist (PRISMA, STARD etc). These are available by clicking on "Download associated files".

The authors provide a full accounting of their methods in the STROBE statement attached with the paper.

Additional Questions:

Please enter your name: Andrew Moran

Job Title: Assistant Professor of Medicine

Institution: Columbia University Medical Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: I have no competing interests to declare.

Reviewer: 3

Comments:

In the manuscript by Jousilahti P. al. titled "Forty-year change in coronary heart disease mortality among working aged men and women in Eastern Finland: the role of primary prevention and risk factor reduction", authors conclude, "Population based primary prevention and reduction in the levels of major risk factors are crucial in lowering of disease burden and mortality due to CHD. An additional gain can be achieved by secondary prevention among high risk individuals and by treatment of acute events."

Authors may consider the following suggestions for improvements:

Major comments

1. Cause of death data were used as the primary outcome measure. The role of potential misclassification of these data are however not discussed. Instead, very precise rates of deaths from CVD are provided ("From the baseline level at the early seventies (1969-1972) to 2012 CHD mortality decreased from 643 to 118 per 100,000 among working aged men (aged 35 to 64 years) and from 114 to 17 per 100,000 among working aged women (Figure 1).") Also, it is stated that the study had "practically complete mortality data".

While Nordic countries often have accurate and complete data on all-cause mortality, the data quality of cause of death data, in particular from CVD, are often more questionable. In some countries, some researchers argue that these data are too imprecise to be used at all if not validated (typically by autopsy). Are the authors able to reassure the readers that the quality (both sensitivity and positive predictive values) of these data is adequate throughout the study period? Also, cause of death data (at least in Denmark) are often registered with both an "underlying cause of death" and "immediate cause of death". The data quality of these different registrations also differs. If this is the same in Finland elaboration is needed.

2. Authors write, "In the first surveys, participation rate was high, over 90% but declined in the later surveys being 64% in the last survey" and also discuss the consequence of this later on "we know that the risk factor levels among non-participants are somewhat higher than among the participants [42]. Therefore, our model may overestimate the importance of the risk factor change in the last couple of decades."

Individual-level linkage of study participants as well as non-participants to other registers using personal identifiers may enable computation of calibrated weights that can be used in data analyses to reduce bias stemming from differential non-response (nonresponse bias). Such weights can be based on a range of variables for all individuals who were invited in the survey. We have previously described this in more detail (Schmidt M. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* 2014; 29(8), 541-549). Would this be possible in Finland?

3. From these data, the reduction in smoking prevalence seem to play no or only a minor role in the decline in CVD mortality over time. These findings are in contrast to previous reports (below). Please elaborate on the discrepancy and potential explanations?

Nabel, E. G., & Braunwald, E. (2012). A tale of coronary artery disease and myocardial infarction. *The New England Journal of Medicine*, 366(1), 54-63. doi:10.1056/NEJMra1112570

Tarone, R. E., & McLaughlin, J. K. (2012). Coronary arteries, myocardial infarction, and history. *The New England Journal of Medicine*, 366(13), 1259-60- author reply 1260. doi:10.1056/NEJMc1201171#SA2

4. Overall CVD mortality reduction is a measure of both the decline in incidence of CVD and prognosis from CVD. It would be interesting to provide data on these separately to estimate the predictive value of the risk factors on both.

5. Ford et al (*NEJM.* 2007;356(23), 2388-2398) found in a previous study that "Approximately half the decline in U.S. deaths from coronary heart disease from 1980 through 2000 may be attributable to reductions in major risk factors and approximately half to evidence-based medical therapies." The contribution in the current study of evidence based medical therapies is smaller. Please discuss the current findings in relation to findings from other countries.

Minor comments

6. The paper would improve by providing more citations to support the statements made throughout. Preferable it should be clear from each sentence what data are being referenced. For example, citations are missing for each of the following sentences: "Furthermore, CVD mortality is increasing in many developing countries and countries in transition. Of the total of 54.9 million deaths in the world in 2013, 17.3 million (31%) were due to CVDs. Globally CVD is the most common cause of death in all World Health Organization (WHO) regions except in the African region. CHD is the most common CVD in Europe, Americas and Australia, whereas cerebrovascular diseases are more important in many Asian countries."
7. The Introduction section would benefit from being shortened to no more than one page. The description of the data source etc could be moved to the Methods section.
8. Figures would improve by adding colours and more precise titles to the x-axis and y-axis.

Additional Questions:

Please enter your name: Morten Schmidt

Job Title: Research fellow

Institution: Aarhus University Hospital, Denmark

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: I have received various funds for research, but none that would constitute a competing interest for the current study review.

Reviewer: 4

Comments:

This is basically an excellent paper
I have no major concerns .

It is original, with new data, especially the analysis by 5 year periods

It is potentially important. Finland is a global leader in terms of effective, population-wide cardiovascular disease prevention policies, and disease monitoring.

Hence of interest to policymakers, also to clinicians, patients, & teachers

Scientific reliability is high.

Research Question is clearly defined and appropriately answered

Overall design of study very adequate

Participants studied - well described

Methods - well described. Complies with relevant reporting standard .

Results - Answer the research question, credible and well presented

SPECIFICS:

Please reverse order of Tables 1 and 2. Readers will wish to see values and changes in absolute values of risk factors before examining derived estimates.

Table 1 (currently). Showing the contribution of specific RF changes in each five year period would be much more informative than the existing version showing the cumulative effect (where the contribution of the last five years is obscured by the effect of all the previous years).

The current (cumulative effects) table could perhaps be consigned to an Appendix.

Please estimate the CHD mortality INCREASE attributable to the important rise in cholesterol 2007 to 2012. This rise was unequivocal, and consistent with trends in N. Sweden, and possibly elsewhere. A ballpark figure of the additional mortality would be valuable.

DISCUSSION, Interpretation and conclusions - warranted and mostly derived from the data

Basically very good with clear messages

Page 8. The paragraph on Smoking is too triumphalist. Yes, much has been achieved, and should be celebrated. BUT smoking prevalence rates of 29% in men and 19% in women compare badly with exemplars like Australia and California. And the Tobacco Control Scale in Finland is lower than some other European countries. Please say what the next steps in additional Tobacco Control might include.

Page 9. Finland managed to reduce dietary salt intake more than any other country, a huge achievement. Please add a couple more sentences to explain HOW this accomplished.

Please reverse the order of final paragraph on page 9 (In the 1970s and early 1980s...) and first para on page 10 (In addition to the three classical risk factors...) . Because it makes more sense to talk about major risk factors, then other risk factors before moving onto healthcare contributions.

Page 11. Conclusion paragraph. The first and second sentences are very good, and sufficient.

Please delete the final sentence because:

- a) It cannot be justified on the basis of these data or analyses,
- b) It cannot be justified on the basis of previously published papers from Finland, Europe or the USA.

Population wide policy interventions are consistently more powerful than therapeutic interventions for established disease. They are also rapid and equitable, and usually cost saving.

References - up to date and relevant. No glaring omissions

Abstract/summary/key messages/What this paper adds

ABSTRACT, Results section is a bit texty, add a bit more numeric detail?

ABSTRACT Conclusions, and What this Paper Adds

This analysis did not quantify treatment contributions. So the one third contribution is speculative (although likely correct), therefore speculative.

Therefore, please minimally rephrase Final sentence along lines of:

"The additional gain might be reasonably attributed to primary prevention medications, treatment of acute events and secondary prevention".

Additional Questions:

Please enter your name: Simon Capewell

Job Title: Professor of Clinical Epidemiology

Institution: University of Liverpool

Reimbursement for attending a symposium?: No

A fee for speaking?:

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: I have collaborated with some of the authors on half a dozen past papers (IMPACT model).

Reviewer: 5

Comments:

As patient reviewer I ask myself the question: 'What is the benefit or added value of an investigation for patients?'

This paper describes the effects of risk factor reduction on CHD mortality in men and women who participated in the National FINRISK Studies over a period of 40 years.

The authors should describe better whether the participants are from eastern Finland only or all parts of Finland. This is important because I understand that around 1972 only participants from Karelia were included, a region which was known for high CHD mortality. In case participants from all parts of Finland were included (assuming less CHD mortality) the question arises whether this affects the positive effects of the Karelia population.

Also is missing the every 5-year total population (may be this can be included in the tables).

Apart from these detailed questions the results (fig 1) are clear: two more or less parallel declining curves. The authors should explain whether these curves are typical for the participants from Finland or applicable to the western countries (already published data?).

The authors explain in the discussion that the measured effects are mainly caused by the three used risk factors. The argument that the increased use of drugs and interventions cause a further decline is obvious.

Figures 2 and 3 are confusing.

Based on fig 2 (men) the conclusion may be drawn that the decrease of cholesterol levels has greatest impact. It is not clear whether smoking and/or blood pressure are responsible for the extra decrease.

Fig 3 (women) shows a comparable decline to about 20% in 2012. Also the cholesterol curve is comparable. Differences were found in smoking (increase) and blood pressure (stronger decrease as compared to men).

It would be strange to state 'Mind your cholesterol, try to diminish blood pressure but keep smoking'. The authors need to clarify.

This paper caused more questions than answers. Also the final statement (last 2 lines page 11) is generally known and should be clearer in the paper to justify acceptance.

Additional Questions:

Please enter your name: JWCM Jansen

Job Title: Patient reviewer, pharmacologist

Institution: The Expert Cardiovascular Patient Panel, De Hart&Vaatgroep, The Netherlands

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: no competing interests

Reviewer: 6

Comments:

This study's aims are laudable, and if its outcomes were repeatable in other communities' as readily as seems the case in Finland, both patients and their carers, who emulate the interventions could be assured of a least a reduction in the incidence of CHD. However, as an informed patient, I am highly sceptical that this would be the case, for a number of reasons.

This study is the latest in a long history of the remarkable reduction strategies undertaken in Finland to reduce the heavy burden of CHD in men especially, since 1972, which has been revisited every five years. But, I find the predicted change to observed change, difficult to attribute to the primary risk factor reductions that were measured. The prediction calculations have been very wide of the mark, such that I question their validity. However, whilst the actual mortality to CHD cannot be refuted, some of the reasons for it surely must be.

What I find to be missing is the data that might explain this remarkable volte face, because there surely have to be other unexplained factors that contributed. These could be the large reduction in smoking, which seems to have been underestimated in its efficacy, which fell from 53% to 31%, and is now reported as being 20% (2014); the rapid rise in exercise activities' together with State provision of facilities for this, became one of the highest in the Western World.

The extremely high intake of Polyphenols, in the form of newly cultivated berries that were part of the initiative to increase fruit and vegetable consumption, which lent themselves more readily to the harsh climate, and which had been a large part of the native diet prior to WW11. These antioxidants have been attributed as being hugely important for health and well-being, as well as CHD reduction.

Also; during the study period, intake of refined flour and cereals declined from 57 kgs per person year to 15 kgs. Sucrose intake also declined by some 50% since its level in the 1960's.

Reduction in serum cholesterol, blood pressure, and saturated fat intake were unlikely to be solely responsible for the stellar reduction in CHD which the authors do admit as responsible for only two thirds of the last ten years reduction in CHD mortality. They acknowledge that some of the factors I allude to as being responsible equally as these three, were not included in their analysis: why?

I have serious doubts as to whether this type of intervention would work in the UK and many other societies. We are nothing like as compliant to Government initiatives and interventions as the Fin's. And science has moved on from these simplistic interventions to a better understanding of how diet reflects on both CHD and all-cause mortality. Ancel Keys in fact in his 1980 Seven Countries Study, stated that in the Finnish arm, "the lowest serum cholesterol concentrations at entry (in men) were associated with an excessive ten year death rate from causes other than coronary heart disease".

Of course today, we no longer associate saturated fats with heart disease; we no longer equate dietary cholesterol with serum cholesterol levels; we do not demonise sodium with the same vigour and acknowledge its need for humans (albeit at quite low levels). We no longer view seed oils high in linoleic acid, as benign, or indeed any PUFA's because of their fragility (even n-3).

Partially hydrogenated spreads as butter replacements, which were in use until recently as part of this intervention,+ are now seen as dangerous.

The outcomes in this study are one's that all patients would find important to achieve but how they would go about reproducing them I do not believe is informed by this study. There has to be some reason, perhaps unique to Finland that is not being revealed here. Something I think that those conducting the study are missing altogether. Whilst I cannot refute the actual outcome of CHD mortality; if it's at the expense of some other demise that occurs within the same time frame as CHD, we may perhaps want to stick with our (slightly) higher serum cholesterol.

Finally, even with this vast reduction from such a huge burden of premature CHD mortality from 643 to 118 (per100, 000) this is still somewhat high compared with the UK (60/100k); the USA (78/100K), and of course the 'paradoxical' French (30/100k). I feel the research has to be widened and re-evaluated to take account of the factors that have been missed because it's vital that we know.

Additional Questions:

Please enter your name: Ernest Berry

Job Title: Security Systems Engineer and Consultant. Patient Advocate. Carer for Type 2 Diabetic.

Institution: Self Employed

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here: I have in the last thirty years been employed by a number of Pharmaceutical Companies as contractor for security services. I have not participated in any activity related to drugs or medical devices or research in these roles.

Reviewer: 7

Comments:

General comments

This is an ecological study of the 40-year change in coronary heart disease (CHD) mortality among men and women age 30-59 in Eastern Finland. Finland at one time had the highest CHD mortality in the world, and certainly it is of interest to patients to understand the results of public health programs that were undertaken to reduce this source of premature mortality through reductions in smoking, blood pressure and blood cholesterol levels in the Finnish population. I hope that public health officials in Finland will make available these results to citizens in Finland on social media or other easily accessible forums. I do wonder if the BMJ is the best journal for this study. Many similar studies have already been published based on data from various countries and regions within countries. Perhaps a more specialized journal, such as one focused on epidemiology or quality of care, such as European Heart Journal: Quality of Care and Clinical Outcomes or European Journal of Epidemiology, would be more appropriate.

Other comments

1. The paper could benefit from some discussion of the limitations of ecological studies, such as the inability to infer causality and the potential for unmeasured confounding.
2. Has data been collected on trends in other risk factors, such as BMI and diabetes?
3. Are there other potential explanations for the reduction in cholesterol levels, other than reduction in intake of saturated fat and the use of cholesterol-lowering medications? Have all countries reduced saturated fat intake at the same time as cholesterol levels have declined (France?)?
4. Do these data suggest the need for any changes in public health programs in Finland?

Additional Questions:

Please enter your name: Marilyn Mann

Job Title: retired (patient reviewer)

Institution: not applicable

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests ([please see BMJ policy](#)) please declare them here:

Reviewer: 8

Recommendation:

Comments:

The present manuscript is a well-written interesting analysis on the effect of population strategy to reduce CVD risk factor burden on the CHD mortality. The authors demonstrate a clear secular trend associating the reduction in smoking prevalence, systolic blood pressure and cholesterol with the reduction of CHD mortality in middle-aged individuals. The current results are a follow up of a similar analysis performed 20 years ago and published at the BMJ, and supports a continued reduction in mortality through the reduction in the three parameters listed above. Interestingly, the association between the predictors and CHD mortality explains the outcome a bit less than predicted in recent years as compared to early years.

The authors conclude that a population strategy aiming those risk factors is still the main stem for reduction in CHD mortality. The paper is overall very clear and easy to follow, and the results give a comprehensive understanding of the main points presented by the authors. However, I have some points, which I think need to be addressed by the authors. I also believe the authors can easily address all of the points raised here.

Major:

1. Although the authors list some reasons for the higher than expected mortality rate in the recent years, they forgot to mention the possibility that their model is imperfect. The logistic model proposed by the authors assume a linear association between SBP & cholesterol with mortality, and a binary association between smoking and events. I think the authors need to bring the limitation of their model as part of the reason why this gap may occur. Some evidence to support this is:
 - a. Although the authors measured smoking as a binary variable, it is well documented since the 60 that the duration of smoking habit, as well as its intensity are associated with CAD. It is also well documented that the overall pack-years smoked is much lower now than before. Thus, the effect of "smoking" today may be lower than in the sixties (probably about half). Similarly, many of the non-smokers are ex-smokers, which have an intermediate association with events when compared to non-smokers and smokers. Since the prevalence of smokers is dropping, so is the proportion of ex-smokers, and this has not been accounted for
 - b. A similar problem is seen with SBP & cholesterol although the models proposed by the authors assume a linear relationship; this may not be the most appropriate form of dealing with such predictions. One very clear example of this is the new ASCVD equation for risk assessment proposed by the ACC/AHA in 2013, where some parameters are included in the model as quadratic terms as well as linear. In fact, a quadratic association may even be more plausible from a pathophysiological standpoint, particular for parameters which may have a threshold where further reduction may not further improve outcomes, or may even worsen prognosis (such as hypertension).
 - c. There is a potential for interaction between the parameters included in the model. This is also demonstrated by the ASCVD, which included interaction terms.
 - d. Overall, I think the current analysis and discussions are adequate enough and do not need to be repeated with the inclusion of the items above, but I think a clear statement bringing up the potential limitation in modeling as a plausible explanation for the difference between predicted and expected is needed.
2. The authors do not provide the actual sample size per year. I think this numbers are crucial in understanding the potential limitations of their analysis. They have nine time points of data and 34000 individuals. Thus, I would assume about 1900 from each gender at each time point. Since the response rate was lower in recent year, this number is probably lower to. If this is too low, it may limit some of the proposed conclusion. Thus, please provide sample size per year. My personal suggestion is to bring this up in table 2.
3. I do not agree with the abstract conclusion or with section 2 "what this paper adds". The authors mention risk factor reduction is "crucial" and that "a smaller gain can be achieved by secondary prevention". Neither is clearly the core of the current analysis. My understanding is that: risk factor reduction at a population level is a very effective way of reducing CHD mortality, though other parameters, such as secondary prevention may have added additional reduction in recent years. Since the authors have not tested a different strategy, saying their effective one is crucial (although probably correct) is not fully supported by the evidence (due to lack of a counterfactual) and should be avoided in order to maintain scientific rigor.
4. Similarly, the last sentence of the conclusion of the manuscript is a bit overstated. I would rather say "might" than "can".
5. I think figure 2 should include the 95% CI of the predicted reduction for the combination of the three predictors as a light gray area. This would allow a visual interpretation of the precision of the difference between predicted and observed findings.
6. The second paragraph of page 10 lists other risk factors not included in the model. Instead of listing all minor non-important ones, I think this paragraph would add a lot more to the understanding of the current impacts if the authors mentioned what has happened to such risk factors over the last 40 years. Has obesity increased? DM? Physical activity? Others? It seems to me that DM and obesity have increased, and would not explain the excess reduction in events. On the contrary, they could have increased it. Thus, some discussion on the potential impact of this other risk factor would be of interest in my personal opinion.

Minor:

1. The last sentence of page seven (ending in page 8) is a bit confusing and could be rephrased.

I would like to conclude by saying that the findings of the current manuscript are, in my opinion, of great interest to readers of

BMJ as well as to health planners and policy makers at large.
Once again, I would like to thank authors and editors for the opportunity to give my opinion to such a high-level manuscript submitted to this very remarkable journal.

Additional Questions:

Please enter your name: Marcio Sommer Bittencourt

Job Title: Attending Cardiologist

Institution: University Hospital - University of São Paulo

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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