

Helsinki 04.12.2015

Dear Editors,

We would like to thank the manuscript committee and the reviewers for their valuable comments and suggestions on our 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".

Kindly find following our detailed responses to the comments. Due to large number of comments and fairly detailed suggestions, the discussion is quite long, and we are ready to shorten it if needed. The revised manuscript, both a plain copy and a copy with track changes, have been submitted to the editorial system.

We hope very much that the revised manuscript will satisfy you. However, if needed, we are happy to make further changes according to your advice. We are looking forward hearing from you, and we hope, that your decision for publication will be positive.

Yours sincerely,

Pekka Jousilahti

pekka.jousilahti@thl.fi

Responses to the manuscript committee and the reviewers (ID BMJ.2015.027895.R1) :

Report from The BMJ's manuscript committee 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:

We would like to thank the reviewers and the manuscript committee for their valuable comments and suggestions on our manuscript. Kindly find our responses after each comment.

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.

Thank you.

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?

We have added the number of participants enrolled in each survey year in table 1 (table 2 in the original manuscript). Main cardiovascular health related characteristics of the participants are presented in the same table. Some other factors, such as trends in obesity prevalence, physical activity and alcohol consumption are included in the discussion (page 9). Because our sample is a random sample of the population, the changes in the sample reflect the changes in the population in the study area. In the two first surveys in the 1970s, the sample size was 6.6.% of the population (in 1972 aged 25-59 years and in 1977 aged 30-64 years) of the study area. Later on a by sex and 10-year age group stratified random sample was taken in both provinces according to the WHO MONICA protocol and the later recommendations of the European Health Risk Monitoring project. The common age range of the all surveys was 30-59 years. Participants in this age group with complete data on all three risk factors are included in the present study.

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 there performance (model fit) as the analysis is underpinned by these models.

The three main risk factors, smoking, serum cholesterol level and blood pressure, were selected for two reasons, first because they were the main target risk factors for the CHD prevention when it was started in the 1970s, and their causal roles in the development of CHD and other cardiovascular diseases are well established. Second, these three risk factors were also the strongest predictors of CHD mortality in the

prospective analysis. Obesity and sedentary lifestyle were not particular problems in eastern Finland in the 1970s, but have become major issues later on. Including BMI in the model changed the result only marginally, because the effect of obesity is largely mediated through its effect on blood pressure, which is included in our analysis. Assessment of total physical activity is complicated in large epidemiological studies: we know that physical activity in work and travel to and from work has decreased whereas leisure time physical activity has increased during the four decades of our study. The prevalence of diabetes has been increasing, partly due to increasing obesity and partly due to change of the diagnostic criteria for diabetes. These issues are included in more detail in the discussion (page 9).

In the original stepwise model we had both systolic and diastolic blood pressure in the model, both of them predicted CHD deaths but the predictive value of systolic blood pressure was stronger and it was selected in the final model. Due to strong inter- correlation between systolic and diastolic blood pressure, including both of them in the model is not meaningful. Including age in the models was considered as self-evident, and age was also a strong predictor of CHD mortality in the model.

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

These years were selected to get the maximum number of end point events (CHD deaths) and statistical stability on the predictive model. In predictive model building, all participants were followed up for 15 years. Because our follow-up was until the end of 2012, this 15-year follow-up was available for the participants in 1972-1997 surveys.

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

Thank you for noting this; the original sentence was not clear and we have now clarified it. Confidence intervals for the differences in predicted mortality were calculated by first estimating the probability of death based on the actual risk factors levels in each of the survey cohorts and the logistic regression model coefficients, together with the corresponding standard errors. Next, the differences in these estimated probabilities were calculated, and the corresponding standard error for the difference was estimated based on the assumption of independent samples and common variance.

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

The figures in brackets represent 95% Confidence interval, and it is now stated in the table (table 1 in the revised manuscript).

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

The role of competing (other) risk (and protective) factors, such as diet, BMI, physical activity, diabetes and alcohol consumption, and their change during the four decades of the study is now emphasized in more

detailed in discussion (page 9). The issue was raised also by several referees. Kindly see our responses to the referee comments.

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

The abstract has been revised based on the comments of the editorial committee and the reviewers, and we have added more numeric data in the abstract. Kindly see also our responses to the reviewers.

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.

We have read the comments of the patient reviewers carefully, and also their comments have been taken in consideration in the revision.

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.

We have done our best to reply to all of the comments made by the reviewers and the editors. We hope that our responses will satisfy you. However, if needed we are happy to provide more information on our study and revise the manuscript according to your advice.

Comments from the external peer reviewers:

Reviewer: 1

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.

We would like to thank the reviewer for his supportive comment.

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.

We have changed the wording according to the reviewer's suggestion.

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.

This issue was raised by several reviewers (1, 3, 4 and 8). We have revised the conclusions (in abstract, discussion, and in the "what this study adds" section) based on the comments of the reviewers.

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

We have checked the language throughout the text, and hope that it is now improved. However, we are happy to make further changes, if needed.

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."

We have edited the text according to the reviewer's suggestion (page 8).

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.

We have shortened the paragraph by deleting the detailed data on changes and trends in other countries (page 10).

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.

Thank you.

Reviewer: 2

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.

We appreciate this comment very much.

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.

We agree with the reviewer. Our study demonstrates the strength of primary prevention and the role of the three classical risk factors for CVD prevention over long period of time. The IMPACT method provides more detailed information on the role of secondary prevention and treatment. Collection of data for IMPACT analysis is quite demanding requiring usually also search of patient records and possible only for relatively short time periods and in small population groups. Thus, our study and the IMPACT modelling are complementary.

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.

We have provided more data and discussed these issues in more detail. We have added data on the trends in other factors, such as obesity, physical activity, alcohol consumption, and dietary changes, as well as secondary prevention and treatment practices, in the discussion (kindly see also our reply to the reviewer 1). Because we do not have individual-level data on the changes in secondary prevention and treatment of acute CHD events, our interpretation on their role is only indirect. This is now stated more clearly in the discussion (page10).

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 average number of cigarettes smoked by the smokers daily reduced during the 40 year period slightly in men (from 18.5 to 16.8) and increased slightly in women (from 10.9 to 12.2). This change in the amount of daily smoking has only a minor effect on the prediction. However, we agree that our model most probably underestimates the importance of smoking change on CHD mortality reduction. Because smoking was assessed only at the beginning of the follow up, we do not have data on the quitting during the follow up. This issue is now raised up in the discussion (page 11) and we have added a new reference. Unfortunately we do not have reliable data on medication use for the whole survey period. However, medication effect (for cholesterol lowering medication and anti-hypertensives) is reflected already in reduction of serum cholesterol and blood pressure levels.

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?

Please see our previous responses on risk factor selection.

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:

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.

Thank you for the comment. We have now raised this issue in the discussion (page 11).

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.

Kindly see our previous responses concerning the effect of the change of tobacco smoking on the predicted CHD mortality decline. This is now added to the discussion (page 11).

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

More data on the trends in overweight, obesity, diabetes and also physical activity are now included in the discussion. Kindly see our previous responses.

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.

Analysing the role of risk factors on the trends of ischemic stroke mortality is a large topic. It also needs modification of methodology as ischaemic stroke is fairly rare among the working age population. We see that a detailed analysis is an issue of another paper. Because the discussion is already quite long, we have not raised this issue in the discussion, but if need we are ready to do it.

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.

Because we do not have individual level data on treatment practices, we can assess the role of treatment in CHD mortality decrease only indirectly. Major developments in secondary prevention and treatment practices are described in the discussion (page 10). The paragraph is already lengthy, but if needed we can provide more details.

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.

These three topics are now included in the discussion (page 9 and 10). Kindly see also our previous responses on the role of other risk factors.

Reviewer: 3

Major comments:

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”.

Misclassification of causes of death and other end points is always a potential problem in large population based studies using register data. The reliability of causes of death register data can be assessed by comparing the register data with the data in more specific disease registers and patient records. Validation studies have shown that the reliability of causes of death register data is fairly good. This is now stated also in the discussion (page 11). The Finnish causes of death register is practically complete, covering the whole country, and also most of the deaths occurred abroad. The number of deaths which are not registered or the registration is delayed is very small and cannot affect the results anyhow.

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.

See our previous response. Individual verification of the cause of death (through patient records and autopsy) is not possible in large population studies. However, in Finland several validation studies have been conducted in different time periods showing that the accuracy of CHD diagnosis in the death certificates is fairly good. Reliability of diagnosis in death certificates is also better in deaths in relatively young age (in our study below 65) compared with the death in older age among people with multiple morbidities. We have now included one reference on the issue.

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?

Thank you for the comment and suggestions how to reduce possible bias due to non-response. However, as correcting the model with indirect data on non-participants is very complicated methodology and based on many assumptions, we feel this kind of a modelling would need to be a separate study. We have raised this issue now in the discussion as a limitation. In addition, even though the participation in our studies has

decreased during the decades, the participation rate even during the last survey years was fairly high compared with many other large population-based studies.

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

We agree that our model may underestimate the role of the change of tobacco smoking on the predicted mortality change. This issue is now covered more detailed in the discussion (page 11). It should also be noticed that the effect of the change in smoking prevalence on mortality change depends both on the baseline prevalence and the size of the change which vary between countries.

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.

We have analysed the change of CHD mortality over 40 year period of time. Unfortunately we do not have comparable data on CHD incidence over the same period of time.

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.

This issue is now included in the discussion. The relative importance of primary prevention and treatment in mortality change varies between countries, depending on original level of risk factors, changes on treatment system, time period and the age group of the study population. In the US study, the age group included also elderly people until the age 84 year whereas our study population covered the working age men and women. However, if we look the same time period, 1980-2000, our findings are fairly similar with the US study. We have added the article of Ford et al as a reference.

Minor comments:

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."

The statement on the general epidemiological situation is based on the findings of the Global Burden of Diseases study, which is the reference 1. We have now moved the place of the reference in the text. In our understanding, we have included adequate reference in the manuscript, but if needed we are happy to add new references.

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.

We have shortened the introduction as suggested.

Figures would improve by adding colours and more precise titles to the x-axis and y-axis.

The figures have been improved by adding colours, as suggested by the reviewer, and we have added also 95% confidence intervals of the predicted mortality reduction curve, suggested by the reviewer 8. In our understanding the titles of x- and y-axis have the needed information when looked together with the figure legends.

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

We appreciate very much of these comments from the reviewer.

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.

We have reversed the order of the tables, and also revised the order of text in the results and abstract accordingly.

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.

In our understanding the current form of cumulative presentation is more informative. The change for each five year period, either relative or absolute, can easily be calculated based on the cumulative figures. However, if the presentation of the change for each 5-year period is preferred by the editors, we are ready to change the presentation format.

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.

The effect of the small increase of the serum cholesterol level between 2007 and 2012 is included in our predictive model on the mortality change between the last five years of the study. Because our mortality data is until the end 2012, we most probably cannot see the effect of the cholesterol increase in the observed mortality yet.

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.

We have added a few sentences in the discussion on smoking control and diet. Due to limited space and the scope of the study, longer discussion on the public health programs and their challenges may not be warranted in this paper.

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.

We have reversed the order of the paragraphs as suggested.

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.

We have revised the conclusions based on the comments of the reviewers. Kindly see the comments and our previous responses to the reviewer 1 and 3.

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

We agree with the referee, even though we do not have health economic analysis in our study.

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

We have revised the abstract and added more numeric data.

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”.

We have revised the conclusions both in the abstract and discussion. Kindly see our previous responses on the issue.

Reviewer: 5

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.

The study population is from two provinces in Eastern Finland. The study population is described in the methods (page 5).

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

We have added, as suggested by the reviewer 1, the number of participants in the risk factor surveys each year in the table 1 (table 2 in the original manuscript). We do not see that including the total population of the study area in the tables would provide additional information relevant.

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?).

Age-adjusted CHD mortality has been declining in most western industrialized countries in the last decades but increasing in many countries in eastern central Europe. The speed of the change varies largely between different countries. CHD mortality decrease in Eastern Finland has been one of the fastest in the world. Kindly notice that in the figure 1 CHD mortality decline is presented in logarithmic scale. Therefore, even though the curves are parallel, the absolute mortality decrease is much larger in men than in women.

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.

We do not have complete individual-level data on treatment and use of drugs during the forty year period of our study. Therefore, we can assess the effect of treatment and drug use only indirectly, which we have now stated more clearly in the discussion.

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.

It is true that the decrease of cholesterol level contributes most of the CHD mortality decline, particularly in men. However, the reviewer's statement on cholesterol, blood pressure and smoking is not correct. We see that reduction of all three risk factors is important. See also our previous responses related to smoking.

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.

We are sorry if the reviewer found the paper confusing. We hope that the additions, modifications and corrections made have clarified both the results and discussion text.

Reviewer: 6

Comments:

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?

We have extended the discussion related to the changes on smoking, physical activity and diet in the discussion. Kindly see our previous responses on the issue.

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 Finish 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.

These comments are a bit polemic and controversial. In our understanding, the scientific community has a large consensus on the role of high cholesterol as a risk factor for CHD, and that the fat content of the diet is a major determinant of serum cholesterol level.

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.

We agree that CHD mortality in Finland is still higher compared with some other countries. In the early 1970s, CHD mortality in eastern Finland was the highest known in the world, now it is on European average level.

Reviewer: 7

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.

According our knowledge this is the only study analysing the effect of primary prevention and risk factor change on CHD mortality over decades. Because primary prevention is the responsibility of general practice, and done also by other sectors outside of health care, we see that the publication in BMJ, as a leading general medical journal, is well grounded.

Other comments

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.

We do not quite agree with the description of the study being ecological. We have individual level cross-sectional population survey data covering years 1972 and 2012, and individual-level follow-up data cover

15 years. However, we agree that we may have unmeasured confounding, such as changes in diet (other than reduction of salt and saturated fat) which may affect the results. This issue is now included in the discussion (page 11).

Has data been collected on trends in other risk factors, such as BMI and diabetes?

Kindly see out previous responses related to other risk factors.

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?)?

Diet and pharmaceutical drug treatment are the main modifiable factors affecting the cholesterol levels in a population. In diet, high intake of saturated and trans-fats and dietary cholesterol increases serum cholesterol levels whereas polyunsaturated fats reduce serum cholesterol.

Do these data suggest the need for any changes in public health programs in Finland?

There is still need for further reduction of the levels of the three classical CVD risk factors, as well as reduction of obesity and increase of physical activity in Finland, as in many other countries.

Reviewer: 8

Comments:

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:

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:

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

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).

There is a potential for interaction between the parameters included in the model. This is also demonstrated by the ASCVD, which included interaction terms.

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 modelling as a plausible explanation for the difference between predicted and expected is needed.

We fully agree with the reviewer that the models here are imperfect, as all statistical models are. Interactions, nonlinear associations and imprecise measurements of explanatory variables all contribute to the models performance. Even though the association between serum cholesterol levels and blood pressure with CHD mortality may be non-linear, the non-linearity is seen at the extrem ends of the distribution, and at the normal population levels the association is fairly linear. Imprecise measurements of the explanatory variables will lead to regression dilution bias, and therefore our analyses of the explanatory role of the selected risk factors can be regarded as conservative.

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.

The sample size in each study year is now included in the table 1 (table 2 in the original manuscript)

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.

We have modified this statement also in this connection (“what this paper adds”), as we have done in the abstract and discussion. Kindly see our previous responses.

Similarly, the last sentence of the conclusion of the manuscript is a bit overstated. I would rather say “might” than “can”.

The wording has been changed as suggested.

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.

We have added the confidence intervals in the figures as suggested. Kindly see also our response to the reviewer 3.

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.

These risk factors and their trends are now included in the discussion. Kindly see our previous responses.

Minor:

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

The sentence has been 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.

We agree with the reviewer.

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.

Thank you. We appreciate the comment very much.

