Author's response to reviews

**Title:** Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. An analysis of 8360 patients in the Northern Sweden MONICA Study

**Authors:**

Rose-Marie Isaksson (rose-marie.isaksson@nll.se)
Jan-Håkan Jansson (JanHakan.Jansson@vll.se)
Dan Lundblad (dan.lundblad@nll.se)
Ulf Näslund (ulf.naslund@vll.se)
Karin Zingmark (karin.zingmark@nll.se)
Mats Eliasson (mats.eliasson@nll.se)

**Version:** 2  **Date:** 30 November 2010

*Author's response to reviews:* see over
Revised version 1.

Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006.
An analysis of 8360 patients in the Northern Sweden MONICA Study

Dear Editor
We thank the BMC Cardiovascular Disorders for the opportunity to revise our manuscript. We also thank the reviewers for their careful and very helpful comments. After considering the issues raised by the three reviewers we are now confident that the paper has improved substantially.

Our comments are enclosed below and highlighted in bold text in the revised manuscript.

We hope the BMC Cardiovascular Disorders now will accept this report for publication.

Best wishes

Mats Eliasson, MD, PhD
Senior consultant, Endocrinology,
Sunderby Hospital, 971 30 Luleå, Sweden

Associate professor
Department of public health and clinical medicine
Umeå University, Umeå, Sweden
Mail: mats.eliasson@nll.se
Phone: +46 920 28 34 53, +46 70 513 02 93 (cell phone)
Reviewer’s report
Title: Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. An analysis of 8362 patients in the Northern Sweden MONICA Study
Version: 1 Date: 9 November 2010
Reviewer: Abel E. E Moreyra

Reviewer’s report:
Major Compulsory Revisions
1. Conduct specificity analysis by including and then excluding death before hospitalization.

We thank the reviewer for this interesting proposition. We performed an analysis by omitting those who died out of hospital and re-ran the Kaplan Meier and Cox analysis. These data are included in the Results for Survival according to sex (p. 6). As expected (as it was previously known that men had a higher proportion of out-of-hospital deaths) this abolished all gender differences (but women did still not fare any worse than men). The important implications for the interpretation of studies based solely on those admitted to hospital (an apparent worse prognosis for women) is now addressed in the discussion (p. 9).

2. Describe proportion by gender of before hospitalization death,=.
Done

3. Provide clinical characteristics comparison of men and women.

We now provide data on previous angina, hypertension, diabetes and smoking but only from year 1989 as such data were not routinely registered until then (p. 5 and Table 1). We had no data on high cholesterol or lipid-lowering drugs.

4. Include adjustment for clinical comorbidities.

We abstain from presenting Cox regressions adjusted for clinical comorbidities due to the high proportion of missing data (also unevenly distributed over the period). MONICA was designed for “epidemiological monitoring of incidence and mortality” and our data are not of such quality that such an analysis would be valid enough. The second reason is that we do not know how to interpret such an analysis in a meaningful way when our hypothesis solely concerns survival or not. The only adjustment that we found reasonable is age as women were one year older, and older age at MI confers a worse prognosis.

Minor Essential Revisions
1. Because number of patients is 6763 (M) plus 1868 (W) - the title should read ‘An analysis of 8361 patients...’ - not 8362! Also fix this number in the methods.
Done, and a new data analysis showed the proper figure to be 8630.

2. Check the decimal points for death (45.3% of men... not 45.2%) .. abstract results section.
Done.
Reviewer’s report

Title: Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. An analysis of 8362 patients in the Northern Sweden MONICA Study

Version: 1 Date: 7 October 2010
Reviewer: Tom Briffa

Reviewer’s report:
The studies stated aim was to analyse sex-specific time trends in the survival of patients aged 25-64 years for up to 23 years after a first myocardial infarction (MI) in Northern Sweden. Given the null finding the authors have instead elected to highlight survival findings for the cohort. An alternative interpretation of their findings is the apparent absence of differences in median time to survival following a first MI in 25-64 year old Swedish men and women.

1. We have clarified that the primary aim was to analyse differences between the sexes but also to study if any such differences changed over the uniquely long time period. This has been added in the Abstract and Introduction (p.3)

Thus, for our primary aim there was not a null finding as the Cox regression showed a slightly higher survival among women after age adjustment (see answer to comment no. 4 from Reviewer Moreyra). The hypothesis is not tested by the median survival times (or rather log rank test) which are just cited to help the reader interpret the graphical depiction of the survival curves.

General remarks
The paper is easy read and intelligible but would benefit from additional methods and more discursive interpretation.
Methods could be strengthened; e.g. how was the introduction of troponin biomarker testing handled in accordance with the “strict WHO MONICA criteria”, and whether data was available for all registered cases, if not, how was this handled in the analysis.

2. We would like to avoid reprinting all Methodological issues that are given in ref. 16 and easily available but added a short paragraph on troponins in Methods (p. 4) and a longer part in Discussion (pp.9-10).
Data on survival was available for all cases, and that has been included in the Methods section, thus there are no missing data on our major and only outcome.

A greater appreciation for the data presented is more likely if the limitations raised in reference [16; also a co-author on this paper] were evidenced in the present study.

3. The major limitation discussed in ref. 16 is the issue of troponins which now has been addressed.

The standards of reporting should be tightened throughout the manuscript; e.g. in the abstract a 20-year survival is referred to; no reference to the null finding in either of the conclusions; include an average follow-up time; is any additional clinical information available other than mean age and sex to describe the characteristics of the four sub-cohorts.

4. We removed the figures on 20 y survival as this duration of follow-up was only reached by a minority but instead cited 5 y survival (as median f-u was 7 y).

As stated above we rephrased our main hypothesis and thus do not have any null finding but added a line in the Conclusion that there were no time trend differences between sexes.

Median follow-up time, total patient years and clinical characteristics (from the 1989 cohort and onward) are now presented.

A more considered discussion, in particular the limitations would add impact and context to the studies findings. Consider balancing the conclusion by reporting no difference in median survival time between men and women.

5. We extended our discussion upon the effects of troponins but also as to the effects of the sensitivity analysis done by excluding those subjects who died before reaching hospital (p. 9). For conclusion based on median survival time, see comment 1 above.

Additional specific remarks:
1. p7 3rd paragraph 3rd sentence: The contribution of lowering cholesterol level on reducing CHD mortality in Sweden is well raised but then subsequently glossed over when discussing the findings of the Northern Sweden MONICA study (p8 2nd paragraph) as a possible moderator on the results of the present study. Also, were rates of diabetes in men and women available?

6. The impact of lower cholesterol in the population primarily influences the incidence of MI and thus strongly impacts on mortality before reaching hospital. If lower cholesterol in the population has any influence on the long
pital. If lower cholesterol in the population has any influence on the long time survival once you suffered your MI is not clear (although RCT of secondary prevention strongly supports the effect of statins). We added a line on this subject (although our data in ref 19 show no differences in time trend in cholesterol levels between men and women which is the focus in our analysis).

Rates of diabetes are now presented for the subjects in the study and mentioned in the discussion when presenting data on risk factors in our population.

2. P8 1st paragraph 2nd sentence: “That primary prevention has worked less well in women” is overstating the present studies findings. Your co-author in reference [16] offers up the introduction of troponin testing and increased sensitivity for the diagnosis of MI in women as a plausible explanation as to why the rates of first MI in young women may not have declined. Further, they go on to say the number of events particularly in those under 55 years of age is small and caution concluding remarks. Alternatively, its possible that no room for substantial further improvements in CHD mortality in young women is likely.

7. We agree that this sentence did not make sense and have deleted it.

3. P5 results 1st paragraph, 3rd sentence: There is mention of a declining age on presentation with MI among women over time, which was not evident in men. Again, I note an apparent discrepancy to data reported in reference [16] for first events in women up until 2004 where no age decline was reported. Assuming your analysis is correct how would it inform the interpretation and understanding of differences between men and women in the present study?

8. Compared to our previous report we have included more patients and the reference 16 has a different subdivision of cohorts. Using year of onset as a continuous variable the time trend is of borderline significance. After discussion with our statisticians we decided to omit any hypothesis testing as we have a total population sample and also as this was not the hypothesis to test. The hypothesis testing was done by Cox regression including age as a covariate.

We can offer no explanation for the somewhat decreasing age of women but the growing impact of smoking as risk factor among them may partly explain it. We prefer to abstain from discussion on this as age was adjusted for.

4. P9 3rd paragraph: Consider including a remark about the possibility of MI severity being a confounder with interpreting your findings.
9. Perhaps it would rather be phrased as severity being a part of a causal pathway? We understand the reviewer to suggest that women would have not as severe MI as men and thereby a higher chance to survive. We added a line in this paragraph on this issue.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests'

---

**Reviewer's report**

**Title:** Better long-term survival in young and middle-aged women than in men after a first myocardial infarction between 1985 and 2006. An analysis of 8362 patients in the Northern Sweden MONICA Study

**Version:** 1  **Date:** 2 November 2010  **Reviewer:** Jose P Henriques

**Reviewer's report:**


The authors should be congratulated for this manuscript. Although there are many reports on gender specific difference clinical outcome after acute myocardial infarction, this manuscript has unique points. Especially, the large number of patient in this cohort is one of its strengths. Also, the fact that pre-hospital death data are available is remarkable.

I have only some suggestion to further improve the manuscript

1- Please start by reporting the whole cohort using survival figures. May be this is figure 1 but it is not clear to me. You also state “Over the whole study period women had a 2.6%-units higher survival than men, 57.3 vs. 54.7% (Table 1).’Is this not significant?

We thank the reviewer for pointing out the illogical sequence of reporting. We now start with the main issue of survival according to gender. The cited figures on proportional survival have been deleted from the text, and we focus on HR and median survival as the proper way of describing our finding. See also our answer, comment nr 8, to Reviewer Briffa above, which explains why we do not do any significance testing on differences in Table 1.
2- Please address in a table and figure on the pre-hospital deaths in men and women and not only in one sentence “The proportion of death before admission to hospital was 14.5% in men and 11.1% in women.” These are unique data. Please elaborate and describe in figures.

Our aim was to compare long-term survival and not to focus on events before hospital. We did perform a complementary analysis excluding those who died before hospital, though (see our answer to comment no.1 from Reviewer Moreyra).

We added mean age and numbers of those dead before hospital but further analysis of these data is presently under way in a separate report focusing solely on this issue.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being Published

The manuscript has been re-checked by a native English speaking physician.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests.