Author's response to reviews

Title: Are Coronary Event Rates Declining Slower in Women Than in Men? - Evidence From Two Population-Based Myocardial Infarction Registers in Finland

Authors:

Hanna-Riikka Lehto (hrleht@utu.fi)
Seppo Lehto (seppo.lehto@kuh.fi)
Aki S Havulinna (aki.havulinna@ktl.fi)
Matti Ketonen (matti.ketonen@pkssk.fi)
Aapo Lehtonen (aapleh@utu.fi)
Y. Antero Kesaniemi (antero.kesaniemi@oulu.fi)
Juhani Airaksinen (juhani.airaksinen@tyks.fi)
Veikko Salomaa (veikko.salomaa@ktl.fi)

Version: 2 Date: 21 September 2007

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Helsinki 21.09.2007

Scott Edmunds PhD
Assistant Editor
BMC-series Journals
BioMed Central
Middlesex House
34-42 Cleveland Street
London W1T 4LB


Dear Dr Edmunds,

Thank you for your e-mail of August 9, 2007, and the interest of BMC Cardiovascular Disorders in our manuscript mentioned above. We have now carefully revised the manuscript according to the suggestions of the reviewers. Our detailed responses to the points raised by the reviewers are enclosed.

We hope that the paper in its present form is acceptable for publication in BMC Cardiovascular Disorders.

Yours sincerely,

Veikko Salomaa, MD, PhD
Research Professor
KTL-National Public Health Institute
Mannerheimintie 166
FI-00300 Helsinki
Finland
Responses to the Reviewer 1

We thank the reviewer for her constructive comments and criticism. Our responses are as follows:

1) “The authors describe, that studies have shown that the incidence of MI has decreased especially in younger men and increased in older women. They suggest that younger women are considered to be protected from CHD, especially during the fertile age. Thus, it is unclear why the authors chose to conduct the analysis on the entire study population only. I would suggest, to conduct an age-stratified analysis too – for example an analysis comparing the event rates (incidence, attack rate, case fatality) among men and women above and below the age of 50 could be performed”.

We have now included in the modelling the gender by age group interaction using 55 years as the cutpoint (<55 and ≥55 years). Graphical examination of the data suggested that the cutpoint of 55 years is more appropriate than 50 years. Furthermore, the cutpoint of 50 years suggested by the reviewer would have been problematic, because of the small number of events among young women. Even with the cutpoint of 55 years analyses of the FINAMI data suffered from the lack of statistical power, but the larger CVDR produced meaningful results. These models revealed that the slower declines in women than in men originated from the younger age group (<55 years), whereas no difference between men and women was seen in the older age group (≥55 years). The new modelling strategy is explained in the Statistical Methods-section (p. 8, 2nd paragraph) and the results are presented in the Results-section (p. 10, 2nd paragraph) and in Table 3.

2) “Abstract: The numbers of total events recorded in men and women in the two registers differ from the numbers given in the Results section. Please clarify.”

This is based on misunderstanding. The numbers in the Abstract and in the Results-section do not differ. In the Abstract we present the total numbers of MI events in the FINAMI register and in the CVD register for men and women separately, both consisting the total sum of MI events recorded in the first and in the latter study period. In the Results-section we compared the total sums of MI events between the two study periods summing up the events in men and women. (The event numbers for men and women separately are shown in parentheses). Perhaps the following table helps to clarify the matter.

Numbers of MI Events Included in the Study

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>FINAMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>2370</td>
<td>2882</td>
<td>5252</td>
</tr>
<tr>
<td>women</td>
<td>2216</td>
<td>2682</td>
<td>4898</td>
</tr>
<tr>
<td>all events</td>
<td><strong>4586</strong></td>
<td><strong>5564</strong></td>
<td>(not presented in article)</td>
</tr>
<tr>
<td>CVDR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>38849</td>
<td>39860</td>
<td>78709</td>
</tr>
<tr>
<td>women</td>
<td>33850</td>
<td>36614</td>
<td>70464</td>
</tr>
<tr>
<td>all events</td>
<td><strong>72699</strong></td>
<td><strong>76474</strong></td>
<td>(not presented in article)</td>
</tr>
</tbody>
</table>
Since the numbers are correct, the manuscript has not been changed.

3) “The authors state that persons ≥ 35 years were included. It would be good to give an age-range and a gender-specific age-distribution of the included subjects.”

As requested by the reviewer, we have now added the mean age and interquartile range for both genders, both study periods, both registers and for each event type in Table 1.
Responses to the Reviewer 2

We thank the reviewer for his constructive comments and criticism. Our responses are as follows:

1) “Methods: To what extent could the transition from ICD-9 to ICD-10 affect the results? Also, could the improved validity of CHD diagnosis and mortality data (Pajunen et al., Eur J Cardiovasc Prev Rehabil 2005) play a role in the present temporal trend analysis?”

These questions are controlled by our study design, since we analyzed in parallel a large administrative data set (CVD register) and specific AMI register data (FINAMI). The FINAMI data are based on detailed reviewing of hospital documents, death certificates, autopsy reports etc, according to a standardized protocol. Therefore, the FINAMI results are not influenced by changes in ICD version or by improved validity of routine CHD diagnoses in hospitals. In principle, the points mentioned by the reviewer could have had an effect on diagnoses in the administrative data, but fortunately the results in both registers were generally consistent. Furthermore, we have no reason to suspect that the possible effects of changes in the ICD version or in validity of CHD diagnoses would differ by gender, which is the main topic of the present study.

2) “Statistical Methods: The assumptions of using Poisson regression are restrictive. Did the authors test for overdispersion and autocorrelation?”

We thank the reviewer for this important comment. There was significant overdispersion in our Poisson regression models. Therefore, we have now re-analyzed our data using a different analysis strategy. (Please see the Statistical Methods-section, pp 7-8, for details. The results are shown in new Tables 2 and 3 and in the Results-section, p 9, last paragraph - p.10, first and second paragraphs). The main findings remained the same as in the previous version of the paper, but the new analyses further revealed that the slower declines in MI event rates among women originated from the younger age groups (<55 years), while no differences between the genders were seen in the older age groups (≥55 years).

3. “Statistical Methods: “…were the gender by time period-interaction was the main outcome of interest”. Isn’t the time by gender the main exposure and CHD counts the outcome?”

This sentence has been now removed.

4. “Results: Confidence intervals of two rates can overlap and still be highly significant at “standard” levels (e.g., <.01). I bet that most of the overlapping 95% CIs reported for women in the FINAMI between the 2 periods (e.g., from 726 [688-764] to 656 [625-688] in the age-standardized incidence, or from 282 [266-298] to 256 [241-270] in mortality) are in fact highly significant. Anyway, I
would deemphasize the significant/non-significant issue and focus more on the absolute and relative differences in decline between men and women”. We agree with the reviewer and have rewritten the paragraph in question (Results-section, p. 9, first paragraph) accordingly.

5. “Discussion: p. 11: In reviewing the literature, one important paper might have been missed: Roger et al. Ann Intern Med. 2002;136:341-8”.

We have now added this important reference. (p 11, third paragraph, ref # 20).

6. “Discussion: p. 12: “Our current finding, abolishing the gender difference in CHD incidence trends after adjusting for the effect of troponins, is in line with our previous report…”. Is this surprising given that the authors modeled the Poisson regression in a way that “takes into account the effect of troponins using the correction coefficients derived in our previous work”?"

We have now removed this sentence.

7. “Is it possible that the gender by year interaction is in fact a reflection of the age by year interaction? Did the authors try to adjust for the latter effect?”

Graphical examination of the data does not seem to support this possibility. Furthermore, in the new models we have included a gender by age group interaction, which suggests that the slower declines in women originate from the younger age groups (<55 years), while no differences between the sexes were seen in persons aged ≥55 years.

8. “Needs some language corrections before being published”

We have now checked the language in more careful manner.