PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sex-specific trends in four-year survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. A register-based cohort study.
AUTHORS	Nielsen, Susanne; Björck, Lena; Berg, Johanna; Giang, Kok Wai; Zverkova-Sandström, Tatiana; Falk, Kristin; Määttä, Sylvia; Rosengren, Annika

VERSION 1 - REVIEW

REVIEWER	Kate Smolina, Postdoctoral Fellow Centre for Health Services and Policy Research School of Population and Public Health University of British Columbia Canada
REVIEW RETURNED	03-Feb-2014

GENERAL COMMENTS	Abstract conclusion: suggest "women in the general population" as opposed to "healthy women". Introduction, P1, last sentence: study was in England, not UK; specify that the stated risk is for those who survived at least 3 years or just say "long-term". Methods, P1: Clarify if validity information of IPR is available for AMI diagnosis in particular; if so, please state what the PPV/sensitivity is. Methods, P2: How did you deal with suspect AMIs that present to the hospital with chest pain but turn out to be something else? Do they get coded differently on the discharge abstract? Please clarify how you dealt with those cases. Methods, P6: Please clarify what reference mortality rates were used in the calculation of SMR - a mean for each 4-year period or a mean of 20-year period or otherwise? Methods generally: It appears that sex and gender are used interchangeably. Please reconsider and clarify. Results, P3, first sentence: It appears that "risk" and "rate" are used interchangeably. Please reconsider and clarify. Results, Table 2 and Table 4: I question the usefulness of these tables. Given that mortality rates have been falling over the 20 years, overall results are somewhat meaningless. Also unclear how the reference rate for SMR was calculated. Table 3 footnote: "Absolute [excess] risk after 4-year death per 100 person-years" is confusing. Please rephrase.

	Discussion, P4: The possible reasons behind the increased mortality among young women in the last period could be better explained/explored. This paragraph should also address the result that much of the increased mortality in 2002-06 was driven by higher mortality for non-CVD causes, which is interesting and surprising. Discussion, P5: Happy to provide more results for comparison. In that English study, SMR for men 30-54 after 4 years was 261 and for women 30-54, it was 555, which is comparable to your results. At 7 years, these numbers were 208 and 524, respectively. Overall, a great paper and an important contribution to the literature. I applaud the authors for using AER, as it is indeed a very useful measure to report in this type of study. A more in-depth exploration/discussion of what the finding about recent higher mortality among young women could mean would make this a stronger paper.

REVIEWER	Karin Humphries, DSc University of British Columbia Canada
REVIEW RETURNED	05-Feb-2014

GENERAL COMMENTS	This is an interesting paper focussed on young adults with MI and their long term survival over a 20-year period in Sweden. Using their enviable health data, the authors describe changes in all cause and CHD-specific mortality in men and women stratified into two age groups - 25-44 and 45-54 - from 1987 to 2006. The population is divided into four 5-year periods and follow-up is up to 4 years for each group. A seven year wash-out is used for each group to ensure all MI's are incident MIs. Major comments: • while the focus is clearly on long-term mortality amongst those who survive an incident MI by at least 28 days, a key piece of information that should also be provided is the rate of MI, by sex in each of these groups. While absolute numbers are provided in the supplementary table, this is difficult to interpret as the underlying population numbers will have changed over the 20-year time frame. Therefore, the drop in MIs observe red in the final period, may or may not be a drop in rate. This information is also key because the authors speculate that more women would have been diagnosed with MI in the later period, than men. This can easily be supported or refuted by providing the MI rates • There is a missed opportunity here to provide information on sex differences in changes in long-term mortality by sex. In the final paragraph on page 11, the author compare the changes in HR over time in the respective age-sex groups. What would also be interesting is to determine if the decline in risk is significantly different by sex overall and/or by age group. The 25-44 group appears to be too small, but an examination of the 95% CI for the 45-54 group strongly suggests the decline is significantly greater in men than women. The authors should formally test this.

	Minor comments: • Page 4, 2nd sentence, last paragraph - 'However, there have since been marked changes…' What is 'since' referring to? Since when? please clarify. • Page 5, line 14 - here the age range is 24-54; elsewhere it is 25-54. Please correct • Page 5, line 30 - 'Positive predictive values… - which PPVs are you referring to? The most important would be the PPV for MI and further whether the PPV changed between ICD 9 and ICD10. • Page 5 -Please provide sex-specific morality rates (or %'s) for the deaths that occurred in the first 28 days. While these are excluded from the study, any sex difference in early morality would be of interest. • Page 6 - Can the authors provide any information on the validity of coding of cause of death in the Swedish Cause of Death Registry in the section 'Follow-up'? • Page 5, line 25, please also describe how AR was calculated, not just AER • Page 7, line 43, please replace 'multivariate' with 'multivariable' • Page 16, first paragraph - the authors suggest that the adoption of troponin in the diagnosis of MI differentially impacted women compared to men. As suggested above, this can be supported or refuted by giving the MI rates by sex for the first 3 periods, and then the last period. Page 16, line 51, the authors suggest that greater use of evidence-based medications and repercussion may have contributed to the decline in mortality. Reperfusion is only associated with improve survival among STEMI patients, and STEMI rates have decline over the years, so this is a tenuous explanation. Page 17, line 18, the authors suggest that the increase in comorbidities is probably due to improvements in clinical reporting. Please cite papers to support this assertion. The explanation for hypertension cites reference 26, but this reference does not talk about WHO guidelines. Please correct. Page 17, line 41, the authors again allude to a differential impact of troponin measurement on diagnosis by sex. They cite a single paper that reviewed patients who had both CK-MB and troponin measured. If troponin truly is more sensitive in women than men, one might hypothesize that it then detects milder cases of MI than would have been detected by CK-MB alone. Milder MI would normally be associated with better outcomes. The rationale for this argument is unclear to this reviewer. And, again, if the introduction of troponin really did result in an increase in MI, the MI rates would have increased, and if the authors' speculation is correct, it would have increased more in women than men. The authors appear to have this data - they are encourage to provide it.

REVIEWER	Louise Pilote McGill University Canada
REVIEW RETURNED	07-Feb-2014

GENERAL COMMENTS	This is a register-based cohort study of 37 276 Swedish men and

	women who survived a first acute myocardial infarction between 1987 and 2006. The authors compared four-year mortality from all causes, and Standard Mortality Ratio (SMR) for four 5-years periods (1987-1991, 1992-1996, 1997-2001, 2002-2006) by sex and age groups. They observed that throughout the four periods, the absolute excess risk of mortality decreased from 1.38 to 0.50 per 100 person-year in men aged 25-44 and 45-54 years, respectively. In women aged 25-44 and 45-54 years, the risk decreased from 2.26 to 1.17 and from 1.93 to 1.45 per 100 person-year, respectively. They also observed that, inversely to men, trends in women were non-linear, decreasing to the same extend as those for men until the third period (1997-2001), then increasing until 2006. Compared with men, women were also more likely to die from causes other than cardiovascular. From 1987 to 2006, non-cardiovascular deaths increased from 21.5% to 44.6% in men and from 41.5% to 65.9% in women, respectively. The novel aspects of that study are that authors assessed mortality in a younger (25 to 54 years) cohort of men and women who survived a first AMI, and assessed specific versus all-causes mortality. The 20-year assessment period is also a notable strength of this study. Major comments: 1. The major concern with this study is that it includes data from 1987 to 2006. Eight years has passed since these data were collected and they therefore may not be representative of the evolution in post-AMI survival in the last decade. Could the authors review recent data (i.e. between 2006 and 2013) regarding mortality trends, and comment whether their data are representative of what has been observed in the last data? 2. We are unclear about why the increasing use of troponins in the diagnosis process around the year 2000 would increase detection of AMI in women but not in men (which, according to the authors, would explain the increment in mortality during the last follow-up period in women but not in men). Could the authors clarify why this change in troponins utilization would lead to an enhanced detection among women but not among men, and why the utilization of troponins would help capturing other and more complicated types of myocardial damage in women but not in men? (page 17, lines 35 to 50) 3. Another concern regards limited clinical and treatment data. As mentioned by the authors, they could not collect data regarding characteristics of the index AMI (AMI severity), treatments received, biomarkers, and socio-demographic characteristics, which play a major role in survival post-AMI. This lack of data limits considerably the interpretations the authors can make of their results. 4. To ensure that the index AMI was the first in patients' life, the authors collected data as of 1980 with regards to diagnosis of AMI. However, I am wondering if this method is appropriate given the age range from 25 to 54 years. It is unlikely that 25 years old patients have had a previous event before the age of 18, while it is well possible that 54 years old patients have had a previous event before the age of 47 years. Is it possible that the index AMI was not the first one for a certain proportion of the oldest patients? 5. Minor comments:

	Abstract Design: Is this really a prospective study? I would suggest revising the design for a register-based cohort study. Results: Please specify which is the third period. Results: In the last sentence, please indicate from when to when the risk of non-cardiovascular deaths increased. Conclusion: In the last sentence, please change “healthy women” for “women in the general population”. Main text 1. There seems to be a problem with the references. For example, references 26 and 27 seem to have been inverted. Please fix citations and references. 2. Please specify which codes were used for AMI in the ICD 8th revision 3. The authors mentioned that 1537 patients died within 28 days of the index AMI and were therefore excluded from the study. Do the authors have data regarding the proportion of men and women, and the age of these patients? 4. Page 4, line 42: “However, there have since been…” please specify since when? 5. Page 5, line 32: Please fix typo by removing the semicolon 6. Page 10, line 55: Please fix typo “with an” should be “with a” 7. Page 17, line 32: “to the nearly” should read “to nearly” In the Statistical analyses section, the authors mentioned that they conducted Cox proportional hazard models adjusted for age, hypertension, valvular and congenital heart disease, stroke, chronic respiratory disease, malignancy and renal failure. However, the models were not adjusted for other important confounders such as dyslipidemia, cigarette smoking, and ethnicity, which characteristics are known to differ between men and women and to influence comorbidities and survival. Could the authors compare their results with previous studies having adjusted their models of analyses for these confounders, and comment on the implications of not having included them as covariate in their study.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer Name Kate Smolina, Postdoctoral Fellow
Institution and Country Centre for Health Services and Policy Research
School of Population and Public Health
University of British Columbia
Canada
Please state any competing interests or state ‘None declared’: None declared

1. Abstract conclusion: suggest "women in the general population" as opposed to "healthy women".

Authors reply:
We agree with the reviewers comment and made the suggested change in the abstract/conclusion section.

Section: Abstract/Conclusion:
Young male survivors of AMI have low absolute long-term mortality rates, but these rates remain 2- to 4-fold that of the general population. After favourable development until 2001, women now have higher absolute mortality than men and a 6- to 14-fold risk of death compared with women in the general population.

2. Introduction, P1, last sentence: study was in England, not UK; specify that the stated risk is for those who survived at least 3 years or just say "long-term".

Authors reply:
We apologize for our mistake and thank the reviewer for highlighting this and have made the suggested change.

Section: Introduction (p 4)
In a recent study from England, the long-term risk of death of any cause among survivors of a first AMI was twice that of the general English population of equivalent age.7

3. Methods, P1: Clarify if validity information of IPR is available for AMI diagnosis in particular; if so, please state what the PPV/sensitivity is.

Authors reply:
Thank your for the recommendation. We have added following information for validity of MI diagnoses in the IPR register:

Section: Methods (p 5)
Sweden has a publicly financed health care system, with some health care facilities privately run but still fully integrated into the health care system. The Swedish National Inpatient Register (IPR), has established complete national coverage since 1987. One study stated that positive predictive values (PPV) differ among diagnoses in the IPR, but are generally 85–95%. PPV for myocardial infarction was about 98-100% and the sensitivity was 77-91.5%.13 Another validation study concluded that the accuracy of correct diagnosis in AMI was 86 % regardless (1987-1995) of age and gender. 14 More recent data are lacking.

4. Methods, P2: How did you deal with suspect AMIs that present to the hospital with chest pain but turn out to be something else? Do they get coded differently on the discharge abstract? Please clarify how you dealt with those cases.

Authors reply:
Thank you for raising this question. In Sweden all hospital follows international standards for AMI criteria. Only those patients with a clinical manifest AMI receive the diagnosis code for AMI. Therefore a patient who arrives with suspected AMI is not included in the study. To clarify we changed the wording in the Methods slightly to:

Section: Methods (p 6)
The present study included all 38,836 cases in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006

5. Methods, P6: Please clarify what reference mortality rates were used in the calculation of SMR - a

mean for each 4-year period or a mean of 20-year period or otherwise?

Authors reply:
Thank you for highlighting the need of more information regarding the calculation of SMR. The SMR was calculated in a mean for 4-year follow up by each period. To clarify this we have added the following information below to the method section:

Table 2 SMR show an average for mean of the four periods. Although we agree with your suggestion (point number 9) to remove this table since is not consistent with the aim of the study and the usefulness is not given.

Section: Methods (p 7)
Standardized mortality ratios (SMR) with 95% confidence intervals (CIs) were calculated as the ratio of the observed to expected number of deaths for 4-year follow up by each period, estimated from rates in the general Swedish population, by age, gender, and calendar year, using life expectancy tables from Official Statistics of Sweden (SCB).

6. Methods generally: It appears that sex and gender are used interchangeably. Please reconsider and clarify.

Authors reply:
We agree that sex and gender are used inconsistent and made changes accordingly. We are now using gender constantly throughout the method section.

7. Results, P3, first sentence: It appears that "risk" and "rate" are used interchangeably. Please reconsider and clarify.

Authors reply: We have done corrections according to the reviewer's suggestion and made changes in the result section.

8. Results, Table 2 and Table 4: I question the usefulness of these tables. Given that mortality rates have been falling over the 20 years, overall results are somewhat meaningless. Also unclear how the reference rate for SMR was calculated.

Authors reply:
We agree with your suggestion to remove table 2 since is not consistent with the aim of the study and the usefulness is not given. We replaced Table 4 with the former Supplementary Table 2

9. Table 3 footnote: "Absolute [excess] risk after 4-year death per 100 person-years" is confusing. Please rephrase.

Authors reply:
We agree that this footnote information can lead to misunderstandings since the AR and AER estimates the annual risk as a mean during the four years follow up in each period. We have therefore rephrased the footnotes in both Table 2 (previous Table 3).
In addition in order to increase the methodological transparency we have developed the method section to avoid misunderstandings regarding how the calculations were performed in both AR and AER respectively.

Section: Results, Footnote Table 2 (p 14)
c Absolute risk per 100 person-years
d Absolute excess risk per 100 person-years

Section: Methods (p 7)
To examine the excess mortality risk in the study population the absolute risk (AR) was calculated separately for both the general population and the study population by dividing the observed mortality with person time. This yields an average annual excess risk for each period. The absolute excess risk (AER) is the difference between the observed and the expected AR. For standardization purposes, the estimates were then multiplied by 100 person-years. The AER calculations add a useful measure of excess risk in absolute terms. Life expectancy tables from Official Statistics of Sweden (SCB) were used to calculate the expected mortality in the Swedish general population by gender, age and calendar year.

10. Discussion, P4: The possible reasons behind the increased mortality among young women in the last period could be better explained/explored. This paragraph should also address the result that much of the increased mortality in 2002-06 was driven by higher mortality for non-CVD causes, which is interesting and surprising.

Authors reply: Thank you for your comment. We have added further explanations for the increased mortality in the discussion section.

Section: Discussion (p 18)
Accordingly, the increasing mortality among women hospitalized in 2002–2006 could be due to the capture of other and more complicated types of myocardial damage because an increase in troponin levels is also seen in other conditions.30 Even so, comorbidities, although increasing over time, were still low in the most recent period. Since the most marked change between the third and the fourth period of our study was the change from CK-MB to troponins as the predominant marker for myocardial damage, we speculate that the additional AMIs captured by this more sensitive method are clinically different, not only in being smaller but also to an unknown extent reflecting myocardial damage not due to atherosclerotic disease. Circumstantial evidence for this might be derived from the increasing and much higher proportion of non-CVD deaths, as well as more comorbidities, in women compared to men over the study period. In the present study the results showed an increased rate of survivours but a decreasing trend in death in CVD among young women. These results strengthen that the increased all-cause mortality is likely a result of a combination between the use of troponin and increasing comorbidities.

11. Discussion, P5: Happy to provide more results for comparison. In that English study, SMR for men 30-54 after 4 years was 261 and for women 30-54, it was 555, which is comparable to your results. At 7 years, these numbers were 208 and 524, respectively.

Authors reply: Thank you for this additional information. We added the following sentence in the discussion section:

Section: Discussion (p 19)
Estimates for individuals younger than 55 years were not stated in the study by Smolina, et al., but we have since been provided with information that mortality ratios were 2.6 for men and 5.6 for women aged 30-54 years after 4 years, which is more or less comparable to our findings (Smolina K, personal communication).

Reviewer Name Karin Humphries, DSc
Institution and Country University of British Columbia
Canada
Please state any competing interests or state ‘None declared’: None declared

Major comments:

1. While the focus is clearly on long-term mortality amongst those who survive an incident MI by at least 28 days, a key piece of information that should also be provided is the rate of MI, by sex in each of these groups. While absolute numbers are provided in the supplementary table, this is difficult to interpret as the underlying population numbers will have changed over the 20-year time frame. Therefore, the drop in MIs observe red in the final period, may or may not be a drop in rate. This information is also key because the authors speculate that more women would have been diagnosed with MI in the later period, than men. This can easily be supported or refuted by providing the MI rates

Authors reply:

We acknowledge the need of more information and AMI rates are now provided in Figure 1. We have also extended the reasoning regarding the increased mortality among women in the discussion section.

Section: Results (p 10)
During the study period (1987-2006) annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days decreased from 92.3 per 100.000 in 1987 to 72.1 in 2006 (Figure 1). Women, on the other hand, showed a different pattern with an increase from 17.4 per 100.000 in 1987 to 22.3 in 2006 (p for men <0.0001, for women 0.0003).

See figure 1 Annual rate per 100.000 population in men and women aged 25-54 years surviving a first AMI for at least 28 days.

Section: Discussion (p 18)
Since the most marked change between the third and the fourth period of our study was the change from CK-MB to troponins as the predominant marker for myocardial damage, we speculate that the additional AMIs captured by this more sensitive method are clinically different, not only in being smaller but also to an unknown extent reflecting myocardial damage not due to atherosclerotic disease. Circumstantial evidence for this might be derived from the increasing and much higher proportion of non-CVD deaths, as well as more comorbidities, in women compared to men over the study period. In the present study the results showed an increased rate of survivors but a decreasing trend in death in CVD among young women. These results strengthen that the increased all-cause mortality is likely a result of a combination between the use of troponin and increasing comorbidities.

2. There is a missed opportunity here to provide information on sex differences in changes in long-term mortality by sex. In the final paragraph on page 11, the author compares the changes in HR over time in the respective age-sex groups. What would also be interesting is to determine if the decline in risk is significantly different by sex overall and/or by age group. The 25-44 group appears to be too small, but an examination of the 95% CI for the 45-54 group strongly suggests the decline is significantly greater in men than women. The authors should formally test this.

Authors reply:
Thank you for this valuable suggestion. This is slightly beside the focus for this paper which centres on the comparison between men and women with AMI and men and women in the general population, with a focus on patients below 55 years of age. Because we have a fairly advanced draft of another paper dealing with this in men and women aged 25 to 84 we would like to refrain from further expansion of the present manuscript.

Minor comments:

3. Page 4, 2nd sentence, last paragraph - 'However, there have since been marked changes…' What is 'since' referring to? Since when? please clarify.

Authors reply:
Thank you for your comment. We refer to the results of the two studies by Rosengren et al. (2001) and Vaccarino et al. (2001). We agree the need of a clarification and made changes in the manuscript as follows:

Section: Introduction (p 4)
Further, younger, but not older, women hospitalized with AMI have a worse long-term prognosis than men, as shown in analyses of patient populations dating from the 1980s and 1990s .9,10 However, there have since been marked changes in treatment, diagnostic criteria, and post-AMI prognosis. A recent study found that reductions in long-term mortality after 1985 were at least as high for women as for men with AMI,11 but the study did not specifically report findings for young patients. An additional study, found that reductions in mortality were similar regardless of age but that younger patients are more likely to receive evidence based care.12

4. Page 5, line 14 - here the age range is 24-54; elsewhere it is 25-54. Please correct

Authors reply:
Thank you for indicating out this mistake which has now been corrected.

Section: Introduction (p 5)
In the present study, we examined sex-specific trends in long-term survival in a register-based cohort of patients aged 25-54 years hospitalized with a first AMI during 1987–2006, and compared death rates for men and women separately with those of the general population.

5. Page 5, line 30 - 'Positive predictive values… - which PPVs are you referring to? The most important would be the PPV for MI and further whether the PPV changed between ICD 9 and ICD10.

Authors reply:
Thank you for these comments. In order to clarify what PPV we are referring to, information for both PPV in general and specified PPV for MI is added in the manuscript. We have also added validation information by sensitivity for MI according to Ludvigsson et al (2011).
Whether there were changes in PPV between ICD 9 and ICD10 has not been evaluated, The Swedish National Board of Welfare (2000) made a validation study for correct diagnostic in IPR for AMI which was conducted during the ICD 9 era (1987-1995). This study concluded that the used diagnosis codes at discharge for AMI are valid for 86% in 1995, regardless of age and gender. More recent data are lacking, but a more serious problem is that new criteria for AMI have been adopted. This is clearly stated, with a reference (18) provided, and we also state "Also, we were unable to

apply uniform criteria for diagnosis over time." We now acknowledge the lack of recent data and have rewritten the Methods section as below:

Section: Methods (p 5)
Sweden has a publicly financed health care system, with some health care facilities privately run but still fully integrated into the health care system. The Swedish National Inpatient Register (IPR), has established complete national coverage since 1987. One study stated that positive predictive values (PPV) differ among diagnoses in the IPR, but are generally 85–95%. PPV for myocardial infarction) was about 98-100% and the sensitivity was 77-91.5%.13 Another validation study concluded that the accuracy of correct diagnosis in AMI was 86 % regardless (1987-1995) of age and gender 14. More recent data are lacking.

6. Page 5 -Please provide sex-specific morality rates (or %'s) for the deaths that occurred in the first 28 days. While these are excluded from the study, any sex difference in early morality would be of interest.

Authors reply: We agree with the reviewer´s suggestion and have complemented this section with sex-specific mortality for the excluded patients during the 28 first days.
Due to comments from reviewer 3 we have rephrased the methods section in the manuscript regarding the selection process and the effects of the use of 7- years time frame. We are now using cases instead of patients to avoid misunderstanding.

Section: Methods (p 6)
The present study included all 38,836 cases (31216 men, 7620 women) in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006; AMI was defined as a principal discharge code according to the ICD -8 : 410 (until 1987), ICD-9: 410 (until 1996) and ICD-10: I21 (from 1997 onward). After excluding 1,560 cases who died during the first 28 days 1169 men (3.01% of cases), median age; 50) (391 and women (1.01% of cases), median age; 49.0 , 37,276 cases (7,229 women and 30,047 men) with a first AMI remained for analysis. Data from 1980 onward were used to identify first AMIs only, with a time frame of 7 years throughout, to ensure that AMIs registered each year had the same chance of being identified as a first AMI. Due to the 7-years time frame, 443 cases were recurrent AMI after seven years (53 women median age; 52, 390 men median age; 51)

7. Page 6 - Can the authors provide any information on the validity of coding of cause of death in the Swedish Cause of Death Registry in the section 'Follow-up'?

Authors reply:
Thank you for your recommendations to improve information concerning the validity in the Cause of Death register. We have added supplementary information regarding the validity in the method section below the heading; Registries and study population and in the discussion section.

Section: Methods (p 5)
The Cause of Death Register is based on diagnosis from death certificates. In 2008, 0.8% of death certificates were missing or insufficient (2.7%). Validity for a correct diagnosis of ischemic heart disease in the general population in 1995 was 87%.17

Section: Discussion (p 20)
Incorrect death certificates could lead to uncertainty with respect to attributing cause of death15, but

IHD diagnoses has been estimated to be correct in 87% for ischemic heart disease although the data from this study were collected two decades ago. 16 The causes of death are also considered to be more reliable for the younger population than for the elderly population. 15

8. Page 5, line 25, please also describe how AR was calculated, not just AER

Authors reply:
We acknowledge that it must be clarified how we did the AR and AER estimations. Therefore, we have revised the section regarding the calculations for AR and AER.

Section: Methods (p 7)
To examine the excess mortality risk in the study population the absolute risk (AR) was calculated separately for both the general population and the study population by dividing the observed mortality with person time. The absolute excess risk (AER) is the difference between the observed and the expected AR. For standardization purposes, the estimates were then multiplied by 100 person-years. This yields an average annual excess risk for each period. The AER calculations add a useful measure of excess risk in absolute terms. Life expectancy tables from Official Statistics of Sweden (SCB) were used to calculate the expected mortality in the Swedish general population by gender, age and calendar year.

9. Page 7, line 43, please replace ‘multivariate’ with ‘multivariable’

Authors reply:
Thank you for this comment. We have done the correction in the methods section.

Section: Methods (p 8)
Cox proportional hazard regression, providing hazard ratios (HR) with 95% CIs, was used to estimate age, and gender-specific changes in all-cause mortality over time.19 The first period (1987–1991) was used as reference; The multivariable models were adjusted for age, diabetes, hypertension, valvular and congenital heart disease, stroke, chronic respiratory disease, malignancy and renal failure.

10. Page 16, first paragraph - the authors suggest that the adoption of troponin in the diagnosis of MI differentially impacted women compared to men. As suggested above, this can be supported or refuted by giving the MI rates by sex for the first 3 periods, and then the last period.

Authors reply: Please see our response to the above comment – AMI rates are now provided.

11. Page 16, line 51, the authors suggest that greater use of evidence-based medications and repercussion may have contributed to the decline in mortality. Reperfusion is only associated with improve survival among STEMI patients, and STEMI rates have decline over the years, so this is a tenuous explanation.

Authors reply: We do not agree with this statement – please see current and past ESC guidelines for STEMI and for NSTEMI. While STEMI is usually successfully treated with immediate reperfusion, NSTEMI patients are generally subjected to coronary angiography and reperfusion as needed (please see FRISC II criteria). Other evidence-based medications included in current guidelines include statins, an increasing array of antithrombotics, beta-blockers, ACE-inhibitors or AT2-receptor

blockers.

12. Page 17, line 18, the authors suggest that the increase in comorbidities is probably due to improvements in clinical reporting. Please cite papers to support this assertion. The explanation for hypertension cites reference 26, but this reference does not talk about WHO guidelines. Please correct.

Authors reply:
Regarding the increased comorbidities during the study period can partly be explained by financial incitements. The ICD codes has formed a base for management and financing for Swedish hospitals and other services in Swedish health care.

The reference number 26 and 27 had unfortunately been inverted but it is now corrected in the manuscripts reference section. Due to changes in the manuscript, these references have also changed number. The text was changed as follows:

Section: Discussion (p 17)
Comorbidities increased during the study period. However, this can probably at least partly be derived to improvements in clinical reporting due to financial incitements. 13 The striking increase in hypertension can also probably be attributed to changes in criteria and guidelines management by the WHO.28

Section: References (p 25)
28. World Health Organization, international Society of hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-1992

29 Luepker RV, Duval S, Jacobs DR Jr, et al. The effect of changing diagnostic algorithms on acute myocardial infarction rates. Ann Epidemiol 2011;21:824-829.

13. Page 17, line 41, the authors again allude to a differential impact of troponin measurement on diagnosis by sex. They cite a single paper that reviewed patients who had both CK-MB and troponin measured. If troponin truly is more sensitive in women than men, one might hypothesize that it then detects milder cases of MI than would have been detected by CK-MB alone. Milder MI would normally be associated with better outcomes. The rationale for this argument is unclear to this reviewer. And, again, if the introduction of troponin really did result in an increase in MI, the MI rates would have increased, and if the authors' speculation is correct, it would have increased more in women than men. The authors appear to have this data - they are encourage to provide it.

Authors reply: We would like to refer to our prior response to comment from reviewer 1 (question number 10) with the following text added to the discussion – unfortunately, despite our best efforts, we found no additional references, so this remains slightly conjectural. MIs picked up by troponins may be milder, but not always, they may also be associated with more comorbidities.

Section: Discussion (p 18)
Accordingly, the increasing mortality among women hospitalized in 2002–2006 could be due to the capture of other and more complicated types of myocardial damage because an increase in troponin levels is also seen in other conditions.30 Even so, comorbidities, although increasing over time, were still low in the most recent period. Since the most marked change between the third and the fourth period of our study was the change from CK-MB to troponins as the predominant marker for

myocardial damage, we speculate that the additional AMIs captured by this more sensitive method are clinically different, not only in being smaller but also to an unknown extent reflecting myocardial damage not due to atherosclerotic disease. Circumstantial evidence for this might be derived from the increasing and much higher proportion of non-CVD deaths, as well as more comorbidities, in women compared to men over the study period. In the present study the results showed an increased rate of survivors but a decreasing trend in death in CVD among young women. These results strengthen that the increased all-cause mortality is likely a result of a combination between the use of troponin and increasing comorbidities.

Reviewer Name Louise Pilote
Institution and Country McGill University Canada
Please state any competing interests or state 'None declared': None declared

Major comments:

1. The major concern with this study is that it includes data from 1987 to 2006. Eight years has passed since these data were collected and they therefore may not be representative of the evolution in post-AMI survival in the last decade. Could the authors review recent data (i.e. between 2006 and 2013) regarding mortality trends, and comment whether their data are representative of what has been observed in the last data?

Authors reply:
Thank you for highlighting these issues regarding the follow up. Our aim was to use the data to get as long follow up as possible for each period. With the current use of data we had the possibility to follow patients until 2010. Because we followed the cases until the end of 2010 and submitted the paper before the end of 2013 it is not quite fair to describe our study as based on eight year old data. The completion of collection of death certificates by the Board of Health and Welfare takes almost a year after the end of a calendar year, there is quite a complicated procedure involved from our part in obtaining the data, and further, some time must be allowed for the actual analysis and writing of the paper. Because nothing really dramatic has happened with respect to diagnostics, procedures or other treatment during the last 2 years, we think that these data are sufficiently representative for the present time and contribute to research in survival after AMI, and that a time-consuming attempt to obtain a brand-new dataset is not justified. We also changed the title of the paper as follows:

Title (p 1):
Sex-specific trends in four-year survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. A register-based cohort study.

2. We are unclear about why the increasing use of troponins in the diagnosis process around the year 2000 would increase detection of AMI in women but not in men (which, according to the authors, would explain the increment in mortality during the last follow-up period in women but not in men). Could the authors clarify why this change in troponins utilization would lead to an enhanced detection among women but not among men, and why the utilization of troponins would help capturing other and more complicated types of myocardial damage in women but not in men? (page 17, lines 35 to 50)

Authors reply: Again, we would like to refer to our prior response to reviewer 1 (question number 10) with the following text added to the discussion – unfortunately, despite our best efforts, we found no

additional references, so this remains slightly conjectural. MIs picked up by troponins may be milder, but not always, they may also be associated with more comorbidities.

Section: Discussion (p 18)
Accordingly, the increasing mortality among women hospitalized in 2002–2006 could be due to the capture of other and more complicated types of myocardial damage because an increase in troponin levels is also seen in other conditions.30 Even so, comorbidities, although increasing over time, were still low in the most recent period. Since the most marked change between the third and the fourth period of our study was the change from CK-MB to troponins as the predominant marker for myocardial damage, we speculate is that the additional AMIs captured by this more sensitive method are clinically different, not only in being smaller but also to an unknown extent reflecting myocardial damage not due to atherosclerotic disease. Circumstantial evidence for this might be derived from the increasing and much higher proportion of non-CVD deaths, as well as more comorbidities, in women compared to men over the study period. In the present study the results showed an increased rate of survivors but a decreasing trend in death in CVD among young women. These results strengthen that the increased all-cause mortality is likely a result of a combination between the use of troponin and increasing comorbidities.

3. Another concern regards limited clinical and treatment data. As mentioned by the authors, they could not collect data regarding characteristics of the index AMI (AMI severity), treatments received, biomarkers, and socio-demographic characteristics, which play a major role in survival post-AMI. This lack of data limits considerably the interpretations the authors can make of their results.

Authors reply: This is obviously quite true, and was indicated in the limitations of the first version. We now further emphasize this as follows;

Section: Discussion (p 19-20)
The main limitation in the present study is the reliance on administrative registers with no details of changes in several characteristics, such as biomarkers, electrocardiographic findings, smoking, medication, hyperlipidemia, family history, ethnicity and socioeconomic status and a lack of other clinical information, notably hospital treatment and clinical presentation. Also, we were unable to apply uniform criteria for diagnosis over time. This limits considerably the interpretation that can be made, however, the findings should be applicable to current patients with AMI in an industrialized modern country.

4. To ensure that the index AMI was the first in patients' life, the authors collected data as of 1980 with regards to diagnosis of AMI. However, I am wondering if this method is appropriate given the age range from 25 to 54 years. It is unlikely that 25 years old patients have had a previous event before the age of 18, while it is well possible that 54 years old patients have had a previous event before the age of 47 years. Is it possible that the index AMI was not the first one for a certain proportion of the oldest patients?

Authors reply:
Thank you for these comments which are very valuable for the validity. We have realized that it is not clear how the selection process was performed and therefore we rephrased the text to avoid misunderstandings. Due to the 7-years' time frame we now use cases instead of patients.

Section: Methods (p 6)
The present study included all 38,836 cases (31216 men, 7620 women) in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006; AMI was defined as a principal

discharge code according to the ICD -8 : 410 (until 1987), ICD-9: 410 (until 1996) and ICD-10: I21 (from 1997 onward). After excluding 1,560 cases who died during the first 28 days 1169 men (3.01% of cases) median age; 50, and 391 women (1.01% of cases) median age; 49.0, 37,276 cases (7,229 women and 30,047 men) with a first AMI remained for analysis. Data from 1980 onward were used to identify first AMIs only, with a time frame of 7 years throughout, to ensure that AMIs registered each year had the same chance of being identified as a first AMI. Due to the 7-years time frame, 443 cases were recurrent AMI after seven years (53 women median age; 52, 390 men median age; 51)

Minor comments:

5. Abstract: Design: Is this really a prospective study? I would suggest revising the design for a register-based cohort study.

Authors reply:
We agree with the reviewer´s comment and made changes in the title accordingly.

Title:
Sex-specific trends in four-year survival in 37,276 men and women with acute myocardial infarction before the age of 55 years in Sweden, 1987–2006. A register-based cohort study.

6. Results: Please specify which is the third period.

Authors reply:
We agree with the reviewer´s comment and added the suggested information.

Section: Results (p 9)
Survival in men improved continuously over the four 5-year periods (Figure 2), while the prognosis in women improved until the third period (1997-2001), then reverted to a risk nearly identical to that in the second period (Figure 3).

7. Results: In the last sentence, please indicate from when to when the risk of non-cardiovascular deaths increased.

Authors reply:
We agree with the reviewer´s comment and added the suggested information.

Section: Results (p 22)
Table 3 shows causes of death for the 2,076 deaths that occurred within 4 years in this cohort. In 1987–1991, 74,8% of all deaths within 4 years were due to CVD (78.6% for men and 58.5% for women) with a majority to IHD. However, during the last period (2002-2006), only 48.4% of all deaths were due to CVD (55.4% for men and, notably, only 34.1% for women)

8. Conclusion: In the last sentence, please change “healthy women” for “women in the general population”.

Authors reply:
We agree with the reviewers comment and made the suggested change in the abstract/conclusion section.

Section: Abstract/Conclusion (p 2)
Conclusion Young male survivors of AMI have low absolute long-term mortality rates, but these rates remain 2- to 4-fold that of the general population. After favourable development until 2001, women now have higher absolute mortality than men and a 6- to 14-fold risk of death compared with women in the general population.

Main text
9. There seems to be a problem with the references. For example, references 26 and 27 seem to have been inverted. Please fix citations and references.

Authors reply:
Thank you for the attention regarding the mistake in the reference section. Due to changes in the manuscript, these references have changed number. We have now corrected this in the reference section.

Section: References (p 25)
28. World Health Organization, international Society of hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003;21:1983-1992

29 Luepker RV, Duval S, Jacobs DR Jr, et al. The effect of changing diagnostic algorithms on acute myocardial infarction rates. Ann Epidemiol 2011;21:824-829.

10. Please specify which codes were used for AMI in the ICD 8th revision.

Authors reply:
The codes for AMI in ICD 8 now specified in the methods section.

Section: Methods (p 6)
The present study included all 38,836 cases (31216 men, 7620 women) in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006; AMI was defined as a principal discharge code according to the ICD -8 : 410 (until 1987), ICD-9: 410 (until 1996) and ICD-10: I21 (from 1997 onward).

11. The authors mentioned that 1537 patients died within 28 days of the index AMI and were therefore excluded from the study. Do the authors have data regarding the proportion of men and women, and the age of these patients?

Authors reply:
This was also pointed out by reviewer 2 and we agree that this information would be of interest and have therefore added this information.
Due to previous comments (point number 4) concerning the use of 7-years time frame we have also rephrased the manuscript and use cases instead of patients to avoid misunderstandings.

Section: Methods (p 6)
The present study included all 38,836 cases (31216 men, 7620 women) in Sweden aged 25–54 years, discharged from hospital after a first AMI in 1987–2006; AMI was defined as a principal discharge code according to the ICD -8 : 410 (until 1987), ICD-9: 410 (until 1996) and ICD-10: I21

(from 1997 onward). After excluding 1,560 cases who died during the first 28 days 1169 men (3.01% of cases) median age; 50, and 391 women (1.01% of cases) median age; 49.0, 37,276 cases (7,229 women and 30,047 men) with a first AMI remained for analysis. Data from 1980 onward were used to identify first AMIs only, with a time frame of 7 years throughout, to ensure that AMIs registered each year had the same chance of being identified as a first AMI. Due to the 7-years time frame, 443 cases were recurrent AMI after seven years (53 women median age; 52, 390 men median age; 51)

12. Page 4, line 42: “However, there have since been…” please specify since when?

Authors reply:
Thank you for your recommendation. We refer to the results of the two studies by Rosengren et al. (2001) and Vaccarino et al. (2001). We agree that this must be clarified and have made changes in the manuscript.

Section: Introduction (p 4)
Further, younger, but not older, women hospitalized with AMI have a worse long-term prognosis than men, as shown in analyses of patient populations dating from the 1980s and 1990s .9,10 However, there have since been marked changes in treatment, diagnostic criteria, and post-AMI prognosis. A recent study found that reductions in long-term mortality after 1985 were at least as high for women as for men with AMI,11 but the study did not specifically report findings for young patients. An additional study, found that reductions in mortality were similar regardless of age but that younger patients are more likely to receive evidence based care.12

13. Page 5, line 32: Please fix typo by removing the semicolon.

Authors reply:
Thank you for this comment, we have removed the semicolon. This sentence has also been partly been rephrased due to suggestions from reviewer 1, regarding the validity of the IPR register.

14. Page 10, line 55: Please fix typo “with an” should be “with a”
15. Page 17, line 32: “to the nearly” should read “to nearly”

Authors reply to reviewer´s comments number, 14 and 15:
We are grateful for these comments. We have corrected all the recommendations regarding the English expression described above.

Section: Results (p 10)
Corresponding figures for men aged 45–54 were a decrease from 1.53 to 0.59 with a SMR of 2.43 (95% CI: 2.12–2.76) in the last period (2002–2006).

Section: Discussion (p 18)
Mortality in women decreased until the third period and then increased during the fourth period to nearly the same level as in the second period.

16. In the Statistical analyses section, the authors mentioned that they conducted Cox proportional hazard models adjusted for age, hypertension, valvular and congenital heart disease, stroke, chronic respiratory disease, malignancy and renal failure. However, the models were not adjusted for other important confounders such as dyslipidemia, cigarette smoking, and ethnicity, which characteristics

are known to differ between men and women and to influence comorbidities and survival. Could the authors compare their results with previous studies having adjusted their models of analyses for these confounders, and comment on the implications of not having included them as covariate in their study.

The main focus of our paper was on trends in survival, and we already indicate in our Limitations section that there were a number of variables on which we had no information. In response to the comment by the reviewer we rephrased our limitations section slightly as follows:

Section: Discussion (p 19-20)

The main limitation in the present study is the reliance on administrative registers with no details of changes in several characteristics, such as biomarkers, electrocardiographic findings, smoking, medication, hyperlipidemia, family history, ethnicity and socioeconomic status and a lack of other clinical information, notably hospital treatment and clinical presentation.

We are not aware of any study that have evaluated trends in survival after AMI and which has also considered these factors

VERSION 2 – REVIEW

REVIEWER	Louise Pilote McGill University
REVIEW RETURNED	03-Apr-2014

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