PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Variation in cardiovascular disease care: An Australian cohort study on sex differences in receipt of coronary procedures.
AUTHORS	Fogg, Alexandra; Welsh, Jennifer; Banks, Emily; Abhayaratna, Walter; Korda, Rosemary

VERSION 1 – REVIEW

REVIEWER	Nathaniel Smilowitz NYU School of Medicine New York, NY United States of America
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	Fogg and colleagues present data from a population-based cohort study of adults ≥45 who presented with a new diagnosis of either AMI or stable angina. Follow up was obtained based on linked national hospital and death record data. The authors report higher crude frequency of coronary angiography and coronary revascularization with PCI or CABG in men versus women in patients presenting with both AMI and angina. After adjustment for demographics and baseline characteristics, men were more likely to undergo angiography than women among patients with angina but not MI. In adjusted analyses, men were 50% more likely than women to undergo PCI or CABG in the setting of MI, and more than 2-fold more likely to undergo PCI or CABG in the setting of angina. The authors highlight important sex-differences in care in Australia that warrant further study. -- The authors use the term "gender" throughout the manuscript. Is biological sex or gender used to differentiate subjects in this manuscript? Please clarify, and replace "gender" with "sex" if appropriate. -- The authors acknowledge a failure to adjust for clinical characteristics at the time of presentation - this is a major limitation in the adjusted analyses. Ideally, admission level data should be included in the hierarchical modeling, incorporating troponin levels, eGFR, ejection fraction, and other markers that are associated with the decision to perform coronary angiography.

	-- Mortality data is not reported in this manuscript. How was the competing risk of death handled in these analyses? This is a potential limitation of the study methodology. -- Suggest a sensitivity analysis evaluating the rates of angiography and revascularization after excluding elderly patients >85, who may be more likely to refuse invasive interventions based on goals of care. -- Discussion should be expanded to discuss the sex differences in the frequency of revascularization in the context of differences in the pathophysiology of ischemic heart disease. Women are more likely than men to have MINOCA (MI with non-obstructive CAD (Circ Cardiovasc Qual Outcomes. 2017 Dec;10(12):e003443.) and are more likely to have non-obstructive CAD at angiography in the setting of stable angina (Circulation. 2008;117:1787–1801). Although this is briefly mentioned, it should be highlighted more clearly. In contrast, these differences in the mechanisms of ischemic heart disease should not impact the decision to perform angiography.

REVIEWER	Tobias Heer München Klinik Schwabing Kölner Platz 1 80804 München Germany
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	1. Abstract: Mortality in follow-up is a strong endpoint and should be mentioned in the abstract. 2. 45 and Up study participants were randomly selected from the Department of Human Services database. How many people live in New South Wales? How many acute coronary syndromes were missed by a randomly selection? 3. Patients with history of IHD were excluded. What is the reason for this preselection? 4. Patients had to fill-in a self-administered questionnaire? Do the authors think that this information is reliable? 5. What was the definition of AMI? Did all patients get an ECG? Were patients with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) analyzed separately? Do we have information about troponin and CK levels? Were the blood tests repeated to confirm the diagnosis AMI? 6. Do we have information about hemodynamic instability? How many patients were in cardiogenic shock? 7. How many hospitals in New South Wales have a catheterization laboratory? How many patients were transferred from a hospital without cath lab to a hospital with cath lab?

	8. Do we have information about prehospital delay in women compared to men? What was the first medical contact to balloon time? 9. Is there any possibility to get information about risk factors like hypertension, diabetes, hypercholesteremia, smoking, family history of CAD? Adjustment should be done for these factors. 10. There are other reasons for troponin elevation and symptoms like AMI like takotsubo syndrome, myocarditis, aortic dissection, pulmonary embolism. How often were these diagnoses? 11. It is well known that more than 50% of all women with acute coronary syndromes have non-obstructive coronary artery disease. Do we have information about the results of the coronary angiography? How many women and men had coronary stenoses <50%. 12. The authors should compare women and men with coronary stenoses >50% and analyse the rate of recommendation for PCI or CABG with adjustment for age and other risk factors. This is the only way to confirm the statement that there is an undertreatment of women in their population. 13. What is the rationale to look at coronary angiographies in the year after the index event? According to the guidelines, coronary angiography in STEMI patients should be done immediately and in NSTEMI in up to 72 hours. The authors should analyse if there is a gender difference in time delay in the first hours after an acute coronary syndrome. 14. Mortality in follow-up is very high in both genders. Is this cardiovascular mortality? 15. As the diagnosis “angina” comprises chest pain due to many different diseases, even non-cardiac, physicians cannot be accused if they do not perform a coronary angiography in all these patients. Instead of writing “care is more discretionary” in patients with angina, the authors should concentrate on patients with real myocardial infarctions (STEMI) and leave out the angina population. Ideally, they should look at STEMI and NSTEMI separately. 16. The authors should be very cautious with their conclusion that men are more likely than women to receive coronary procedures. This suggests that women were treated worse than men. The authors should answer the following questions before they can conclude like they did: - What was the influence of randomly selection instead of consecutive inclusion of all patients with acute coronary syndromes like in other registries? - What was the influence of a self-administered questionnaire? - What was the indication for coronary angiography in both genders? Angina is a symptom and not a diagnosis. Were there stress tests done in both genders before coronary angiography? Were other reasons for chest pain excluded? - Did the physicians have good reasons not to perform a coronary angiography in the patients?

	17. As there are a lot of limitations the authors should recalculate their results and attenuate their conclusion. - The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

We would like to thank both reviewers for their thoughtful comments, and in particular their suggestions for improvement. Please find our responses below.

To start, we would like to highlight that the study undertaken was epidemiological in nature, based on questionnaire data linked to large-scale routine data. This permitted the inclusion of large numbers of participants with prospective data on a wide range of personal characteristics and other factors, and virtually complete capture of outcomes. However, we did not have access to clinical variables mentioned in points 1.2, 2.5-8, 2.11-12, and 2.16, and have further clarified this within the manuscript (please refer to point 1.2). We have therefore emphasised the contribution the study makes in quantifying the sex difference that exists in receipt of coronary procedures following first diagnosis of AMI or angina.

While we have made some suggestions as to possible reasons for the sex difference, it is not possible to provide definitive reasons. We have taken care to stress the uncertainties, particularly given the lack of clinical information, and as per point 2.16 below, we have now provided further information on this within the manuscript. We agree with reviewer comments that exploring more detailed explanations for the sex difference found would be a fruitful area of future research, however it was beyond the scope of our paper.

Reviewer: 1

Reviewer Name: Nathaniel Smilowitz

Institution and Country: NYU School of Medicine New York, NY United States of America

Fogg and colleagues present data from a population-based cohort study of adults ≥45 who presented with a new diagnosis of either AMI or stable angina. Follow up was obtained based on linked national hospital and death record data. The authors report higher crude frequency of coronary angiography and coronary revascularization with PCI or CABG in men versus women in patients presenting with both AMI and angina. After adjustment for demographics and baseline characteristics, men were more likely to undergo angiography than women among patients with angina but not MI. In adjusted analyses, men were 50% more likely than women to undergo PCI or CABG in the setting of MI, and more than 2-fold more likely to undergo PCI or CABG in the setting of angina. The authors highlight important sex-differences in care in Australia that warrant further study.

1.1 The authors use the term "gender" throughout the manuscript. Is biological sex or gender used to differentiate subjects in this manuscript? Please clarify, and replace "gender" with "sex" if appropriate.

Thank you for raising this point. The variable ‘sex’ was used as per the Australian Government’s Department of Human Services database. We have replaced “gender” with “sex” throughout the manuscript.

1.2 The authors acknowledge a failure to adjust for clinical characteristics at the time of presentation - this is a major limitation in the adjusted analyses. Ideally, admission level data should be included in the hierarchical modelling, incorporating troponin levels, eGFR, ejection fraction, and other markers that are associated with the decision to perform coronary angiography.

As discussed above, this manuscript is an epidemiological study based on routine linked data, and as such clinical characteristics at the time of presentation were not available. We have clarified this within the manuscript.

> “The use of questionnaire data linked to large-scale routine data enabled a wide range of personal characteristics and other factors to be included in models, such as socio-economic position and physical functioning, however clinical factors relating to patient presentation and symptom severity were not available in the dataset.” (page 13, paragraph 3)

1.3 Mortality data is not reported in this manuscript. How was the competing risk of death handled in these analyses? This is a potential limitation of the study methodology.

Mortality data was used for censoring as per time-to-event analysis, and thus was taken into account. We have clarified this within the manuscript, and added this detail to the abstract.

> “Design: Prospective cohort study. Baseline questionnaire (January 2006-April 2009) data from the Sax Institute’s 45 and Up Study were linked to hospitalisation and mortality data (to 30 June 2016) in a time-to-event analysis, treating death as a censoring event.” (page 2, paragraph 2)

> “Death data included date of death (used for censoring as per time-to-event analysis), based on death from any cause.” (page 5, paragraph 2)

1.4 Suggest a sensitivity analysis evaluating the rates of angiography and revascularization after excluding elderly patients >85, who may be more likely to refuse invasive interventions based on goals of care.

We agree with the reviewer, and have undertaken a sensitivity analysis excluding patients over the age of 85 as suggested. Results were consistent with previous findings. These have now been included as supplementary tables (S8 and S9), and reported within the manuscript on page 11, paragraph 4 .

Table S8: Rates of coronary procedures within one year of admission with AMI by sex and associated hazard ratios, excluding those aged 85 years and over (n=3691)

	Procedures/ pys	Crude rate per py (95%CI)	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
Angiography					
Men	1891/438.3	4.31 (4.12-4.51)	1.08 (0.99-1.16)	1.03 (0.95-1.12)	1.02 (0.94-1.1)
Women	912/258.9	3.52 (3.3-3.76)	1.00	1.00	1.00
PCI/CABG					
Men	1543/767.2	2.01 (1.91-2.11)	1.69 (1.53-1.87)	1.65 (1.49-1.82)	1.61 (1.46-1.79)
Women	517/608.8	0.85 (0.78-0.93)	1.00	1.00	1.00

Notes: py: person-year. Model 1 is adjusted for age at first admission. Model 2 is adjusted for age and sociodemographic variables (country of birth, region of residence, highest qualification, health insurance, marital status). Model 3 is adjusted for age, sociodemographic variables and health-related variables (obesity, physical functioning, psychological distress).

Table S9: Rates of coronary procedures within one year of admission with angina by sex and associated hazard ratios, excluding those aged 85 years and over (n=4076)

	Procedures/ pys	Crude rate per py (95%CI)	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
Angiography					
Men	1603/629.1	2.55 (2.43-2.68)	1.29 (1.19-1.4)	1.25 (1.16-1.36)	1.24 (1.14-1.34)
Women	1010/707.2	1.43 (1.34-1.52)	1.00	1.00	1.00
PCI/CABG					
Men	1066/1131.6	0.94 (0.89-1.00)	2.65 (2.35-2.99)	2.57 (2.28-2.91)	2.53 (2.23-2.86)
Women	347/1322.5	0.26 (0.24-0.29)	1.00	1.00	1.00

Notes: py: person-year. Model 1 is adjusted for age at first admission. Model 2 is adjusted for age and sociodemographic variables (country of birth, region of residence, highest qualification, health insurance, marital status). Model 3 is adjusted for age, sociodemographic variables and health-related variables (obesity, physical functioning, psychological distress).

1.5 Discussion should be expanded to discuss the sex differences in the frequency of revascularization in the context of differences in the pathophysiology of ischemic heart disease. Women are more likely than men to have MINOCA (MI with non-obstructive CAD (Circ Cardiovasc Qual Outcomes. 2017 Dec;10(12):e003443.) and are more likely to have non-obstructive CAD at angiography in the setting of stable angina (Circulation. 2008;117:1787–1801). Although this is briefly mentioned, it should be highlighted more clearly. In contrast, these

differences in the mechanisms of ischemic heart disease should not impact the decision to perform angiography.

Thank you very much for this reference. We have incorporated this into the discussion, and have highlighted this point more clearly, as follows:

> "Previous studies have shown that women who present with AMI or stable angina are more likely to have non-obstructive coronary artery disease compared to men, i.e. <50% stenosis of coronary arteries.[23, 24]" (page 12, paragraph 4)

Reviewer: 2

Reviewer Name: Tobias Heer

Institution and Country: München Klinik Schwabing, Kölner Platz 1, 80804 München, Germany

2.1 Abstract: Mortality in follow-up is a strong endpoint and should be mentioned in the abstract.

Please see point 1.3 above. We have now mentioned mortality in the abstract.

2.2 45 and Up study participants were randomly selected from the Department of Human Services database. How many people live in New South Wales? How many acute coronary syndromes were missed by a randomly selection?

This was an epidemiological study conducted using data from the 45 and Up Study cohort. The data from the cohort study questionnaires were linked to routine hospital data, providing virtually complete capture and follow up of acute coronary syndrome within this population. Standard cohort study methodology was employed, utilising internal comparisons of sex differences in receipt of coronary procedures. We therefore consider that very few if any acute coronary syndrome hospitalisations were missed using the methods employed by this study.

2.3 Patients with history of IHD were excluded. What is the reason for this preselection?

This was done in order to ensure the study only included first "incident" IHD events for both men and women. Including people with a previous history of IHD, and thus the possibility of procedures, would have introduced bias and potentially compromised internal validity. Although beyond the scope of the current paper, quantification of sex differences in procedures following recurrent CVD events is an area with potential for future research, providing that sufficient data on previous CVD events and procedures is available.

2.4 Patients had to fill-in a self-administered questionnaire? Do the authors think that this information is reliable?

The main exposure (AMI or angina) and the main outcome (receipt of coronary procedure) were based on routinely-collected hospital data. Sex was ascertained based on registration data with Australia's Department of Human Services database. Covariates were self-reported, using previously validated study instruments, and are considered reliable for research of the nature reported in our study, including age and region of residence. Furthermore, certain covariates, e.g. psychological distress and education, are generally only available via self-report.

2.5 What was the definition of AMI? Did all patients get an ECG? Were patients with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) analyzed separately? Do we have information about troponin and CK levels? Were the blood tests repeated to confirm the diagnosis AMI?

AMI was defined as per International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) coding I21:

> "A disorder characterised by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area."
>
> (https://www.icd10data.com/ICD10CM/Codes/I00-I99/I20-I25/I21-)

This is in alignment with standard epidemiological studies involving administrating hospital data. A systematic review published by McCormick et al. in 2014 regarding the validity of MI diagnoses in administrative databases found that hospitalisation data for identifying MI had sensitivity and specificity of ≥86% and a positive predictive value of ≥93%. Hence identification of MI using hospitalisation data is appropriate and reliable (McCormick N, Lacaille D, Bhole V, et al. Validity of

Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. PLoS One 2014;9(3):e92286 10.1371/journal.pone.0092286.). This paper has now been cited within the manuscript:

> "Additionally, the diagnosis of AMI is highly valid within hospital data, with sensitivity and specificity of ≥86% and a positive predictive value of ≥93%,[28] and high concordance between diagnostic codes and physician review.[29]" (page 14, paragraph 1)

As stated previously, data on results of ECGs and blood tests were not available.

2.6 Do we have information about hemodynamic instability? How many patients were in cardiogenic shock?

Please refer to our opening statement, and point 1.2 above.

2.7 How many hospitals in New South Wales have a catheterization laboratory? How many patients were transferred from a hospital without cath lab to a hospital with cath lab?

Hospital transfers were taken into account. Information on whether hospitals had a catheterisation laboratory was not available in the dataset. However, this is unlikely to have any material effect on the adjusted relationship between sex and receipt of procedure i.e., while the presence of a catheterisation laboratory in the relevant hospital is likely to be associated with the outcome, it is unlikely to be related to sex, hence it is technically unlikely to be a confounder. (Note that age has been adjusted for).

2.8 Do we have information about prehospital delay in women compared to men? What was the first medical contact to balloon time?

Please refer to our opening statement, and point 1.2 above.

2.9 Is there any possibility to get information about risk factors like hypertension, diabetes, hypercholesteremia, smoking, family history of CAD? Adjustment should be done for these factors.

Thank you for this suggestion. We have undertaken a sensitivity analysis adjusting for smoking, treatment for hypertension, self-rated diabetes, treatment for hypercholesterolaemia, and family history of heart disease. Results did not change materially following additional adjustments. Please see table of results below. This have now been included as a supplementary table to the paper, and reported within the manuscript on page 11, paragraph 4.

Table S10:Hazard ratios for coronary procedures within one year of admission with AMI (n=4,580) or angina (n=4,457) (in relation to sex, adjusted for age, sociodemographic variables and healthrelated variables including cardiovascular risk factors

	AMI HR (95%CI)	Angina HR (95%CI)
Angiography		
Men	1.01 (0.93-1.09)	1.24 (1.14-1.34)
Women	1.00	1.00
PCI/CABG		
Men	1.52 (1.38-1.67)	2.45 (2.17-2.76)
Women	1.00	1.00

Notes: Model 1 is adjusted for age at admission (in 5-year age categories). Model 2 is adjusted for age and sociovariables (country of birth, region of residence, highest qualification, health insurance, marital status). Model 3 is adjusted for age, sociodemographic variables health-related variables (obesity, physical functioning, psychological distress), and CVD risk factors (smoking, self-rated diabetes, treated for high blood pressure, treated for high cholesterol and family history of heart disease).

2.10 There are other reasons for troponin elevation and symptoms like AMI like takotsubo syndrome, myocarditis, aortic dissection, pulmonary embolism. How often were these diagnoses?

The final diagnosis of AMI was made by clinicians. The above differential diagnoses are assigned different ICD-10-AM codes to AMI and angina (e.g. myocarditis has code I51.4, pulmonary embolism has code I26), and hence would not have been included in our study population.

2.11 It is well known that more than 50% of all women with acute coronary syndromes have nonobstructive coronary artery disease. Do we have information about the results of the coronary angiography? How many women and men had coronary stenoses <50%.

Please refer to our point 2.12.

2.12 The authors should compare women and men with coronary stenoses >50% and analyse the rate of recommendation for PCI or CABG with adjustment for age and other risk factors. This is the only way to confirm the statement that there is an undertreatment of women in their population.

In response to points 2.11 and 2.12, results of coronary angiography are not available. Additionally, please see point 1.5 above.

We would like to assure the reviewer that we have not concluded that there is undertreatment in women, noting as follows:

> "While we cannot exclude that this discrepancy reflects appropriate care due to differences in clinical presentation, we must consider the possibility that sex differences, accounting for sociodemographic position and health-related factors, may indicate that the health care needs of a portion of the Australian population are not being adequately met." (page 14, paragraph 2)

Importantly, we discuss possible alternative explanations for the sex differences seen, first and foremost, the likely contribution of differences in clinical presentation (see response 2.16 below), We agree that the degree of coronary stenosis would provide useful information, and would be a fruitful area of future research in a more detailed clinical study.

2.13 What is the rationale to look at coronary angiographies in the year after the index event? According to the guidelines, coronary angiography in STEMI patients should be done immediately and in NSTEMI in up to 72 hours. The authors should analyse if there is a gender difference in time delay in the first hours after an acute coronary syndrome.

We agree that this is true according to guidelines. As our paper includes a time-to-event analysis, it captures all events, with time measured in days. Procedures received according to stated guidelines are included within this. Results would not be impacted if all procedures have occurred within the first 72 hours, regardless of length of follow up, as relative rates will remain the same. Unfortunately we do not have information regarding time delay (in hours) in angiography.

2.14 Mortality in follow-up is very high in both genders. Is this cardiovascular mortality?

Mortality in follow-up is based on all-cause mortality. We have clarified this within the manuscript:

> "Death data included date of death (used for censoring as per time-to-event analysis), based on death from any cause." (page 5, paragraph 2)

2.15 As the diagnosis "angina" comprises chest pain due to many different diseases, even noncardiac, physicians cannot be accused if they do not perform a coronary angiography in all these patients. Instead of writing "care is more discretionary" in patients with angina, the authors should concentrate on patients with real myocardial infarctions (STEMI) and leave out the angina population. Ideally, they should look at STEMI and NSTEMI separately.

We agree that the term “angina” is used clinically to denote chest pain. However, for this study, the final diagnosis of angina was defined according to the clinicopathological ICD-10-AM coding, utilising the code I20, which is included under the broader grouping “ischaemic heart disease (I20I25)” or “coronary heart disease”. It is thus defined as:

> “A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation” and “chest pain caused by coronary heart disease”. (https://www.icd10data.com/ICD10CM/Codes/I00-I99/I20-I25/I20-)

We agree that looking at STEMI and NSTEMI separately would be ideal. Unfortunately the data do not allow for this, with the ICD coding unable to reliably distinguish between different types of AMI (Alexandrescu R, Bottle A, Jarman B et al. Current ICD10 codes are insufficient to clearly distinguish acute myocardial infarction type: a descriptive study. BMC Health Serv Res. 2013(13):468).

We have now included these details within the manuscript for clarity:

> “ICD-10-AM diagnosis codes I21 (acute myocardial infarction), I20 (angina pectoris), and I25 (chronic ischaemic heart disease), were used to ascertain admission. Note that these are clinicopathological diagnoses, with angina specifically referring to chest pain from insufficient myocardial oxygenation and coronary artery disease. I21 coding for AMI includes both ST-elevation and non-ST elevation myocardial infarcts, with current ICD-10 coding unable to reliably distinguish between these.[12]” (page 6, paragraph 2)

2.16 The authors should be very cautious with their conclusion that men are more likely than women to receive coronary procedures. This suggests that women were treated worse than men. The authors should answer the following questions before they can conclude like they did:

- What was the influence of randomly selection instead of consecutive inclusion of all patients with acute coronary syndromes like in other registries?
- What was the influence of a self-administered questionnaire?
- What was the indication for coronary angiography in both genders? Angina is a symptom and not a diagnosis. Were there stress tests done in both genders before coronary angiography? Were other reasons for chest pain excluded?
- Did the physicians have good reasons not to perform a coronary angiography in the patients?

In stating that men are more likely to receive coronary intervention following first admission with AMI or angina compared to women, we have not concluded that women were treated worse than men. We have suggested possibilities as to why the sex difference was found, but have taken care to stress the uncertainties. In particular, we note the likely contribution of differences in clinical presentation. To further emphasise this point, we have provided further information in paragraphs 3 and 5 of the Discussion.

Specifically In response to the each of the above questions:

- Please see point 2.2 above regarding the complete capture of acute coronary syndrome within our study population. Our data include all consecutive cases of AMI and angina in this population as we agree this is the best method.
- Please see point 2.4 above regarding the validity of variables used within this manuscript.

- The indication for angiography was final diagnosis of AMI or angina as per ICD-10 diagnostic codes. We agree that the term angina is commonly used to refer to a symptom experienced. In this manuscript, however, the term angina refers to a clinicopathological diagnosis as per ICD-10 coding (I20). We have made this clearer within the manuscript (page 6, paragraph 2). Information regarding stress tests were not available. Please also see points 2.10 and 2.15 above.
- Individual patient and clinical factors influencing management were not available to us, as per our opening paragraph, and point 2.6 above.

2.16 As there are a lot of limitations the authors should recalculate their results and attenuate their conclusion.

We thank you for your review, and suggestions for improvement. We have further qualified our conclusions as outlined above. Please refer to our responses above, and to results of sensitivity analyses a) excluding participants aged 85 and over (see point 1.4), and b) adjusting for additional factors of smoking, hypertension, diabetes, hypercholesterolaemia treatment, and family history of heart disease (see point 2.9). These have now been included in the manuscript (S8-10).

VERSION 2 – REVIEW

REVIEWER	Tobias Heer Klinikum München Schwabing, Cardiology, Munich, Germany
REVIEW RETURNED	13-Jan-2019

GENERAL COMMENTS	Fogg et al have resubmitted their paper „variation in cardiovascular disease care: An Australian cohort study on sex differences in receit of coronary procedures. They included some minor changes in their manuscript, but the main questions were not addressed. 1. Abstract: Mortality in follow-up is a strong endpoint and should be mentioned in the abstract. Mortality is not mentioned in the abstract. 2. 45 and Up study participants were randomly selected from the Department of Human Services database. How many people live in New South Wales? How many acute coronary syndromes were missed by a randomly selection? These questions were not answered. 3. Patients with history of IHD were excluded. What is the reason for this preselection? This question was not answered. 4. Patients had to fill-in a self-administered questionnaire? Do the authors think that this information is reliable? This question was not answered.

	5. What was the definition of AMI? Did all patients get an ECG? Were patients with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) analyzed separately? Do we have information about troponin and CK levels? Were the blood tests repeated to confirm the diagnosis AMI? These questions were not answered. Apparently this information is not available. 6. Do we have information about hemodynamic instability? How many patients were in cardiogenic shock? These questions were not answered. Apparently this information is not available. 7. How many hospitals in New South Wales have a catheterization laboratory? How many patients were transferred from a hospital without cath lab to a hospital with cath lab? These questions were not answered. Apparently this information is not available. 8. Do we have information about prehospital delay in women compared to men? What was the first medical contact to balloon time? These questions were not answered. Apparently this information is not available. 9. Is there any possibility to get information about risk factors like hypertension, diabetes, hypercholesteremia, smoking, family history of CAD? Adjustment should be done for these factors. The authors adjusted for self-rated diabetes, treatment for high cholesterol, and family history of heart disease. 10. There are other reasons for troponin elevation and symptoms like AMI like takotsubo syndrome, myocarditis, aortic dissection, pulmonary embolism. How often were these diagnoses? 11. It is well known that more than 50% of all women with acute coronary syndromes have non-obstructive coronary artery disease. Do we have information about the results of the coronary angiography? How many women and men had coronary stenoses <50%. These questions were not answered. Apparently this information is not available. 12. The authors should compare women and men with coronary stenoses >50% and analyse the rate of recommendation for PCI or CABG with adjustment for age and other risk factors. This is the only way to confirm the statement that there is an undertreatment of women in their population. This question was not answered. Apparently this information is not available. 13. What is the rationale to look at coronary angiographies in the year after the index event? According to the guidelines, coronary angiography in STEMI patients should be done immediately and in NSTEMI in up to 72 hours. The authors should analyse if there is a gender difference in time delay in the first hours after an acute coronary syndrome. This question was not answered.

	14. Mortality in follow-up is very high in both genders. Is this cardiovascular mortality? Apparently this information is not available. 15. As the diagnosis “angina” comprises chest pain due to many different diseases, even non-cardiac, physicians cannot be accused if they do not perform a coronary angiography in all these patients. Instead of writing “care is more discretionary” in patients with angina, the authors should concentrate on patients with real myocardial infarctions (STEMI) and leave out the angina population. Ideally, they should look at STEMI and NSTEMI separately. The authors state that they cannot differenciate between STEMI and NSTEMI. 16. The authors should be very cautious with their conclusion that men are more likely than women to receive coronary procedures. This suggests that women were treated worse than men. The authors should answer the following questions before they can conclude like they did: - What was the influence of randomly selection instead of consecutive inclusion of all patients with acute coronary syndromes like in other registries? - What was the influence of a self-administered questionnaire? - What was the indication for coronary angiography in both genders? Angina is a symptom and not a diagnosis. Were there stress tests done in both genders before coronary angiography? Were other reasons for chest pain excluded? - Did the physicians have good reasons not to perform a coronary angiography in the patients? These questions were not answered. Apparently this information is not available. 17. As there are a lot of limitations the authors should recalculate their results and attenuate their conclusion. The conclusion was not changed at all. Most of the questions were not answered. There were no changes to the manuscript. In their different models the authors found that there is no difference in rates of coronary angiography in patients with AMI (table S1 (30 days), S3 (one year)). This is in contrast to the conclusion of the abstract. The second question about differences in rates of PCI or CABG cannot be answered without having information about the coronary status. If a woman presents with signs of a myocardial infarction in the ECG, but the coronary angiography shows no coronary stenosis, it is clear that there should be no PCI or CABG. Women more often present with acute coronary syndromes and non-obstructive coronary artery disease than men. Information about 30 day mortality and mortality after one year is not given.

VERSION 2 – AUTHOR RESPONSE

Thank you for the opportunity to address further comments from Reviewer 2 on our revised manuscript. Our responses are in bold below. We assume Reviewer 1 had no further concerns.

Fogg et al have resubmitted their paper “Variation in Cardiovascular Disease Care: An Australian cohort study on sex differences in receipt of coronary procedures”. They included some minor changes in their manuscript, but the main questions were not addressed.

2.1 Abstract: Mortality in follow-up is a strong endpoint and should be mentioned in the abstract. Mortality is not mentioned in the abstract.

We agree that mortality is an important variable as patients are no longer “at risk” of having a procedure if they die. Hence we used mortality as a censoring endpoint. We do not use mortality as an outcome in this analysis, as the paper focuses on variation in coronary procedures according to sex. Sex-related variation in mortality is a large and different topic.

We explicitly outline the use of mortality data in the ‘Design’ section of the abstract:

“[…] linked to hospitalisation and mortality data (to 30 June 2016) in a time-to-event analysis, treating death as a censoring event.” (pg 2, para 2)

See also point 2.20 below

2.2 45 and Up Study participants were randomly selected from the Department of Human Services database. How many people live in New South Wales? How many acute coronary syndromes were missed by a randomly selection? These questions were not answered.

The 2016 Census states that the population of New South Wales at that time was 7,480,228. Of this number, 3,085,402 people were aged 45 and over. The 45 and Up Study participants thus represent almost 10% of their cohort, making it the largest population-based cohort study in Australia (45 and Up Study Collaborators et al. Cohort profile: The 45 and Up Study. Int J Epidemiol 2008;37(5):941-7 10.1093/ije/dym184).

Our study population includes 45 and Up Study participants only, with linkage to routine hospital data. This means that there is virtually complete capture and follow up of all hospital admissions with a primary diagnosis of AMI or angina within our population. Hence there are very few hospitalisations for AMI or angina that would be “missed” in the cohort using our methods.

Internal comparisons of receipt of coronary procedures between male and female participants within this population is standard epidemiological cohort study methodology and has been shown algebraically and empirically to be both valid and generalisable (Mealing et al. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs BMC Med Res Methodol 2010;10:26 10.1186/1471-2288-10-26; Rothman et al. Why

representativeness should be avoided. Int J Epidemiol 2013;42:1012-4 10.1093/ije/dys22).

2.3 Patients with history of IHD were excluded. What is the reason for this preselection? This question was not answered.

It is standard epidemiological methodology to focus on “incident” events. The study of repeated events is generally considered separately and is often problematic, as treatments and outcomes are often influenced by prior events. For example, if there is sex-related variation in acute treatment for a first admission for AMI or angina, this might influence survival, morbidity, and severity of disease for subsequent events. This could then introduce greater sex-related variation than should reasonably be attributed to treatment at the specific event being investigated.

Hence, excluding patients with a prior history of IHD reduces bias and allows a clearer interpretation for researchers and clinicians, ensuring that all study participants were being admitted for their ‘incident’ event, with clinical decision making not being influenced by previous events or procedures.

2.4 Patients had to fill-in a self-administered questionnaire? Do the authors think that this information is reliable? This question was not answered.

As stated, our main exposure and outcome variables were based on routinely-collected hospital data and not on self-report.

The self-administered questionnaire was filled out by 45 and Up Study participants on enrolment, with baseline health and demographic data then used in our study. These data were used as covariates in the analyses. There is a wide range of published evidence attesting to the validity and reliability of such data and, in many cases, (for example educational attainment, psychological distress, and physical functioning), self-reported evidence is most appropriate. This is also the type of data used in high-quality, large-scale epidemiological studies of the type reported here: The British Doctors Study, Oxford Clinical Trial Service Unit & Epidemiological Studies Unit; The Million Women Study, Oxford Cancer Epidemiology Unit; research by the American Cancer Society.

2.5 What was the definition of AMI? Did all patients get an ECG? Were patients with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) analysed separately? Do we have information about troponin and CK levels? Were the blood tests repeated to confirm the diagnosis of AMI. These questions were not answered. Apparently this information is not available.

As stated, AMI was defined as per International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) coding I21. This coding looks at STEMI and NSTEMI events together. As per Alexandrescu et al (2013), accurately identifying the proportion of STEMI versus NSTEMI events based on ICD10 codes is problematic and insufficient. STEMI and NSTEMI events are thus analysed together in this study.

The outcomes are based on the conclusions of the treating medical staff, based on current Australian standards (Chew et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016. Med J Aust 2016;205(3):128-133 10.5694/mja16.00368). Although the clinical variables of ECG, troponin and CK levels, and the results of confirmatory blood tests, were not available to us these represent the standard of care in Australia and hence would have contributed to the outcomes used in this epidemiological study. There is also clear evidence that AMI is reliably ascertained from hospital data in Australia, when compared with the gold standard (McCormick N, Lacaille D, Bhole V, et al. Validity of Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. PLoS One 2014;9(3):e92286 10.1371/journal.pone.0092286).

This has been clarified within the manuscript (page 13, para 3, as per last review).

2.6 Do we have information about haemodynamic instability? How many patients were in cardiogenic shock? These questions were not answered. Apparently this information is not available.

As noted above, this is an epidemiological study based on outcomes in routine administrative data and hence information about haemodynamic instability and whether patients were in cardiogenic shock was not available.

2.7 How many hospitals in New South Wales have a catheterization laboratory? How many patients were transferred from a hospital without a cath lab to a hospital with a cath lab? These questions were not answered. Apparently this information is not available.

It is not known how many patients were transferred to another hospital for catheterisation, but results are not likely to be affected by this information. The linked hospital data include all hospital admissions including transfers, and thus captures all procedures regardless of which hospital within New South Wales they were undertaken. Furthermore, whether a patient was transported to a cath lab or not is highly unlikely to be due to their sex, and thus will not be a confounding variable. Additionally, region of residence was controlled for within the analysis, with Table 1 demonstrating that sex differences in location are minimal.

2.8 Do we have information about prehospital delay in women compared to men? What was the first medical contact to balloon time? These questions were not answered. Apparently this information is not available.

Our analysis measured time from admission to procedure. As stated previously, data regarding prehospital delay and specific door to balloon time were not available to us.

2.9 Is there any possibility to get information about risk factors like hypertension, diabetes, hypercholesterolaemia, smoking, family history of CAD? Adjustment should be done for these factors. The authors adjusted for self-rated diabetes, treatment for cholesterol and family history of heart disease.

Yes, we performed a sensitivity analysis in which we adjusted for diabetes, treatment for hypercholesterolaemia, family history of heart disease, and also for smoking and treatment for hypertension, as reported on the study questionnaire. These results can be found in Supplementary Table 10, demonstrating that additional adjustment led to no material difference compared to our main analysis.

2.10 There are other reasons for troponin elevation and symptoms like AMI like takotsubo syndrome, myocarditis, aortic dissection, pulmonary embolism. How often were these diagnoses?

Every participant in our study had been diagnosed with either AMI or angina as the primary reason for their hospital admission. This was identified in the hospital data by the ICD-10-AM discharge code, which is based on clinician diagnosis. There were no additional primary diagnoses in our sample.

2.11 It is well known that more than 50% of all women with acute coronary syndromes have non-obstructive coronary artery disease. Do we have information about the results of the coronary angiography? How many women and men had coronary stenosis <50%. These questions were not answered. Apparently this information is not available.

We recognise that results of angiography impact upon subsequent treatment (including coronary interventions), however this information was not available in this epidemiological study, and the analysis of such clinical factors in explaining any sex differences in procedure rates is beyond the scope of the study. Our study aimed to quantify sex differences in the receipt of coronary angiography and other coronary interventions. We ask the question: “Is there a difference?”. The questions raised in point 2.11, and 2.12 below, lend themselves to future research into the subtleties of: “Why is there a difference?”.

2.12 The authors should compare women and men with coronary stenoses >50% and analyse the rate of recommendation for PCI or CABG with adjustment for age and other risk factors. This is the only way to confirm the statement that there is an undertreatment of women in their population. This question was not answered. Apparently this information is not available.

Please see point 2.11 above. Please note that we report lower procedure rates among women, but we have taken care not to conclude that there is an undertreatment of women in our population.

2.13 What is the rationale to look at coronary angiographies in the year after the index event? According to the guidelines, coronary angiography in STEMI patients should be done immediately and in NSTEMI in up to 72 hours. The authors should analyse if there is a gender difference in time delay in the first hours after an acute coronary syndrome. This question was not answered.

The hospital data available to us shows number of days between admission and receipt of procedure; hours between admission and procedure are not available in the dataset.
Setting our time-to-event analysis censoring date to one year after the index event enables all procedures to be captured, regardless of any delay that may have occurred. This is particularly

important for angina patients. We have also performed sensitivity analyses using 30 days as the follow up period in which there was no material difference in results (see Supplementary Tables S1 and S2).

2.14 Mortality in follow-up is very high in both genders. Is this cardiovascular mortality? Apparently this information is not available.

As stated, mortality is based on all causes (not simply cardiovascular mortality). This has been clarified within the manuscript as per the last review.

2.15 As the diagnosis “angina” comprises chest pain due to many different diseases, even non-cardiac, physicians cannot be accused if they do not perform a coronary angiography in all these patients. Instead of writing “care is more discretionary” in patients with angina, the authors should concentrate on patients with real myocardial infarctions (STEMI) and leave out the angina population. Ideally, they should look at STEMI and NSTEMI separately. The authors state that they cannot differentiate between STEMI and NSTEMI.

This study specifically defines angina as per ICD-10-AM coding as “a disorder characterised by substernal discomfort due to insufficient myocardial oxygenation, and “chest pain caused by coronary heart disease”. It is to this population of patients that our results refer. We have removed the phrase ‘more discretionary’ from the manuscript.

We feel it important to look at the angina population because a large proportion of coronary procedures ae performed in these patients.

Yes, ICD-10 coding cannot accurately distinguish between STEMI and NSTEMI, as per point 2.5 above.

2.16 The authors should be very cautious with their conclusion that men are more likely than women to receive coronary procedures. This suggests that women were treated worse than men. The authors should answer the following questions before they can conclude like they did: - What was the influence of randomly selection instead of consecutive inclusion of all patients with acute coronary syndromes like in other registries? – What was the influence of a self-administered questionnaire? – What was the indication for coronary angiography in both genders? Angina is a symptom and not a diagnosis. Were there stress tests done in both genders before coronary angiography? Were other reasons for chest pain excluded? – Did the physicians have good reasons not to perform a coronary angiography in the patients? These questions were not answered. Apparently this information is not available.

Our results demonstrate that a difference exists between men and women in receipt of coronary procedures following first admission to hospital with AMI or angina. In concluding this, we have been cautious to not place a value judgement on this statement, as we recognise that our study is not able to address exactly why a difference exists. We have made suggestions as to why this result may have occurred, and discussed whether this reflects a true inequality, however it does not necessarily follow that women were treated worse than men, nor perhaps that men are being

treated too often.

As stated above in point 2.2, all patients with incident acute coronary syndrome within our population were included in the study.

Please see point 2.4 above in regards to the validity of self-administered questionnaires in health data.

The 'indication' for angiography, beyond diagnosis of AMI or angina, was not available in the dataset.

Please see point 2.16 above as to the fact that angina in our study is specifically defined by the ICD-10-AM, and as such is categorised as a diagnosis, not a symptom as per common usage.

Information regarding stress testing was not available in the dataset.

All patients within the study sample had a final diagnosis of AMI or angina. Please see point 2.10 above.

The dataset does not have information on clinician reasoning beyond their final diagnosis.

2.17 As there are a lot of limitations the authors should recalculate their results and attenuate their conclusion. The conclusion was not changed at all. Most of the questions were not answered. There were no changes to the manuscript.

We thank you for your comments, and hope that the responses we have provided now answer the questions asked. We acknowledge the limitations of our study in lacking access to clinical variables. It is important that the study be recognised as an epidemiological rather than clinical study, with a large number of participants, prospective data on a wide range of personal characteristics, and virtually complete capture of outcomes. Such studies are very important in describing patterns of care in the population. Many of the follow-up questions regarding explanations for the differences are being the scope of such studies.

2.18 In their different models the authors found that there is no difference in rates of coronary angiography in patients with AMI (table S1 (30 days), S3 (one year)). This is in contrast to the conclusion of the abstract.

The conclusion of the abstract does not state that there were differences in coronary angiography rates in patients with AMI.

2.19 The second question about differences in rates of PCI or CABG cannot be answered without having information about the coronary status. If a woman presents with signs of a myocardial infarction in the ECG, but the coronary angiography shows no coronary stenosis, it is clear that there should be no PCI or CABG. Women more often present with acute coronary syndromes and non-obstructive coronary artery disease than men.

The purpose of the study was to quantify sex differences in diagnostic and revascularisation coronary procedures (adjusting for potential confounders); it was beyond the scope of the study to explain why these differences exist. However, we do discuss possible reasons for the sex differences in PCI/CABG, first and foremost, differences in clinical presentation (3rd para of discussion):

> "There are established sex differences in the pathophysiology, diagnosis and outcome of therapies related to AMI and angina.[7] For example, greater proportions of small vessel coronary disease among women, including Takotsubo cardiomyopathy and other forms of myocardial infarction with non-obstructive coronary arteries,[22] could contribute to lower rates of PCI/CABG following AMI. Previous studies have shown that women who present with AMI or stable angina are more likely to have non-obstructive coronary artery disease compared to men, i.e. <50% stenosis of coronary arteries.[23,24]"

Of course, this does not explain sex differences in angiography among angina patients.

2.20 Information about 30 day mortality and mortality after one year is not given.

We have now included this in the revised manuscript as requested. See first para, p.11 and last para on p. 11; and notes in supplementary tables S1 and S2. Please note that people who died were censored in the analysis.

> "The proportion of AMI patients who survived the one year follow-up period was 86.9% (88.6% men vs 84.0% women)." (paragraph 1, page 11)

> "The proportion of angina patients who survived to the end of the one year follow-up period was 97.4% (96.9% men vs 98.0% women)." (paragraph 4, page 11)

ADDITIONAL EDIT

Please note we have also made minor editorial changes to the supplementary material. We have:

- Updated the title on the first page (the title was from the original rather than revised version of the paper)
- Updated table titles to replace "gender" with "sex" (in line with remainder of manuscript) and to clarify how each analysis differs from the main analysis