PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Influence of socio-economic status on the referral process to cardiac rehabilitation following acute coronary syndrome: a cross-sectional study
AUTHORS	Graversen, Christina Boesgaard; Johansen, Martin; Eichhorst, Regina; Johnsen, Søren Paaske; Riahi, Sam; Holmberg, Teresa; Larsen, Mogens Lytken

VERSION 1 – REVIEW

REVIEWER	Sara L Schroeder Institute of Medical Sociology Martin Luther University Halle-Wittenberg Germany
REVIEW RETURNED	16-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review this interesting manuscript reporting on socioeconomic inequalities in the referral process to CR after ACS. The topic is of relevance, but I have some major concerns, that need to be taken into account before a decision of acceptance can be done. First of all, in the results and discussion I would recommend not to state that there is an association when the association did not reach statistical significance, especially only some insignificant associations are mentioned but not all. Subsequently I recommend the authors to refer primary to the results from the adjusted model and state in the discussion that "after adjustments were made only income was associated with phase 1 and 2 go the referral to CR". Second, in the discussion the authors might want to argue why income but not education civil status and occupational status influenced the referral to CR in their study and the new insights gained from investigating the referral process to cardiac rehabilitation (CR) using a three phase structure and the subsequent practical and theoretical implications. Third, the the three phases were hard to understand for me before reading the results, it might be helpful to explain them earlier in the manuscript, e.g. - figure 1 is very illustrative and might be referred to earlier, - the connection of the three phases with the division into the system and person-level and their connection to the "referral process" needs to be explained, - why the "assigned CR setting (in-hospital or community centre)" is part of the referral process and might be influenced by SES is explained only in the methods (page 6, lines 127-130) and might be placed better in the introduction.

	Additionally, I have some minor concerns: Abstract: 1. Please introduce the Abbreviations, like e.g. ACS and CR (although they are well-known) 2. "Socioeconomic predictors" might not be the right term in the objective. 3. Adjustment for "diagnosis" might be explained in brackets. 4. I would recommend to add socioeconomic status, cardiac rehabilitation and referral process in the keywords. Strengths: 5. "rather than the person-level)," is hard to understand, the bracket might be an error. Introduction: 6. p.4, line 78 please add CR "participation and completion" or "referral". Methods: 7. p. 5, line 103 The authors might state, if it was a first diagnosis of ACS or any diagnosis of ACS? 8. p. 5, line 104 It seems there is an error in the ICD-Code, is it I20 and I21? 9. p 5, lines 107-109 How many patients were excluded? Do they differ from the patients included, especially those with "acceptable reasons for not being informed about CR". 10. p. 6, lines 132-136 The covariate "diagnosis" should be explained here as well. Results: 11. tab 1: The CCI is remarkable low. I recommend to consider this finding in the discussion and conclusion. 12. The authors might want to add the unadjusted results regarding the civil status from tab 2 and occupational status from tab 3 in the text.

REVIEWER	Jissa Vinoda Thulaseedharan Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	1) In abstract: provide the full form of RR and ACS while using the first time and then the short form. 2) Tables and Graphs a) In table 2, 3 and 4, it is useful to provide the number and percentage of patients being informed about cardiac rehabilitation across each category of variables. To reduce the width of the table while adding the two columns, you can remove the percentages presently provided in the table, they have less importance than the number and percentage of outcome across each category of variables. b) Combining Figure1 and Figure S2 as a single flowchart and attach with the methodology section would be useful. c) What does Figure S1: Directed acyclic graph indicate? Logic is not clear. It can be avoided. 3) Incorporate in Discussion. a) Around 30% of patients from the original cohort (1721) was excluded due to different reasons in which the main reason was

	transfer to another hospital. What is the basis for such a change? Is it something related to the SES of patients? Can you make a comparison of characteristics of those excluded with that of your actual study population? Again you have exclusions in the next two phases of analysis. That is around 100 people were not informed about CR and 269 were not willing to participate in CR. Here also you can make a comparison of the characteristics of people (informed Vs not informed; willing VS not willing) so that you can have an assessment of possible biases in the relationship between low SES and being informed, SES and willingness to participate etc. b) You said CR is free of charge for the patients, then explain why or how CR is related to income. c) In abstract, you mentioned the Exclusion of patients with missing data on SES - how many patients excluded with missing information on SES and whether it is random and why the information is missing? Also, this information is not provided in Figure. d) Your statement at the end of Discussion “Fourthly, several of the results only showed weak association, which most likely was a consequence of the rather small study population” seems inappropriate Best wishes

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Sara L Schroeder

Institution and Country
Institute of Medical Sociology
Martin Luther University Halle-Wittenberg
Germany

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
Thank you for the opportunity to review this interesting manuscript reporting on socioeconomic inequalities in the referral process to CR after ACS. The topic is of relevance, but I have some major concerns, that need to be taken into account before a decision of acceptance can be done.

First of all, in the results and discussion I would recommend not to state that there is an association when the association did not reach statistical significance, especially only some insignificant associations are mentioned but not all. Subsequently I recommend the authors to refer primary to the results from the adjusted model and state in the discussion that "after adjustments were made only income was associated with phase 1 and 2 go the referral to CR".
We value the reviewer’s suggestions about when to report statistical insignificant results.

However, we are concerned about reducing the interpretation of the study findings to a simple dichotomization, i.e., statistical significant yes/no. Hence, we prefer to focus on the magnitude and

precision of the relative risk estimates rather than on the statistical significance. This approach is in accordance with recommendations from the American Statistical Association's statement regarding 'Statistical Significance and P-values' in 2016 – and the updated version from 2019(1,2).

The reviewer suggests primarily to refer to the results from the adjusted model in the discussion section. We agree on this and have tried to make this clearer in the manuscript.

Changes to manuscript:"After adjustment was made, high income was the only variable statistical significantly associated with referral to CR in phase 1 and 2, and insignificantly associated with phase 3 of the referral process. High educational level had a similar pattern, but the association did not reach statistical significance. "

Second, in the discussion the authors might want to argue why income but not education civil status and occupational status influenced the referral to CR in their study and the new insights gained from investigating the referral process to cardiac rehabilitation (CR) using a three phase structure and the subsequent practical and theoretical implications.

We agree with the reviewer about the benefits of a discussion about the findings. We have added two new paragraphs to the Discussion section:

Changes to manuscript, p. 13, line 209-219:
"The finding of patients' income and educational level to be associated with all three phases the referral process to CR may be explained by 'the Nordic Paradox' observed in the Nordic European countries(28,29). These countries, covering Denmark, Norway, Sweden, and Finland, are 'welfare states' with equal access to health care which theoretically ought to diminish the importance of patients' level of income and education regarding access to health care services. However, this is not the case as inequality in e.g. mortality persists(29). Although income inequality is smaller in the Nordic countries, this still covers over inequality in wealth, housing condition, and material living conditions, and are used together with educational level to assess latent socio-economic factors (health literacy, greater burden of behavioral and biological risk factors, and reduced access to quality care and medication)(30). Thus, our finding may imply such latent socio-economic factors to be important in the referral process to CR."

Changes to manuscript, p. 14, line 229--234:

"By splitting the referral process into three phases, new insights regarding importance of taking patients SES into consideration when referring them to CR was gained. Our results show the importance of being aware of system-level barriers present in the referral process. Moreover, identifying those patients who need more motivation before being willing to enter a CR programme is highly important. In that way, patients are well-informed about CR and able to make a well-considered decision regarding participation."

Third, the the three phases were hard to understand for me before reading the results, it might be helpful to explain them earlier in the manuscript, e.g.
- figure 1 is very illustrative and might be referred to earlier,
- the connection of the three phases with the division into the system and person-level and their connection to the "referral process" needs to be explained,
- why the "assigned CR setting (in-hospital or community centre)" is part of the referral process and might be influenced by SES is explained only in the methods (page 6, lines 127-130) and might be placed better in the introduction.
We thank the reviewer for making us aware of this issue.

We also find figure 1 very illustrative for the phases, and have now referred to it in the Methods sections. Furthermore, we have merged figure 1 and supplementary figure 2 into one new figure. The updated figure 1 includes information about the exclusion of patients.

We agree that the relation between the three phases and the system/person-level barriers to the referral process was not described sufficiently clear in the original version of the manuscript. We have tried to address this in the revised introduction section.

Changes to manuscript, p. 4, line 79-87:

“Obstacles in referral and participation to CR among patients with lower SES may be due to system-level and personal barriers.(16) System-level barriers covers physicians recommendations, the interaction with the healthcare team, and misconceptions about CR. Personal barriers includes perception about IHD and CR, and belief about the ability to control IHD.(16) However, vulnerable elements in the referral process prone to socio-economic inequality among patients with ACS remain unexplored. By dividing the referral process into three phases, it is possible to evaluate if such inequality is the result of selection of patients at the system-level (the process of informing patients about CR and the setting of CR that patients are referred to) rather than the person-level (patients’ own willingness to participate in CR).”

Introduction to ‘assigned CR setting’ is now included in the introduction section.

Additionally, I have some minor concerns:
Abstract:
1. Please introduce the Abbreviations, like e.g. ACS and CR (although they are well-known)

We thank the reviewer for making us aware of the mistake of not introducing the abbreviation of ACS and CR.

2. "Socioeconomic predictors" might not be the right term in the objective.

We have rephrased the objective, so it no longer include this term.

Changes to manuscript, p. 2, line 26-28:

“to evaluate the association between socio-economic status and referral to cardiac rehabilitation (CR) after incident acute coronary syndrome (ACS) by dividing the entire referral process into three phases (1. informed about CR, 2. willingness to participate in CR, and 3. assigned CR setting).”

3. Adjustment for "diagnosis" might be explained in brackets.

Patients were included in the study population if they were diagnosed with an ACS. Earlier studies have found ACS diagnosis (STEMI, NSTEMI, or UAP) to be important for who are referred to CR. In general, patients with NSTEMI and UAP are less likely referred to CR compared to patients with

STEMI.(3) Therefore, to get a more precise estimate of the impacts of patients' SES, we included the ACS diagnosis as a covariate to adjust for.

Changes to manuscript, p. 2, line 41-45:

"**Results:** A total of 854 (69.5 %) patients were referred to CR. After adjustment for age, gender, ACS diagnosis (ST-Elevated Myocardial Infarction, Non-ST-Elevated Myocardial Infarction, Unstable Angina Pectoris) and comorbidity, high income level had the strongest association of referral to CR in all three phases (informed about CR: OR 2.17, 95% CI: 1.0- 4.64; willingness to participate in CR: OR 1.55, 95% CI: 1.02-2.35; assigned in-hospital CR: OR 1.47, 95% CI: 0.91-2.36).".

4. I would recommend to add socioeconomic status, cardiac rehabilitation and referral process in the keywords.

We have updated the keywords and thanks for the good suggestion.

Changes to manuscript, p. 3, line 49:

"**Keywords:** Acute Myocardial Infarction, Cardiac Rehabilitation, Referral Process, Socio-economic Status"

Strengths:
5. "rather than the person-level)," is hard to understand, the bracket might be an error.
Correct, this sentence was mistakenly included and have now been deleted. Thank you for making us aware of the matter.

Introduction:
6. p.4, line 78 please add CR "participation and completion" or "referral".
This have now been corrected.

Changes to manuscript, p. 4, line 72-73:

"It therefore seems irrational that international research in general continues to find CR "referral" or "participation and completion" rates to be unsatisfactory".

Methods:
7. p. 5, line 103 The authors might state, if it was a first diagnosis of ACS or any diagnosis of ACS?

We included all patients hospitalized with ACS. Clinical guidelines recommend all patients hospitalized with ACS to be referred to CR, irrespectively of number of events. Therefore, our study population includes both incident and recurrent ACS diagnosis, why we don't find it necessary to specify it further in the text.

8. p. 5, line 104 It seems there is an error in the ICD-Code, is it I20 and I21?

We have specified the ICD-10 codes as requested. We only included I20.0 (and not the entire I20) as this code includes diagnosis of Unstable Angina Pectoris. I21 includes both STEMI (ICD-10: I21,0, I21.1, I21.3) and NSTEMI (ICD-10: I21.4).

Changes to manuscript, p. 5, line 110-111:

"The study population was identified in the Rehab-North Register as patients diagnosed with ACS (ICD-10: I20.0, I21.)."

9. p 5, lines 107-109 How many patients were excluded? Do they differ from the patients included, especially those with "acceptable reasons for not being informed about CR".

We have made a non-response analysis of those excluded from the study and included it in the supplementary material. Furthermore, the original figure 1 and supplementary figure 2 are now combined into one figure (new figure 1), which hopefully make the inclusion/exclusion process of the study population more clear. In total, 593 patients were excluded from the study.

During the process of the non-response analysis, we unfortunately found an error in the stated number of patients diagnosed with ACS. This has been corrected.

Those excluded with 'acceptable reasons for not being informed about CR' includes patients who were transferred to other departments in which they were to receive information and referral to CR. Patients undergoing coronary artery bypass grafting is informed about cardiac rehabilitation at the Thoracic Surgery Department performing the operation. Patients 'transferred to another hospital' were to receive information about CR at other departments of cardiology.

Abovementioned patients were lost to follow-up, and we have not received any confirmation regarding referral to CR.

Changes to manuscript, p. 5-6, line 113-119:

"Patients were excluded if in one of the following criteria were fulfilled: 1) missing data on SES 2) acceptable reason for not informing patients about CR, including treatment with coronary artery bypass graft, transfer to another hospital, still under treatment, or death. Patients who underwent coronary artery bypass grafting was informed about CR at the Thoracic Surgery Department performing the operation. Patients who were 'transferred to another hospital' received information about CR at other cardiology departments. We were not able to receive confirmation regarding referral to CR in this patient group."

10. p. 6, lines 132-136 The covariate "diagnosis" should be explained here as well.
We have included a description of the variable as requested.

Changes to manuscript, p. 7, line 143-148:

“In general, patients with NSTEMI and UAP are less likely referred to CR compared to patients with STEMI. (25) Therefore, to get an accurate estimate of the impacts of patients’ SES on CR referral, ACS diagnosis (STEMI, NSTEMI, UAP) were included as a covariate.“

Results:

11. tab 1: The CCI is remarkable low. I recommend to consider this finding in the discussion and conclusion.

In the Rehab-North Register, it was only possible to calculate CCI from the year 2011 until hospitalisation. This is the most likely explanation on why the CCI is such low.

Changes to manuscript, p. 7, line 141-143:

“Comorbidity diagnoses were defined by the Charlson Comorbidity Index (CCI), but only diagnoses from the year 2011 until hospitalisation were accessible. Comorbidity diagnoses was drawn from the NPR.(24) “

Changes to manuscript, p. 15, line 261-263:

“The CCI variable may be inaccurate which is caused by the limited time-frame for inclusion of comorbidities. This increases the risk of unaccounted confounding and should be taken into consideration when interpreting the results.”

12. The authors might want to add the unadjusted results regarding the civil status from tab 2 and occupational status from tab 3 in the text.

We have now included the suggested unadjusted analyses in the result section.

Changes to manuscript, p. 9, line 170-171:

Higher income and educational level had positive crude associations with being informed about CR whereas being unemployed/retired and single-living had a negative association (table 2).

Changes to manuscript, p. 10, line 179-180:

“Being unemployed/retired was negatively associated with being willing to participate in CR.”

References:

1. Wasserstein RL, Lazar NA. The ASA’s Statement on p-Values: Context, Process, and Purpose. Am Stat [Internet]. 2016;70(2):129–33. Available from: http://dx.doi.org/10.1080/00031305.2016.1154108

2. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond “p < 0.05.” Am Stat. 2019;73(sup1):1–19.

3. Brown TM, Hernandez AF, Bittner V, Cannon CP, Ellrodt G, Liang L, et al. Predictors of Cardiac Rehabilitation Referral in Coronary Artery Disease Patients. Findings From the American Heart Association’s Get With The Guidelines Program. J Am Coll Cardiol.

2009;54(6):515–21.

Reviewer: 2

Reviewer Name
Jissa Vinoda Thulaseedharan

Institution and Country
Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below

1) In abstract: provide the full form of RR and ACS while using the first time and then the short form.

This has been corrected in the revised manuscript.

Changes to manuscript, p. 2, line 26-28:

"to evaluate the association between socio-economic status and referral to cardiac rehabilitation (CR) after incident acute coronary syndrome (ACS) by dividing the entire referral process into three phases (1. informed about CR, 2. willingness to participate in CR, and 3. assigned CR setting)."

2) Tables and Graphs

a) In table 2, 3 and 4, it is useful to provide the number and percentage of patients being informed about cardiac rehabilitation across each category of variables. To reduce the width of the table while adding the two columns, you can remove the percentages presently provided in the table, they have less importance than the number and percentage of outcome across each category of variables.

The percentages given in table 2, 3, and 4 have been corrected. It now illustrates the percentage of patients being informed vs. not informed (table 2), willingness to participate vs. no willingness to participate (table 3), and in-hospital CR vs. community-based CR.

b) Combining Figure1 and Figure S2 as a single flowchart and attach with the methodology section would be

useful.

We agree that combining the figures will be useful. This has now been done and the new figure is named 'Figure 1'.

c) What does Figure S1: Directed acyclic graph indicate? Logic is not clear. It can be avoided.

We used the Directed Acyclic Graph to identify possible variables to include in our multivariable logistic regression model. The figure itself is not that important and has now been removed. Instead, we have stated the use of it in the methods section.

Changes to manuscript, p. 6, line 138-139:

"The selection of covariate to be included in the multivariable analyses was done based on a directed acyclic graph (not shown)."

3) Incorporate in Discussion.

a) Around 30% of patients from the original cohort (1721) was excluded due to different reasons in which the main reason was transfer to another hospital. What is the basis for such a change? Is it something related to the SES of patients? Can you make a comparison of characteristics of those excluded with that of your actual study population? Again you have exclusions in the next two phases of analysis. That is around 100 people were not informed about CR and 269 were not willing to participate in CR. Here also you can make a comparison of the characteristics of people (informed Vs not informed; willing VS not willing) so that you can have an assessment of possible biases in the relationship between low SES and being informed, SES and willingness to participate etc.

Thank you for this important observation.

We have made a non-response analysis of those excluded from the study and made these analyses available in the supplementary material. Furthermore, the original figure 1 and supplementary figure 2 are now combined into one figure (new figure 1), which hopefully make the inclusion/exclusion process of the study population clearer.

The results of the non-response analysis is presented in the result section under the subheading 'Supplementary analyses' and discussed in the discussion section.

Changes to manuscript, p. 15, line 254-257:

"Moreover, the non-response analyse found excluded patients to have lower SES compared to the included study population. As exclusion was due to clinical implications (patients were to receive CR referral elsewhere), this should not pose a problem for selection bias introduction in our study population.".

During the process of the non-response analysis, we unfortunately found an error in the stated number of patients diagnosed with ACS. This mistake has been corrected.

Our study outcome is to evaluate the association between SES and referral to CR. Possible SES variable differences during the three phases are evaluated in the discussion section:

Changes to manuscript, p. 12, line 201-204:

"After adjustment, high income was the only variable statistical significantly associated with referral to CR in phase 1 and 2., and insignificantly associated with phase 3 of the referral process. High educational level had a similar pattern, but the association did not reach statistical significance."

b) You said CR is free of charge for the patients, then explain why or how CR is related to income.

We agree that this issue should be elaborated further. We have tried to do so by including following section in the discussion:

Changes to manuscript, p. 13, line 209-219:
"The finding of patients' income and educational level to be associated with all three phases the referral process to CR may be explained by 'the Nordic Paradox' observed in the Nordic European countries(28,29). These countries, covering Denmark, Norway, Sweden, and Finland, are 'welfare states' with equal access to health care which theoretically ought to diminish the importance of patients' level of income and education regarding access to health care services. However, this is not the case as inequality in e.g. mortality persists(29). Although income inequality is smaller in the Nordic countries, this still covers over inequality in wealth, housing condition, and material living conditions, and are used together with educational level to assess latent socio-economic factors (health literacy, greater burden of behavioral and biological risk factors, and reduced access to quality care and medication)(30). Thus, our finding may imply such latent socio-economic factors to be important in the referral process to CR."

c) In abstract, you mentioned the Exclusion of patients with missing data on SES - how many patients excluded with missing information on SES and whether it is random and why the information is missing? Also, this information is not provided in Figure.

We thank the reviewer for pointing out this missing element.

In total, 593 patients are excluded from the study. This is now illustrated in the figure 1. The element of randomness is discussed in the discussion section.

Changes to manuscript, p. 15, line 254-257:

"Moreover, the non-response analysis found excluded patients to have lower SES compared to the included study population. As exclusion was due to clinical implications (patients were to receive CR referral elsewhere), this should not pose a problem for selection bias introduction in our study population."

d) Your statement at the end of Discussion "Fourthly, several of the results only showed weak association, which most likely was a consequence of the rather small study population" seems inappropriate

We agree on this.

Changes to manuscript:

Deletion of Discussion "Fourthly, several of the results only showed weak association, which most likely was a consequence of the rather small study population".

VERSION 2 – REVIEW

REVIEWER	Sara L Schroeder Institute of Medical Sociology Martin Luther University Halle-Wittenberg Germany
REVIEW RETURNED	14-Feb-2020

GENERAL COMMENTS	All remarks have been encountered sufficiently by the authors.

REVIEWER	Jissa Vinoda Thulaseedharan Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.
REVIEW RETURNED	28-Jan-2020

GENERAL COMMENTS	Authors incorporated most of the suggestions. However, it seems the authors did not correctly understand my comments regarding percentages in tables 2,3 and 4. The modifications still do not make much sense. The suggestion was to incorporate the total number across each category in the first column (denominator, N) and the number of outcomes (numerator, n) and its percentage (%). For example, in Tale 2, N=1229 in the first column, n=1123 and percentage 91.4 in the second column. Similarly, you should report the total number of participants whose civil status is Married/Partnership (N), the number of people being informed about cardiac rehabilitation among them (n) and that percentage (%). And so on. 2) The text in Figure1 is very small and not clear. 3) The comments regarding discussion are incorporated by the authors.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sara L Schroeder

Institution and Country:

Institute of Medical Sociology

Martin Luther University Halle-Wittenberg

Germany

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

All remarks have been encountered sufficiently by the authors.

Reviewer: 2

Reviewer Name: Jissa Vinoda Thulaseedharan

Institution and Country:

Achutha Menon Centre for Health Science Studies, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Authors incorporated most of the suggestions. However, it seems the authors did not correctly understand my comments regarding percentages in tables 2,3 and 4. The modifications still do not make much sense. The suggestion was to incorporate the total number across each category in the first column (denominator, N) and the number of outcomes (numerator, n) and its percentage (%). For example, in Tale 2, N=1229 in the first column, n=1123 and percentage 91.4 in the second column. Similarly, you should report the total number of participants whose civil status is Married/Partnership (N), the number of people being informed about cardiac rehabilitation among them (n) and that percentage (%). And so on.

We have followed the reviewer’s advice regarding the tables’ percentages. Table 2, 3, and 4 now have a column with the total number of the study population. The percentages for e.g. how many patients were informed about CR is calculated dividing the observations (n=1123) with the full study population (n=1229) etcetera.

2) The text in Figure1 is very small and not clear.

The text size is increased to size 14 and all numbers are written with bold letters.

3) The comments regarding discussion are incorporated by the authors.