PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Disparities in prevalence of heart failure according to age, multimorbidity level and socioeconomic status in Southern Sweden: a cross-sectional study
AUTHORS	Scholten, Mia; Midlöv, Patrik; Halling, Anders

VERSION 1 – REVIEW

REVIEWER	Jovic, Dragana Institut za javno zdravlje Srbije Dr Milan Jovanovic Batut, Centre for Hygiene and Human Ecology
REVIEW RETURNED	18-Aug-2021

GENERAL COMMENTS	Dear Editor, Thank you for the invitation to review manuscript ID bmjopen-2021-051997, entitled "Disparities in prevalence of heart failure according to multimorbidity level and socioeconomic status in Southern Sweden: a cross-sectional study." Main concern for this manuscript is ethical consideration. First, authors used active refusal of participation and advertisement in a local newspaper as an invitation for entering the study. How authors corroborate that all potential participants were considered as participants, that the newspaper was available to each potential participants and that each of them read the ad? Can authors answer how illiterate persons entered the study? All these should be clearly elaborated. Another concerns are related to study design and the results, because authors presented proportion of participants rather than prevalence to which the study is related, did not present statistics for basic and main statistical tests and did not provide detailed description of the Delta method used. It is not clear which exactly observation period authors took as the reference period and why did they use data for 2015. Authors ought to be careful in choosing the type of their study (is it cross sectional or retrospective cohort), in using terms multimorbidity and comorbidity at the same time, especially in their conclusions, and should write more about added value of their scientific work. With kindest regards.

REVIEWER	Squire, Iain University of Leicester, Medicine and Therapeutics
REVIEW RETURNED	23-Aug-2021

GENERAL COMMENTS	This analysis is limited by the methodology applied to define "heart failure" which appears to have been by the simple counting of this diagnosis applied in primary care. There is no "validation" which

	might have been performed by cross checking with data from imaging or from the prescription of loop diuretics, which is prevalent in >80% of patients with heart failure. The Tables are not easy to follow. The major "problem" with the study is that the results are not unexpected; heart failure is well known to be associated with (i) increasing age and (ii) deprivation / multi-morbidity. In this context the study provides very little novel information. Specific points: 1. Over 38% of this relatively young population had multi-morbidity. First of all this is very high and should be compared to the prevalence of MM in previous published work in the area of HF. Secondly, the nature of the multi morbid conditions should be described, even in very broad terms 2. Page 5: "Diastolic heart failure has preserved ejection fraction and often non-specific symptoms..." In what way are the symptoms of HFpEF less specific than thos of HFrEF ?? 3. Page 6. Please describe the age groupings clearly in a single sentence; ie 20-29, 30-39, etc 4. Page 8. The diagnosis of HF was based upon a recorded ICD 10 code 150; In this health care system, what is the accuracy of ICD coding ? The authors should consider validation by () assess the prevalence of co-prescription of loop diuretic, which is >80% prevalent in HF or (ii) comparison with data on natriuretic peptides and / or imaging 5. Is it necessary to repeat "southern Sweden (Scania)" when "Scania" is sufficient after the initial description of the study location ? 6. What is the justification for the grouping of MM in to the categories used ? 7. Page 9. It appears that CNI was applied at the level of the respective primary care health-care facility. This appears very crude to categorise all patients attending a specific health centre as being uniformly "deprived" in SE terms. 8. Page 10: " Logistic regression was used to analyse the associations between the univariate and multivariate models". What does this mean ? I cannot find any regression analyses in the manuscript. 9. Page 12 and Figure 1. Most readers will not be familiar with Lorenz plots. Figure 1 does not convince me at all of meaningful differences among the CNI categories and does not add anything to the messages in the manuscript. 10.Tables 1 and 2 are not easy to interpret and the authors should consider graphical representation. 11. As far as I can tell the authors have not performed age-adjusted assessment of the prevalence of HF by CNI status 12. Page 19: ". The fact that the prevalence of HF was highest in the most deprived CNI percentile of primary health care centres with the lowest prevalence of MM among elderly indicates that HF is a disease associated with socioeconomic deprivation." A very simplistic interpretation; adjustment of the prevalence for age is needed and I think the data will suggest that HF is a condition associated with age as much as with SES 13.

REVIEWER	Tudoran, Cristina University of Medicine and Pharmacy Victor Babes Timisoara, VII Internal Medicine II
REVIEW RETURNED	29-Aug-2021

GENERAL COMMENTS	In Introduction, Line 45, you mention 2 groups of HF, regarding the ejection fraction. According to the guidelines, there is a third one, HF with midrange ejection fraction. The authors should clarify the time period in which they have conducted the study. In Multimorbidity you say July- December and in the Statistical Analyses, the last week of December. You should specify the exact study period also in the Abstract. In Table 1, you could use p values to highlight the statistical significance between the age groups, regarding the incidence of HF and MM. Table 2 could benefit from p values too. At the end of the Results, you should support your affirmations with data from your statistical analyses (p and r values, 95% interquartile range, etc). When you mention a strong correlation, you should mention at least the r value. In the Legend of the figures, you should mention the statistical test you used. Some of your conclusions and discussions are not supported by your results.

VERSION 1 – AUTHOR RESPONSE

This analysis is limited by the methodology applied to define "heart failure" which appears to have been by the simple counting of this diagnosis applied in primary care. There is no "validation" which might have been performed by cross checking with data from imaging or from the prescription of loop diuretics, which is prevalent in >80% of patients with heart failure. The Tables are not easy to follow.

The major "problem" with the study is that the results are not unexpected; heart failure is well known to be associated with (i) increasing age and (ii) deprivation / multi-morbidity. In this context the study provides very little novel information.
A large part of the patients has HF diagnosis from primary- and secondary care, in both cases diagnosed according to the ESC guidelines for HF: typical symptomatology, elevated BNP value, and objective findings of impaired cardiac function on myocardial scintigraphy, echocardiography or magnet resonance tomography. Prescription of loop diuretics was not included as criterion for the HF diagnosis. Please see line 108-112 and line 326-334.
Both tables are revised to facilitate the understanding of the manuscript.
Our results have also revealed a contrast between the most affluent and deprived CNI percentile in prevalence of HF, but the CNI percentiles 2 to 9 did not show a gradual increase in prevalence of HF with socioeconomic deprivation. As 99.07% of the HF patients had multimorbidity at the time of diagnosis, our results revealed that this patient category even affected young and socioeconomic affluent individuals, although in less extent.

Specific points:
1. Over 38% of this relatively young population had multi-morbidity. First of all this is very high and should be compared to the prevalence of MM in previous published work in the area of HF. Secondly, the nature of the multi morbid conditions should be described, even in very broad terms
The most deprived CNI percentiles had a young population, but not the most affluent CNI percentile in our study population, which had the highest prevalence of MM from 60 years of age. The Swedish population is statistically one of the oldest in the world. The high prevalence of MM could be explained

by the socioeconomic difference within the study population and the considerable part of elderly with high prevalence of MM. Only 5.30% of the multimorbid patients had HF. The total prevalence of HF was 2.06%, similar to the prevalence in Sweden and other Western countries. Please see Table 1 and the changes in line 163, 169-170 and 337-340.

2. Page 5: "Diastolic heart failure has preserved ejection fraction and often non-specific symptoms..." In what way are the symptoms of HFpEF less specific than thos of HFrEF ??
Symptoms of HFpEF are usually milder than HFrEF, for example dyspnae and fatigue, but could even be misinterpreted as asthma. Patients with HFrEF present oedema in the lower body in greater extent than HFpEF. The pathophysiologic derangements in HFpEF include concentric remodelling, ventricular-vascular stiffening and loss of ventricular-vascular reserve function are resulted from chronic pressure overload due to arterial hypertension. Thus, the symptoms of HFpEF usually develop insidiously over months or years before diagnosis, meanwhile HFrEF often exhibits after a sudden myocyte damage as complication of a myocardial infarction or myocarditis. Please see the changes in line 77-86.

3. Page 6. Please describe the age groupings clearly in a single sentence; ie 20-29, 30-39, etc
The description of age grouping is moved from data source and measurements to settings and study population. Please see the changes in line 134-136.

4. Page 8. The diagnosis of HF was based upon a recorded ICD 10 code 150; In this health care system, what is the accuracy of ICD coding ? The authors should consider validation by () assess the prevalence of co-prescription of loop diuretic, which is >80% prevalent in HF or (ii) comparison with data on natriuretic peptides and / or imaging
This study represents all diagnoses made for this patient population both in primary and secondary care including the diagnosis criteria for HF according to ESC guidelines. Please see line 108-112, 143-144 and 326-334. We had no access to the data on treatment of HF.

5. Is it necessary to repeat "southern Sweden (Scania)" when "Scania" is sufficient after the initial description of the study location ?
Thank you! We have changed to Scania in the manuscript.

6. What is the justification for the grouping of MM in to the categories used ?
Since MM is so common we needed a categorisation of MM to study HF in relation to different degrees of MM. It was a rough classification of MM for further analyses. This has been clarified in line 174-177. Please see Tabl 2.

7. Page 9. It appears that CNI was applied at the level of the respective primary care health-care facility. This appears very crude to categorise all patients attending a specific health centre as being uniformly "deprived" in SE terms.
All patients are listed at a primary health care centre. Most of the patients are listed close to their place of living. Most primary health care centres are organised similarly irrespective of CNI. The idea to choose CNI at primary care levels is to study the need of care at primary care level. Of course, there can be problems with this way to assign socioeconomic level, but the socioeconomic boundaries are quite sharp and agree with uptake areas of the different primary health care centres. The CNI category was an average socioeconomic level of the patients listed at the primary health care centres.
Please see the changes in line 345-349.

8. Page 10: " Logistic regression was used to analyse the associations between the univariate and multivariate models". What does this mean ? I cannot find any regression analyses in the manuscript.

Uni- and multivariate logistic regression models were used to analyse the investigated variables' association with a heart failure diagnosis (I50-). Only the linear predications of the fully adjusted models were shown in the figures.
This has been clarified in line 198-199.

9. Page 12 and Figure 1. Most readers will not be familiar with Lorenz plots. Figure 1 does not convince me at all of meaningful differences among the CNI categories and does not add anything to the messages in the manuscript.
We understand this, but still believe that Figure 1 gives valuable information about the socioeconomic deprivation in our study. The visual difference is small in Figure 1 between the most affluent and deprived CNI percentiles, but is still obvious if compared to other CNI percentiles. Please see Table 1.

10.Tables 1 and 2 are not easy to interpret and the authors should consider graphical representation.
The tables are revised to facilitate the interpretation of the manuscript and aim to complete the graphical representation: Fig 2 and 3 represent the mean probability of HF in different MM levels and CNI 1 and 10 percentiles, but did not illustrate the number of patients in each MM level, CNI percentile and age group as in the tables.

11. As far as I can tell the authors have not performed age-adjusted assessment of the prevalence of HF by CNI status
For analyse of age-adjusted prevalence of HF by CNI status, please see the line 310-319 and Figure 3.

12. Page 19: ". The fact that the prevalence of HF was highest in the most deprived CNI percentile of primary health care centres with the lowest prevalence of MM among elderly indicates that HF is a disease associated with socioeconomic deprivation." A very simplistic interpretation; adjustment of the prevalence for age is needed and I think the data will suggest that HF is a condition associated with age as much as with SES
The data is adjusted for age and CNI percentile, and presented the highest prevalence of HF in this patient category. We had no space to present our results in all details, and chose only the most important parts in our study. Please see the changes in line 361-365.

Reviewer: 3
Dr. Cristina Tudoran, University of Medicine and Pharmacy Victor Babes Timisoara, Emergency County Hospital Timisoara
Comments to the Author:
In Introduction, Line 45, you mention 2 groups of HF, regarding the ejection fraction. According to the guidelines, there is a third one, HF with midrange ejection fraction.
HFmrEF is added as the third subtype of HF, please see the changes in line 61, 70-75.

The authors should clarify the time period in which they have conducted the study. In Multimorbidity you say July- December and in the Statistical Analyses, the last week of December. You should specify the exact study period also in the Abstract.
The study period is clarified in the abstract and manuscript, please see the changes in line 11-12 and 141.

In Table 1, you could use p values to highlight the statistical significance between the age groups, regarding the incidence of HF and MM. Table 2 could benefit from p values too.
We had no space to present our results in all details, and chose only the most important parts in our study.

At the end of the Results, you should support your affirmations with data from your statistical analyses (p and r values, 95% interquartile range, etc). When you mention a strong correlation, you should mention at least the r value.
The strong correlation between prevalence of HF and socioeconomic deprivation was calculated by logistic regression, and not by Pearson Correlation Coefficient for any r value. The correlation was assessed visually as the difference in prevalence of HF was obvious between the most affluent and deprived CNI percentiles. Please see the changes in line 356-358.
In the Legend of the figures, you should mention the statistical test you used.
The statistical test is added in the legend figures.

Some of your conclusions and discussions are not supported by your results.
“The fact that the prevalence of HF was highest in the most deprived CNI percentile of primary health care centres with the lowest prevalence of MM among elderly indicates that HF is a disease associated with socioeconomic deprivation.”
“HF is one of many conditions with poor prognosis associated with socioeconomic deprivation that challenges efficient preventive strategies and health policies.”
These sentences are changed in the manuscript. Please see the changes in line 361-365 and 432-437.

Following changes are added to the manuscript:
Page 7: (Data source and measurements)
Totally 152 primary health care centres were operating during 2015 in Scania, with on average 8587 listed patients (95% CI 7971.49 – 9292.88) including 133 patients with HF (95% CL 122.60 – 143.80) at each primary health care centre.
Page 17: (Strengths and limitations)
Those patients with HF belonging to the MM0 group were probably underdiagnosed as well, because HF usually constitutes a complication of other comorbidities or treatment.

VERSION 2 – REVIEW

REVIEWER	Squire, Iain University of Leicester, Medicine and Therapeutics
REVIEW RETURNED	12-Nov-2021

GENERAL COMMENTS	The authors have addressed the majority of the concerns raised by my first review of this manuscript. I have a small number of ongoing concerns. 1. In my earlier review I expressed a degree of disquiet at the authors comment that "Diastolic heart failure has preserved ejection fraction and often non-specific symptoms...". The authors appear to wish to persist with this comment; in their response to my comment they have stated "Symptoms of HFpEF are usually milder than HFrEF, for example dyspnae and fatigue, but could even be misinterpreted as asthma. Patients with HFrEF present oedema in the lower body in greater extent than HFpEF." As a clinician with over 25 years specialist experience in the management of heart failure, I disagree, fundamentally, with these assertions. HFpEF is characterised by peripheral oedema, more often than is the case in HFrEF, and both types of HF are often mislabelled as airways disease or chest infection. I would suggest the authors change these comments, as they are inaccurate.

	2. I remain of the view that Figure 1 relays no helpful information beyond the numbers in Table 1 and the comparisons in Figures 2-4. I sugegst this figure is removed.

VERSION 2 – AUTHOR RESPONSE

1. In my earlier review I expressed a degree of disquiet at the authors comment that

"Diastolic heart failure has preserved ejection fraction and often non-specific symptoms...". The authors appear to wish to persist with this comment; in their response to my comment they have stated "Symptoms of HFpEF are usually milder than HFrEF, for example dyspnae and fatigue, but could even be misinterpreted as asthma. Patients with HFrEF present oedema in the lower body in greater extent than HFpEF."

As a clinician with over 25 years specialist experience in the management of heart failure, I disagree, fundamentally, with these assertions. HFpEF is characterised by peripheral oedema, more often than is the case in HFrEF, and both types of HF are often mislabelled as airways disease or chest infection. I would suggest the authors change these comments, as they are inaccurate.

We very much respect your clinical experience and suggestions. Please notice that this content was changed in the first version of revision one month ago. Please see line 50-71 in the manuscript.

2. I remain of the view that Figure 1 relays no helpful information beyond the numbers in Table 1 and the comparisons in Figures 2-4. I sugegst this figure is removed.

We agree, the figure 1 has been removed.

Competing interests of Reviewer: I have published widely in the area of heart failure, including research involving the association with outcomes of socioeconomic deprivation