PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Ambient Particulate Matter with Heart Failure Incidence and All-cause Readmissions in Tasmania: An Observational Study
AUTHORS	Huynh, Quan; Blizzard, Christopher Leigh; Marwick, Thomas; Negishi, Kazuaki

VERSION 1 – REVIEW

REVIEWER	Wenyuan Li Post-Doctoral Research Fellow Harvard T.H. Chan School of Public Health Boston, MA USA
REVIEW RETURNED	16-Feb-2018

GENERAL COMMENTS	The authors conducted a retrospective study that examined the associations between short-term exposure to air pollution and heart failure (HF) incidences and readmissions among 1246 patients resided in two large cities. The authors collected daily fine particulate matter (PM2.5), temperature, and relative humidity, and used Poisson regression to determine the associations. The authors concluded that PM2.5 independently predicted HF incidence in the study sample. Furthermore, they claimed that there was a possible threshold of PM2.5=4 μg/m3, and found that beta-blockers might play a role in preventing “detrimental effects” of air pollution on HF patients. However, the statistical methods require further clarification, the models were inadequately adjusted, and the conclusions were not supported by the results presented. Main comments: 1. Very limited demographic information was provided in the Table 1 (age, sex, and medication use). The two cities included in the current study were not close to each other, socioeconomic positions could affect the associations between PM2.5 and HF in the current study. The analyses should account for basic demographics (age, sex), lifestyles (e.g. BMI, smoking, alcohol, physical activity), and socioeconomic position (e.g. income, education). But on the contrary, the authors provided results mainly from univariable analyses (Table 3). Was 78.1 the mean or median of age at admission? Either way, clinical factors may also need to be accounted for, such as chronic cardiovascular disease, diabetes, COPD. Thus, it is not appropriate to claim “PM2.5 independently predicted HF incidence”. The conclusion should also mention the age range or such. 2. With the median of PM2.5 levels at 2.9 μg/m3 and 75th percentile at 6.0 μg/m3, the authors should clarify the total number of cases and days in each of the nine groups in Figure 4 instead of stating

	"approximately 100 days". 3. While the air quality standard was 25 μg/m3, based on Figure 1, there seemed to be quite a few days of PM2.5 > 15 μg/m3 in the current study. Since PM2.5 at 4 μg/m3 was an arbitrary choice based on crude data in the current study, did the authors try 6 μg/m3 (75th pct)? And were the results for 6 μg/m3 statistically different from the current analyses? The observed threshold may not be true in studies with a wider range of PM2.5 levels that had sufficient cases and days in higher quartiles (e.g. 15-25 μg/m3). The authors failed to recognize this limited generalizability in discussion. 4. Use of a specific type of medication could be a result of limited access to medication, or a surrogate of socioeconomic position. Without adjustment for demographics, lifestyles, and socioeconomic positions, the differing associations may be confounded. 5. The statistical methods section requires clarification. For example: 5.1 What did the authors mean by saying "Daily mean temperature and relative humidity … These measurements were then weighted based on each city's population to derive an average value to be used in analysis"? What was the formula of calculating the weight? What was the rationale to weight the measures? 5.2 Did the authors examine whether the associations differ by season? Since higher pollution days were more commonly seen in winter, the observed "threshold" may be due to the season. 5.3 In Table 4, the authors stated "Further adjusted for current day (lag0 day) temperature, weekday and weekend, school and public holiday, and time trend" in the footnote. What is the rational of examining the associations for Temperature lag1-3 day while adjusting for lag0 temperature, and why did the authors adjust for school and public holiday? 5.4 The statement "HF incidence count per day started to rise when PM2.5 was beyond the 7th decile (median 4.1 μm/m3)" was based on speculation without any statistical significance test. 5.5 Did the authors examine whether the associations in primary analyses differed by season? Moreover, were the differing associations by PM2.5 at 4 μg/m3 observed in different seasons? Minor comments: 1. What is the point of calculating cumulative incidence if the calculation was only based on total population in 2011 but not the real-time population during the study period (2009-2012)? Or did the authors have accurate number of population in the region for all three years? 2. I don't think "influenza epidemic" was relevant to the topic of this article. Why did the authors include this exposure variable in the current analyses? 3. It will help the readers to understand the distribution of PM2.5 by adding a histogram. 4. The data were collected from two hospitals only, were there many other hospitals in the two cities? More information is needed regarding the hospitals, such as the regions that were covered by these two hospital. Were patients with less severe symptoms treated at these two hospitals as well? Could there be patients outside of the cities be treated in these two hospitals for HF?

REVIEWER	Gang LIN Institute of Geographical Sciences and Natural Resources Research, Chinese Academy of Sciences
REVIEW RETURNED	21-Feb-2018

GENERAL COMMENTS	This manuscript reports the relationship between air quality and

	heart failure (HF) incidence and rehospitalization in Tasmania. This type of ecologic analysis in Australian is very useful and important. Although it is not a brand-new idea, the work is completely finished and shows the value in epidemiology, especially in local pollution modelling build up. Specific Comments : (1) Page 4, line 37. PM needs to be defined, particulate matter (PM). (2) In Methods Section, the authors should illuminate why Poisson regression was used here. (3) The authors should improve the quality of Figure 1 as it is blurry on the copy provided for review. (4) In Discussion Section, the sensitivity analysis of the model should be provided.

VERSION 1 – AUTHOR RESPONSE

Response Letter. Manuscript ID bmjopen-2018-021798
We would like to thank the Editors and the Reviewers for their thoughtful and comprehensive comments and suggestions. We have carefully replied to each point made by the Editors and Reviewers, and this has guided our revision of the previous manuscript as detailed below.
In the following response letter, original Editor/Reviewer comments are in listed bold italic, our reply is blue, and verbatim textual changes to the manuscript are in red.

Response to Editor Comments:
- Please include the study design and setting in the title. This is the preferred format of the journal.
Response: Added "….in Tasmania: An Observational Study"

- The Strengths and Limitations section should just contain points on the strengths and limitations of the study and study design. It should not serve as an article summary, or present any results.
Response: Minor revisions have been made to clarify this.

- Please provide another copy of your figures with better qualities and please ensure that figures are of better quality or not pixelated when zooming in. NOTE: They can be in TIFF or JPG format and make sure that they have a resolution of at least 300 dpi. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable.
Response: The figures have been updated.

Response to Reviewer #1
Reviewer Name: Wenyuan Li
Institution and Country: Post-Doctoral Research Fellow, Harvard T.H. Chan School of Public Health, Boston, MA USA
Please state any competing interests or state 'None declared': None declared

The authors conducted a retrospective study that examined the associations between short-term exposure to air pollution and heart failure (HF) incidences and readmissions among 1246 patients resided in two large cities. The authors collected daily fine particulate matter (PM2.5), temperature, and relative humidity, and used Poisson regression to determine the associations. The authors concluded that PM2.5 independently predicted HF incidence in the study sample. Furthermore, they claimed that there was a possible threshold of PM2.5=4 μg/m3, and found that beta-blockers might

play a role in preventing “detrimental effects” of air pollution on HF patients. However, the statistical methods require further clarification, the models were inadequately adjusted, and the conclusions were not supported by the results presented.

Main comments:
1. Very limited demographic information was provided in the Table 1 (age, sex, and medication use). The two cities included in the current study were not close to each other, socioeconomic positions could affect the associations between PM2.5 and HF in the current study. The analyses should account for basic demographics (age, sex), lifestyles (e.g. BMI, smoking, alcohol, physical activity), and socioeconomic position (e.g. income, education). But on the contrary, the authors provided results mainly from univariable analyses (Table 3). Was 78.1 the mean or median of age at admission? Either way, clinical factors may also need to be accounted for, such as chronic cardiovascular disease, diabetes, COPD. Thus, it is not appropriate to claim “PM2.5 independently predicted HF incidence”. The conclusion should also mention the age range or such.
Response: We thank the reviewer for the comment. Hobart and Launceston are the two largest cities in the State of Tasmania, Australia, and are home to nearly 80% of the whole State’s population. Their regional socioeconomic positions are quite similar. This is reflected by the fact that a majority of patients from both cities were from inner/outer regional Australia (Hobart 98%, Launceston 99%) and only a small proportion were from remote/very remote areas (Hobart 2%, Launceston 1%). The average scores of Index of Relative Socioeconomic Advantage and Disadvantage among patients from the 2 cities were also similar (Hobart 912±105 vs. Launceston 914±90, p=0.73). We have modified the manuscript to include these data as follows.

Results, page 7
“Patients from Hobart and Launceston had very similar socioeconomic status (Index of Relative Socioeconomic Advantage and Disadvantage 912±105 vs 914±90, p=0.73). Only a small proportion of patients from both cities were from remote/very remote areas (Hobart 2% and Launceston 1%).”

Because most of our patients were old (median age 80 years [IQR: 72, 86]) who had already retired, personal socioeconomic status is considered to be poorly valid in this context. As the primary outcomes in this study were count variables (number of HF hospitalizations per day), we could not adjust the analyses for patient-level variables. We have now modified the statement as follows.
Abstract
“PM2.5 predicted HF incidence, independent of other environmental factors.”

The 78.1 was the mean age of patients at admission. We have changed it to median age so that it is now consistent with other continuous variables (Table 1).

2. With the median of PM2.5 levels at 2.9 μg/m3 and 75th percentile at 6.0 μg/m3, the authors should clarify the total number of cases and days in each of the nine groups in Figure 4 instead of stating “approximately 100 days”.
Response: Number of days observed and total number of cases have now been added to Figure 4 (now becomes Figure 5).

3. While the air quality standard was 25 μg/m3, based on Figure 1, there seemed to be quite a few days of PM2.5 > 15 μg/m3 in the current study. Since PM2.5 at 4 μg/m3 was an arbitrary choice based on crude data in the current study, did the authors try 6 μg/m3 (75th pct)? And were the results for 6 μg/m3 statistically different from the current analyses?
Response: In our study, PM2.5 was adversely associated with HF incidence. By stratifying this relationship by levels of PM2.5, we found that PM2.5 was predictive of HF incidence when PM2.5 was >4 μg/m3 (RR=1.20 [95% CI: 1.07, 1.34]), but was not associated with HF incidence when PM2.5 ≤4 μg/m3 (RR=0.99 [95% CI: 0.92, 1.07]).

Because PM2.5 was predictive of HF incidence when PM2.5>4 μg/m3, the relationship remained true with PM2.5>6 μg/m3. The difference of using 6 μg/m3 as a cut-off is that the relationship between PM2.5 and HF incidence when PM2.5 below the new threshold (6μg/m3) is greater, but still not significant (RR=1.32 p=0.12). The significance of this relationship would become even greater as we gradually lifted the threshold as shown below. This was the result of mixing a null and a positive association

Threshold of PM2.5 used 6μg/m3 7μg/m3 8μg/m3
Association with HF incidence when PM2.5 below the threshold RR=1.32 p=0.12 RR=1.33 p=0.058 RR=1.34 p=0.035

Accordingly, we have modified the manuscript to clarify this issue further as follows.
Results, page 11
"While the relationship between PM2.5 and HF incidence was null when PM2.5<4μm/m3 (RR=0.99 [95% CI: 0.92, 1.07]), it became more positive when PM2.5≥4μm/m3 (RR=1.20 [95% CI: 1.07, 1.34])."

Results, page 11
"Using any threshold greater than 4μm/m3 would result in a more positive association between PM2.5 and HF incidence when PM2.5 is above the new threshold."

The observed threshold may not be true in studies with a wider range of PM2.5 levels that had sufficient cases and days in higher quartiles (e.g. 15-25 μg/m3). The authors failed to recognize this limited generalizability in discussion.
Response: Our study included 131 days of PM2.5>10μm/m3 and 17 days of PM2.5>20μm/m3. There were 257 new cases of HF during this period. Our study included a much wider range of PM2.5 than any other previous studies of its kind. We agree with the reviewer that it would be ideal to analyse the threshold in a setting with a complete range of PM2.5 that contains both very high and very low PM2.5. However, it is impossible to find such an environment. We don't look upon this as a limited generalizability from our study, but rather the inability of previous studies of PM2.5 and HF to detect a threshold in this relationship because they did not include a low range of PM2.5 as in our study.

4. Use of a specific type of medication could be a result of limited access to medication, or a surrogate of socioeconomic position. Without adjustment for demographics, lifestyles, and socioeconomic positions, the differing associations may be confounded.
Response: Australia has a subsidised system for prescribing. Thus, the use of medication in our study was not associated socioeconomic status or demographic factors. We therefore do not expect this to confound our findings.

5. The statistical methods section requires clarification. For example:
5.1 What did the authors mean by saying "Daily mean temperature and relative humidity … These measurements were then weighted based on each city's population to derive an average value to be used in analysis"? What was the formula of calculating the weight? What was the rationale to weight the measures?
Response: The population and meteorological climate were different in Hobart and Launceston although they share similar socioeconomic status. Therefore, the proportion of patients exposed to environmental factors were different between the 2 cities. We had to weight these measurements based on the ratio of population between the 2 cities to remove this difference. We have modified the Methods to clarify this.
Methods, page 6 (Statistical analyses)
These measurements were then weighted based on the ratio of population in the two cities to derive an average value to be used in analysis.

5.2 Did the authors examine whether the associations differ by season? Since higher pollution days were more commonly seen in winter, the observed "threshold" may be due to the season.
Response: The levels of all environmental factors (including PM2.5, temperature and humidity) vary seasonally. We therefore applied "A smooth function of calendar time (natural cubic splines) with 7 degrees of freedom per year was used to adjust for seasonal patterns and any other time-dependent influences on HF admissions (including long-term trends due to changes in medical practice)." (Methods, page 6)

5.3 In Table 4, the authors stated "Further adjusted for current day (lag0 day) temperature, weekday and weekend, school and public holiday, and time trend" in the footnote. What is the rational of examining the associations for Temperature lag1-3 day while adjusting for lag0 temperature, and why did the authors adjust for school and public holiday?
Response: The final multivariable analyses were not adjusted for current day temperature. That was a mistake and has now been removed from the footnote. Thank you very much for pointing this out. We further adjusted for school and public holiday because participants might have been differently exposed to outdoor environment during these days, compared to their weekday routine.

5.4 The statement "HF incidence count per day started to rise when PM2.5 was beyond the 7th decile (median 4.1 μm/m3)" was based on speculation without any statistical significance test.
Response: This is the same observation as in Figure 5. Any statistical analysis with using the 7th decile of PM2.5 (median 4.1 μm/m3) provided similar results to those we provided when using PM2.5=4μm/m3 as a threshold (Results, page 11)

5.5 Did the authors examine whether the associations in primary analyses differed by season? Moreover, were the differing associations by PM2.5 at 4 μg/m3 observed in different seasons?
Response: As our response to this reviewer's point 5.2 and as shown in Figure 1, the levels of PM2.5 differed seasonally. Specifically, PM2.5 raised during winter and decreased during other seasons. It is therefore not appropriate to perform analysis separately for each season. Instead, we applied "A smooth function of calendar time (natural cubic splines) with 7 degrees of freedom per year was used to adjust for seasonal patterns and any other time-dependent influences on HF admissions (including long-term trends due to changes in medical practice)." (Methods, page 6)

Minor comments:
1. What is the point of calculating cumulative incidence if the calculation was only based on total population in 2011 but not the real-time population during the study period (2009-2012)? Or did the authors have accurate number of population in the region for all three years?
Response: We did not have data on the total population in the region for all three years of the study period. The Tasmanian population is stable. We therefore used total population in 2011 as representative of the period.

2. I don't think "influenza epidemic" was relevant to the topic of this article. Why did the authors include this exposure variable in the current analyses?
Response: An influenza epidemic can be a trigger for exaggerating HF. Indeed, HF Guidelines recommend "annual influenza vaccination should be considered in patients with symptomatic HF without known contraindications" (ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J 2008;29:2388-42) Influenza increased during winter which coincides with an increase in PM2.5, and therefore might confound the relationship between PM2.5 and HF. That was the reason we adjusted our analyses for influenza epidemic.

3. It will help the readers to understand the distribution of PM2.5 by adding a histogram.
Response: A histogram of PM2.5 has now been added to the manuscript as requested (New Figure 1).

4. The data were collected from two hospitals only, were there many other hospitals in the two cities? More information is needed regarding the hospitals, such as the regions that were covered by these two hospital. Were patients with less severe symptoms treated at these two hospitals as well? Could there be patients outside of the cities be treated in these two hospitals for HF?
Response: There is only one public hospital in each of Hobart and Launceston that provides medical service for the whole city. HF patients in Hobart and Launceston are generally admitted to these hospitals. This has been stated in Methods (page 5). We could not exclude the possibility of patients from other cities admitted to these hospitals. However, because of the geographic nature of Tasmania that is isolated from the mainland of Australia, we expect this possibility to be minimal.

Response to Reviewer #2
Reviewer Name: Gang LIN
Institution and Country: Institute of Geographical Sciences and Natural Resources Research, Chinese Academy of Sciences
Please state any competing interests or state 'None declared': None declared

This manuscript reports the relationship between air quality and heart failure (HF) incidence and rehospitalization in Tasmania. This type of ecologic analysis in Australian is very useful and important. Although it is not a brand-new idea, the work is completely finished and shows the value in epidemiology, especially in local pollution modelling build up.

Specific Comments :
(1) Page 4, line 37. PM needs to be defined, particulate matter (PM).
Response: This mistake has been fixed.

(2) In Methods Section, the authors should illuminate why Poisson regression was used here.
Response: We have modified the manuscript as requested.
Statistical analysis, page 6
"Because of the nature of our primary outcomes (count variables), Poisson regression was used to estimate the associations of air pollution and other environmental factors with the primary outcomes of this study."

(3) The authors should improve the quality of Figure 1 as it is blurry on the copy provided for review.
Response: We have improved the quality of all figures.

(4) In Discussion Section, the sensitivity analysis of the model should be provided.
Response: We assumed that the reviewer referred to the analysis restricted to HF specific readmission. The results for these analyses are reported in Supplementary Table 1.

VERSION 2 – REVIEW

REVIEWER	Wenyuan Li Harvard T.H. Chan School of Public Health. Boston, MA 02115. USA
REVIEW RETURNED	13-Apr-2018

GENERAL COMMENTS	I would like to thank the authors for their detailed response. I only have a few minor comments: 1. The word "independent" was used a few times in the manuscript

	to describe the associations between PM2.5 and HF, which I don't totally agree. It might be more accurate or appropriate if the authors change the sentence to "accounting for other environmental factors". For example, instead of saying "PM2.5 was independently associated with increased HF incidence", I prefer "PM2.5 was associated with increased HF incidence after accounting/adjusting for other environmental factors". 2. The word "effect" was also used a few times to describe the associations found in the current study, I would prefer the word "association". For example, "detrimental effects of air pollution on HF" in the abstract can be changed to "positive associations between air pollution and HF". 3. Please use "relative humidity" in Table 2. 4. Please use "PM2.5" (2.5 as subscript) consistently in the manuscript. In some sentences, "PM2.5" was used.

REVIEWER	Gang LIN Institute of Geographical Sciences and Natural Resources Research, Chinese Academy of Sciences
REVIEW RETURNED	17-Apr-2018

GENERAL COMMENTS	The authors have been reasonably responsive to previous comments and suggestions.

VERSION 2 – AUTHOR RESPONSE

Response Letter. Manuscript ID bmjopen-2018-021798. R1
We would like to thank again the Editors and the Reviewers for their time, comments and suggestions. We have carefully replied to each point made by the Editors and Reviewers, and this has guided our revision of the previous manuscript as detailed below.

Response to Editor Comments:
- We do not require the 'Key messages' section - we only need the Strengths and Limitations section.
Response: We deleted the 'Key messages' section.

Response to Reviewer #1
I would like to thank the authors for their detailed response.
I only have a few minor comments:

1. The word "independent" was used a few times in the manuscript to describe the associations between PM2.5 and HF, which I don't totally agree. It might be more accurate or appropriate if the authors change the sentence to "accounting for other environmental factors". For example, instead of saying "PM2.5 was independently associated with increased HF incidence", I prefer "PM2.5 was associated with increased HF incidence after accounting/adjusting for other environmental factors".
Response: Thank you again for your comments and suggestions. We made the following changes.

Page 12
Acute exposure to ambient particulate matter is adversely associated with increased HF incidence after adjusting for other environmental factors,

Page 13
PM2.5 was associated with increased HF incidence after accounting for other environmental factors,

2. The word “effect” was also used a few times to describe the associations found in the current study, I would prefer the word “association”. For example, “detrimental effects of air pollution on HF” in the abstract can be changed to “positive associations between air pollution and HF”.
Response: The following changes have been made.

Abstract. Conclusion.
Our data suggest that beta-blockers might play a role in preventing adverse association between air pollution and HF patients.
Page 3
- The adverse associations of air pollution on HF

Page 11
We further investigated whether HF medications prescribed after the confirmed diagnosis of HF may play a role in protecting patients against the adverse association with air pollution.

Page 15
The adverse association between air pollution and HF

3. Please use “relative humidity” in Table 2.
Response: Fixed as follows:

Table 2: Correlations among the environmental factors

	PM2.5		Temperature		Relative Humidity
PM2.5	1.00				
Temperature	−0.38	*	1.00		
Humidity	0.35	*	−0.23	*	1.00

*p<0.001

4. Please use “PM2.5” (2.5 as subscript) consistently in the manuscript. In some sentences, “PM2.5” was used.
Response: These typos are fixed as follows:
Page 11.
While the relationship between PM2.5 and HF incidence was null when PM2.5<4μm/m3 (RR=0.99 [95% CI: 0.92, 1.07]), it was significantly positive when PM2.5≥4μm/m3 (RR=1.20 [95% CI: 1.07, 1.34]).

Response to Reviewer #2
Reviewer Name: Gang LIN
The authors have been reasonably responsive to previous comments and suggestions.
Response: Thank you.