Association of ambient particulate matter with heart failure incidence and all-cause readmissions in Tasmania: an observational study

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INTRODUCTION
Heart failure (HF) is the leading cause of hospitalisation and rehospitalisation for adults aged over 65 years.1,2 Despite great improvements in medical therapy and management of risk factors for HF, high readmission rates following an index HF admission continue to be a problem worldwide.3-5 In Australia, approximately 30 000 patients are diagnosed with HF each year, and the costs for HF readmissions exceed $1 billion annually.6 Finding and eliminating the triggers of acute cardiac decompensation will reduce the social and economic burden of HF.

The phenomenon of seasonal variations in HF has been well established.7-9 Although the underlying mechanisms are yet to be determined, observed increases in morbidity and mortality in cold weather may be partly due to increased ambient air pollution.10-12 A recent assessment of the global burden of disease ranked particulate matter air pollution as one of the leading causes of death and disability worldwide.12

ABSTRACT
Objectives We sought to investigate the relationship between air quality and heart failure (HF) incidence and rehospitalisation to elucidate whether there is a threshold in this relationship and whether this relationship differs for HF incidence and rehospitalisation.

Methods This retrospective observational study was performed in an Australian state-wide setting, where air pollution is mainly associated with wood-burning for winter heating. Data included all 1246 patients with a first-ever HF hospitalisation and their 3011 subsequent all-cause readmissions during 2009–2012. Daily particulate matter <2.5 µm (PM2.5), temperature, relative humidity and influenza infection were recorded. Poison regression was used, with adjustment for time trend, public and school holiday and day of week.

Results Tasmania has excellent air quality (median PM2.5=2.9 µg/m3 (IQR: 1.8–6.0)). Greater HF incidences and readmissions occurred in winter than in other seasons (p<0.001). PM2.5 was detrimentally associated with HF incidence (risk ratio (RR)=1.29 (1.15–1.42)) and weakly so with readmission (RR=1.07 (1.02–1.17)), with 1 day time lag. In multivariable analyses, PM2.5 significantly predicted HF incidence (RR=1.12 (1.01–1.24)) but not readmission (RR=0.96 (0.89–1.04)). HF incidence was similarly low when PM <4 µg/m3 and only started to rise when PM2.5>4 µg/m3. Stratified analyses showed that PM2.5 was associated with readmissions among patients not taking beta-blockers but not among those taking beta-blockers (pinteraction=0.011).

Conclusions PM2.5 predicted HF incidence, independent of other environmental factors. A possible threshold of PM2.5=4 µg/m3 is far below the daily Australian national standard of 25 µg/m3. Our data suggest that beta-blockers might play a role in preventing adverse association between air pollution and patients with HF.

Strengths and limitations of this study
This observational study was performed in Tasmania, one of the world’s cleanest air areas with median PM2.5 level of 2.9 µg/m3. This has given us an opportunity to investigate the association of air pollution with heart failure (HF) within a range of air quality that was much wider than that of other previous studies of its kind.

Our analyses were based on a wide range of environmental factors to determine the independent association of air pollution with HF.

The separation of HF incidence and readmission enabled us to investigate the differences in their associations with air pollution and other environmental factors.

This study is limited by the absence of available data on personal exposure to active and passive smoking, indoor temperature and other air pollutants.

The adverse associations of air pollution on HF might have been underestimated in our study because our analyses were based on acute events associated with short-term exposures and did not take into account the effects of long-term exposure to air pollution.
A recent systematic review and meta-analysis has shown an adverse relationship between increases in ambient particulate matter and HF hospitalisation and death. However, it is unknown whether there is a threshold of particulate matter concentration in this relationship and whether this relationship may differ between HF incidence (defined as first-ever hospitalisation due to HF) and all-cause readmission.

Tasmania has excellent air quality in comparison with other parts of Australia. While having very low median level of fine particulate matter (PM$_{2.5} <$3 µg/m$^3$) compared with regions with considered good air quality like Colorado, USA (median PM$_{2.5}$ 7.7 µg/m$^3$) or bad air quality like Beijing (PM$_{2.5}$ 94±24 µg/m$^3$), there are days in Tasmania with high level of air pollution (PM$_{2.5}$ of up to 40 µg/m$^3$). This very wide range of air quality provides a unique opportunity to investigate if there is a lower threshold for health outcomes associated with air pollution. The main cause of elevations in particulate matter in this setting is biomass smoke from wood heaters during winter and from bushfires and planned burns at other times of the year. In this retrospective cohort study, we measured air pollution and other environmental factors including temperature, relative humidity and influenza epidemics and investigated the associations of these factors with HF incidence and readmission. Patients may be exposed to different lifestyles, treatments and medications before and after the diagnosis of HF. By being able to separate HF incidence and readmission, we sought to determine the presence and mechanism of any differences in the relationship of these outcomes with environmental factors.

**METHODS**

**Study population**

This retrospective cohort study included all 1246 patients (median age 78 years, 51% male) who had their first-ever admission to a public hospital in Hobart and Launceston (Tasmania, Australia) due to HF between July 2009 and July 2012. These patients were identified by their coded diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification 402.x1, 404.x1, 404.x3, 428.x and 428.xx).

**Primary outcomes**

The primary outcomes of this study were daily count of HF incidence (defined as first hospitalisation due to HF) and subsequent all-cause readmissions that followed the index admission during the study period. Dates of hospitalisation were obtained from administrative data from the Clinical Informatics and Business Intelligence Unit of the Department of Health and Human Services of Tasmania.

**Patient and public involvement**

Patients or public were not involved in this study.

**Environmental data**

The Australian state of Tasmania is an island to the south of the continent, characterised by a colder and wetter climate, and cleaner air quality, than the rest of the Australia. In this southern hemisphere, winter is defined as June–August, spring as September–November, summer as December–February and autumn as March to May. Hobart (population 247 461 in 2011) and Launceston (population 137 561 in 2011) are the two largest cities of Tasmania (total population 495 354 in 2011) and provide residence for nearly 80% of the whole state's population. There is only one public hospital in each of Hobart (the Royal Hobart Hospital) and Launceston (the Launceston General Hospital). Air pollution in Hobart and Launceston was estimated by hourly concentrations of particulate matter less than 2.5 µm in diameter (PM$_{2.5}$) with gravimetric sampling methods. Simultaneous monitoring of air quality was previously conducted at multiple sites and showed highly correlated measurements. After these findings, a representative site was selected for ongoing monitoring air quality in each city all year. Data on daily temperature and relative humidity were from the Bureau of Meteorology. Daily count of positive laboratory tests for influenza in Tasmania was also recorded.

**Demographic and clinical data**

Additional demographic and clinical data were collected from medical records of the first HF admission.

**Statistical analyses**

Cumulative incidence of HF was estimated by taking the ratio of new HF cases to the total population of Hobart and Launceston. We calculated daily concentration of PM$_{2.5}$ by averaging their hourly measurements from each day, for Hobart and Launceston separately. Daily mean temperature and relative humidity were calculated by averaging maximum and minimum temperature and relative humidity of each day. 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. The rolling sum of positive influenza tests during the last 7 days (including the current day) was calculated, and the 90th percentile cut-off was used to define influenza epidemic. Pearson correlation was used to estimate the strength of the relationships among these environmental factors. 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. These associations were estimated for the same day (lag$$_1$$) and up to 5 days before the outcome (lag$$$_{1-5}$$) for the previous 3 days moving average (lag$$_{1-3}$$). Binary variables were created for weekday and weekend, school holidays and public holidays for adjustment. A smooth function of calendar time (natural cubic splines) with 7 df 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).
Because the relationship of temperature with HF admissions appeared to be linear in our study (as shown in Results section, possibly due to the cool climate nature of Tasmania), we fitted a linear term for temperature in our analysis.

**RESULTS**

**Heart failure**

Data on HF hospitalisations are shown in **table 1**.

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%).

There were 1246 HF incidences (median: 1 new case/day). The estimated cumulative incidence of HF was 3.2 per 1000 persons over the study period. After the first HF hospitalisation, there were 3011 subsequent all-cause readmissions (with 35% being HF-specific readmissions) during the study period. The majority of patients (70%) were classified as New York Heart Association (NYHA) class II/III. Diuretics were the most commonly used medication, followed by ACE inhibitors (ACEis) or angiotensin receptor blockers (ARBs).

**Environmental factors**

The distribution of PM$_{2.5}$ is shown in **figure 1**. Median levels of PM$_{2.5}$, temperature and relative humidity are shown in **table 1**. The correlations among these measurements, which are moderate at best, are shown in **table 2**.

**Seasonal variations of HF**

The seasonal variations of HF are illustrated in **figure 2**. The incidence of new cases of HF peaked during winter months (June–August). This phenomenon also aligned well with the peaks in PM$_{2.5}$ and relative humidity and with the lowest levels of temperature. **Figure 3** further demonstrated this seasonal variation in HF by showing significant trends in HF incidence and readmissions that both peaked during winter and reduced during other seasons.

**Associations with primary outcomes**

**Table 3** shows univariable associations of air pollution and other environmental factors with HF incidence and all-cause readmission.

While air pollution was adversely associated with HF incidence, it was not or very weakly associated with readmission. Temperature, relative humidity and influenza epidemic periods, however, were associated with both HF incidence and all-cause readmission. These findings were consistent with those of HF-specific readmissions (online supplementary table 1). It is consistent for all
environmental factors (PM<sub>2.5</sub>, temperature and relative humidity) that their associations with HF incidence were either strongest or second strongest with three lagging days average. This suggests that the environmental effect on HF is through continuous exposure, and for consistency, this three lagging day average (lag1–3) variables will be used for multivariable analysis. The associations between environmental factors and HF are also illustrated in figures 4–6, demonstrating dose–response relationships.

Table 4 shows multivariable associations of air pollution and other environmental factors with the outcomes. Among the environmental factors, only PM<sub>2.5</sub> and temperature remained as significant predictors of HF incidence. However, while temperature, relative humidity and presence of influenza epidemic were significantly associated with readmissions, PM<sub>2.5</sub> did not predict readmissions among HF patients.

Possible threshold of PM<sub>2.5</sub> in predicting HF incidence

The relationship of PM<sub>2.5</sub> with HF incidence count per day is shown in figure 4. Although there was a highly significant trend of increasing HF incidence throughout the whole range of PM<sub>2.5</sub> included in this study, the level of HF incidence count per day appeared to increase when PM<sub>2.5</sub> reached the fourth quintile. This finding suggests that there might be a threshold in the relationship of PM<sub>2.5</sub> with HF incidence. Therefore, we further investigated this relationship by breaking the whole range of PM<sub>2.5</sub> into nine groups each of which contained approximately 100 days of our study period (figure 7). The HF incidence count per day started to rise when PM<sub>2.5</sub> was beyond 4 µm/m<sup>3</sup>. While the relationship between PM<sub>2.5</sub> and HF incidence was null when PM<sub>2.5</sub> < 4 µm/m<sup>3</sup> (RR=0.99 (95% CI 0.92 to 1.07)), it was significantly positive when PM<sub>2.5</sub> ≥ 4 µm/m<sup>3</sup> (RR=1.20 (95% CI 1.07 to 1.34)). This was consistent with no correlation between PM<sub>2.5</sub> and HF incidence when PM<sub>2.5</sub> < 4 µm/m<sup>3</sup> (β=−0.01 (−0.07 to 0.05), p=0.48) and a positive correlation when PM<sub>2.5</sub> ≥ 4 µm/m<sup>3</sup> (β=0.17 (0.07 to 0.35), p<0.008). These findings are controlled for temperature. Consistent findings were found when the PM<sub>2.5</sub> range was broken by deciles (online supplementary figure 1). HF incidence count per day started to rise when PM<sub>2.5</sub> was beyond the seventh decile (median 4.1 µm/m<sup>3</sup>). Using any threshold greater than 4 µm/m<sup>3</sup> would result in a positive association between PM<sub>2.5</sub> and HF incidence when PM<sub>2.5</sub> below the new threshold (not shown).

Possible protective effects of HF medication against air pollution

The concentration of PM<sub>2.5</sub> was adversely associated with HF incidence but not with readmission. 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. We classified patients by whether they were prescribed common HF medications (beta-blockers, ACEi/ARB and diuretics) after their first admission with HF. For ACEi/ARB and diuretics, there was no difference in the association of PM<sub>2.5</sub> with readmission count per day among patients who took these medications (ACEi/ARB: β=0.04 (−0.02 to 0.08), p=0.15, diuretics: β=0.05 (−0.01 to 0.11), p=0.084) and those who did not (ACEi/ARB: β=0.02 (−0.01 to 0.03), p=0.27, diuretics: β=0.04 (−0.02 to 0.09), p=0.11). However, while PM<sub>2.5</sub> was not associated with readmission count per day among patients who took beta-blockers (figure 8, β=−0.01 (−0.07 to 0.06), p=0.89), PM<sub>2.5</sub> was positively associated with readmission count per day among patients who did not take beta-blockers (figure 8, β=0.14 (0.05 to 0.23), p<0.002). There was a significant interaction between beta-blockers use and PM<sub>2.5</sub> in their association with HF readmission (p=0.011). When restricting the analysis to HF-specific readmissions only, the association of PM<sub>2.5</sub> with readmission count per day was also stronger among patients who did not take beta-blockers (β=0.09 (0.01 to 0.19), p=0.01) than that among patients who took beta-blockers (β=0.03 (−0.02 to 0.07), p=0.34).
This study investigated the relationships of particulate air pollution and other environmental factors with HF incidence and all-cause readmission and provided several important and novel findings. Acute exposure to ambient particulate matter is adversely associated with increased HF incidence after adjusting for other environmental factors, even in regions with very low air pollution such as...
as Tasmania. More importantly, the relationship between PM\(_{2.5}\) and HF incidence appeared to have a threshold of approximately 4 µg/m\(^3\), which is far below the daily Australian and WHO standard of PM\(_{2.5}\) of 25 µg/m\(^3\).

While temperature and relative humidity were associated with readmission, air pollution was very weakly associated with all-cause readmission among patients with HF. This might be partly due to protective effects of beta-blockers.

**Air pollution and HF**

Although the mechanisms underlying the relationship between particulate air pollution and HF are not well understood, possible causal pathways through increased oxidative stress and inflammation have been proposed.\(^{21-25}\) These pathways involve adverse effects on both the systemic arterial and venous circulation and lead to an increase in systemic blood pressure, myocardial ischaemia, vasoconstriction, atherosclerosis and arrhythmia. All these factors contribute to the exacerbation of HF. The positive association of air pollution with HF incidence shown in our study suggests that air pollution also plays a role in the development of HF.

To the best of our knowledge, this is the first time a threshold of PM\(_{2.5}\) has been detected for its association with HF. The very low threshold of PM\(_{2.5}\) observed in our study (approximately 4 µg/m\(^3\)) explains the persistent adverse effects of air pollution when PM\(_{2.5}\) levels were lower than the Australian and WHO standard of 25 µg/m\(^3\).\(^{24,25}\) This is even lower than the target concentration of 5.8 µg/m\(^3\) used in the recent meta-analysis,\(^{13}\) which was the lowest concentration observed in 116 cities in the USA during 1999–2000 PM\(_{2.5}\) collection period.\(^{26,27}\) The finding that PM\(_{2.5}\) was linearly associated with HF when beyond the threshold is consistent with that found in other studies\(^{13}\) and suggests that any effort to improve air quality is beneficial if a level of PM\(_{2.5}\) as low as 4 µg/m\(^3\) is too difficult to achieve. Our findings link well to those in previous studies and together they form a complete picture of the relationship between PM\(_{2.5}\) and HF.

**Possible protective effects of beta-blockers**

PM\(_{2.5}\) was associated with increased HF incidence after accounting for other environmental factors but was not associated with HF specific or all-cause readmission. Although there were no interactions of ACEi/ARB or diuretic use on the relationship between PM\(_{2.5}\) level and HF readmission, there was a significant interaction of beta-blocker use with this relationship. This difference in the relationship of PM\(_{2.5}\) with HF incidence and HF specific or all-cause readmission may be partly due to the protective effects of beta-blockers. Because the mechanisms underlying the association between PM\(_{2.5}\) and HF are not fully understood, how the use of beta-blockers may contribute to this relationship is further unclear. However, there are three possible mechanisms: (1) beta-blockers are known to influence the autonomic nervous system; (2) they may reduce sympathetic activity, which could help to control blood pressure and heart rate; and (3) they may reduce the release of angiotensin II, which is a vasoconstrictor and may contribute to the development of HF.

### Table 4

Multivariable Poisson regression of environmental factors with heart failure incidence and readmissions

<table>
<thead>
<tr>
<th></th>
<th>Heart failure incidence</th>
<th>All-cause readmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>P values</td>
</tr>
<tr>
<td>PM(<em>{2.5}) lag(</em>{1-3}) (per 10 µg/m(^3))</td>
<td>1.10 (1.01–1.22)</td>
<td>0.039</td>
</tr>
<tr>
<td>Temperature lag(_{1-3}) (per 10°C)</td>
<td>0.69 (0.59–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative humidity lag(_{1-3}) (per 10%)</td>
<td>0.98 (0.92–1.05)</td>
<td>0.56</td>
</tr>
<tr>
<td>Influenza epidemic (yes vs no)</td>
<td>1.01 (0.80–1.21)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Further adjusted for weekday and weekend, school and public holiday and time trend.

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**Figure 6** Associations of relative humidity with heart failure incidence and readmission.

**Figure 7** Possible threshold of PM\(_{2.5}\) with heart failure (HF) incidence.
This study has some particular strengths. The PM$_{2.5}$ median level of 2.9 µg/m$^3$ is a unique aspect of the study, as Tasmania has some of the world’s cleanest air. This has given us an opportunity to investigate the association of air pollution with HF within a range of air quality that was much wider than that of other previous studies of its kind. Second, our analyses were based on a wide range of environmental factors to determine the association of air pollution with HF. Third, the separation of HF incidence and readmission enabled us to investigate the differences in their associations with air pollution and other environmental factors.

One could argue that the patients without beta-blocker could not have tolerated taking them because they were too sick. Indeed, patients who were prescribed beta-blockers in our study were at younger age at their first admission and had slightly lower mean NYHA class, Charlson comorbidity index, heart rate and respiratory rate (online supplementary table 2), but there was no association with socioeconomic factors. However, patients who were prescribed ACEi/ARB also had similar characteristics (online supplementary table 3). Therefore, the protective effects of beta-blockers use (but not of ACEi/ARB) that were observed in our study were likely not fully explained by these discrepancies. However, because patients with HF usually have respiratory comorbidities such as asthma or chronic obstructive pulmonary disease that may contraindicate the use of beta-blockers, we could not completely exclude the possibility of a residual confounding caused by these conditions in our study. Thus, further studies on this are needed.

**Differences between HF incidence and readmission**

Apart from the differences in the associations with air pollution, HF incidence and readmission were also different in their associations with relative humidity and influenza infection epidemic. While these environmental factors were not independently associated with HF incidence, they were independently and adversely associated with readmission. This may be due to increased vulnerability once patients have developed HF, and a mild trigger might also lead to exacerbation of HF, or this may be due to the attenuation of significant effect of particulate air pollution resulted from beta-blocker use. The consistent findings for HF-specific readmissions and all-cause readmissions in our study support this speculation.

**Strengths and limitations**

This study is limited by the absence of available data on personal exposure to active and passive smoking, indoor temperature and other air pollutants (such as nitrogen dioxide, ozone and sulfur dioxide). Second, the adverse association between air pollution and HF might have been underestimated in our study, because our analyses were based on acute events associated with short-term exposures and did not take into account the effects of long-term exposure to air pollution. Third, our study did not take into account the duration, dosage and adherence of beta-blocker use and factors (including severity of HF) that may influence the use of beta-blockers. Future studies are therefore required to confirm this relationship and further explore if the benefit of beta-blockers use in this context is dose–response. Because most HF patients with reduced ejection fraction would have been prescribed beta-blockers if not contraindicated, it is important to confirm our findings for HF patients with preserved ejection fraction. Finally, due to the retrospective nature of our study, we only had echocardiography data on a subset of 451 patients (online supplementary tables 2 and 3) and were unable to investigate this matter. Further studies are therefore needed for this investigation.

**CONCLUSIONS**

In summary, our findings confirm the seasonal variations of HF and demonstrate an adverse relationship of air pollution with HF even in a very low range of PM$_{2.5}$. For the first time, a possible threshold of PM$_{2.5}$=4 µg/m$^3$ has been detected in our study. This finding should encourage us to keep improving the air quality to reduce the burden of HF. Further studies are required to confirm the possible protective effects of beta-blockers against air pollution.
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Competing interests None declared.

Patient consent Not required.

Ethics approval The study protocol was approved by Human Research Ethics Committee Tasmania (No. H0014931).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The anonymised original data can be shared upon the ethical approval.

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REFERENCES

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