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Intensive Care Admissions and Outcomes Associated with Short-Term Exposure to Ambient Air Pollution: A Time Series Analysis

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Authorship

All authors contributed to study conception and design. Data collection and preparation was performed by CPG. Analysis was performed by BKB. The manuscript was written by CPG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Statement

Ms Butland owns shares in Royal Dutch Shell and Scottish and Southern Energy and her spouse has a deferred Shell pension. All other authors declare no conflicts of interest.

Abstract

Purpose

Short-term exposure to outdoor air pollution has been positively associated with numerous measures of acute morbidity and mortality, most consistently as excess cardiorespiratory disease associated with fine particulate matter ($PM_{2.5}$), particularly in vulnerable populations. It is unknown if the critically ill; a vulnerable population with high levels of cardiorespiratory disease, is affected by air pollution.

Methods

We performed a time series analysis of emergency cardiorespiratory, stroke and sepsis intensive care (ICU) admissions for the years 2008 – 2016, using data from the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD). Case-crossover analysis was conducted to assess the relationship between air pollution and the frequency and severity of ICU admissions having adjusted for temperature, humidity, public holidays and influenza activity.

Results

46,965 episodes in 87 separate ICUs were analysed. We found no statistically significant associations with admission counts. However, ICU admissions ending in death within 30 days were significantly positively associated with short-term exposure to $PM_{2.5}$ (RR 1.18, 95% confidence interval (CI) 1.02 –

1.37, per 10μg/m^3 increase). This association was more pronounced in those aged 65 and over (RR 1.33, 95% CI 1.11 – 1.58, per 10μg/m^3).

Conclusions

Increased ICU mortality was associated with higher levels of $PM_{2.5}$. Larger studies are required to determine if the frequency of ICU admissions is positively associated with short-term exposure to air pollution.

Take Home Message

In a large time series study of emergency ICU admissions for cardiorespiratory disease, sepsis and stroke, fine particulate matter air pollution ($PM_{2.5}$) concentrations were significantly associated with an increased risk of ICU admission that ends in early death in ICU (within 30 days). This adds to existing observational evidence that $PM_{2.5}$ is harmful to health and may lead to increased mortality in intensive care.

Introduction

Outdoor air pollution is a leading cause of death and disability worldwide, estimated to contribute to 9 million premature deaths annually (16% of total deaths) [1], with both short- and long-term exposure thought harmful [2]. Air pollution is a heterogeneous mixture of gaseous, liquid and solid compounds, varying with locale and emission source. Conventional markers of air pollution: particulate matter (PM), nitrogen dioxide (NO_2), ozone (O_3) and sulphur dioxide (SO_2) are individually associated with harm [3-6]. However, they are never found in isolation and the true effect is likely exerted by these and many other unmeasured species.

PM has emerged as the constituent most significantly and consistently associated with harm [7]. PM is subcategorised as $PM_{2.5}$, the mass concentration of particles with a diameter less than 2.5μm ('fine' PM), and PM_{10} if less than 10μm. $PM_{2.5}$ is particularly associated with risks to health, observed 1 and 3 days following exposure [8,9]. Smaller diameter is thought to confer deeper passage into the respiratory tree and circulatory translocation [10,11]. NO_2 is usually representative of motor vehicle traffic and is associated with adverse outcomes in long- and short-term exposure studies [12].

In short-term pollution studies, increases in emergency hospital admissions and mortality have been found. These are mediated by excess cardiovascular, stroke and respiratory disease [9,13-15], particularly in susceptible populations such as the elderly [16,17]. Acute events increase within hours [18], with oxidative stress, pulmonary and systemic inflammation thought to result in vascular endothelial dysfunction, procoagulant states and autonomic dysfunction [19,20]; findings common in critical illness. Furthermore, patients admitted to the intensive care unit (ICU) are often elderly, have cardio-respiratory dysfunction and have a high risk of death and disability, suggesting they may be vulnerable to air pollution. There is little research on the effect of pollution on the ICU population, although PM and NO_2 have been associated with longer mechanical ventilation [21], ozone and $PM_{2.5}$ with an increase in acute respiratory distress syndrome [22,23], and $PM_{2.5}$ with pneumonia-related ICU admissions [24]. It is unknown whether patients admitted to ICU when air pollution is increased have worse outcomes.

Sepsis-related hospital admissions were recently associated with $PM_{2.5}$ [25] and the syndrome is characterised by dysregulated inflammatory response to infection, sharing many features with air pollution exposure. In view of this and robust associations between pollution, cardiorespiratory disease and stroke, we hypothesised that ICU admissions for these diseases are increased, and adverse outcomes more common, with increased air pollution. We conducted a time series analysis of short-term exposure to three pollutants ($PM_{2.5}$, PM_{10}, NO_2) and emergency ICU admissions in two Australian states: New South Wales (NSW) and Victoria.

Methods

Study population

The Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) [26] is one of the world's largest ICU registries, with over 2 million episodes. Demographic, clinical and outcome data are submitted from over 90% of ICUs in these countries.

Access to the APD data was granted according to standing protocol published by the ANZICS Centre for Outcomes and Resource Evaluation (CORE) committee [27]. The study was approved by the Northern Sydney Local Health District Human Research Ethics Committee (LNR/17/HAWKE/430).

The study population and outcomes were defined *a priori*. Episode data were obtained on all unplanned, non-surgical ICU episodes in NSW and Victoria with an admission diagnosis of cardiorespiratory disease, stroke or sepsis (using ANZICS modification of the Acute Physiology and Chronic Health Evaluation (APACHE) III diagnostic codes) (S1) with initial hospital admission between 1st January 2008 and 31st December 2016 and ICU admission occurring within 24 hours of hospital admission. We excluded patients under 18 years, pregnancy, and those with a residential postcode over 10 kilometres (km) from a pollution monitoring station. We included inter-hospital transfers but not transfers between ICUs to avoid double counting patients submitted to the APD twice during the same admission.

Pollution Data

Pollution data were obtained from the Environment Protection Authority of Victoria [28] and the Office of Environment and Heritage of NSW [29] (measurement techniques described in supplementary material). These are accredited by the National Association of Testing Authorities and conform to Australian and International standards. Stations are located away from large roads and industrial areas, and hence represent background pollutant levels.

Covariate Data

Covariates known to influence acute hospital and ICU admissions were considered. These were: temperature, humidity, influenza and public holidays. Meteorological data were obtained from the Australian Bureau of Meteorology and state-wide emergency department attendances for influenza-like illness from the Australian Centre for Epidemiology and Evidence. Public holidays were obtained from public records [30].

Statistical analysis

Initial data manipulation was performed using R version 3.3.3 [31]. We used residential postcode centroids to geographically match ICU episodes with pollution data. For each pollutant, data were obtained from the single monitor within a 10km radius of the postcode that provided the most complete time series of daily mean pollutant concentrations. Where two monitors provided the same amount of data, the nearest was chosen. We calculated the mean daily temperature and mean daily humidity for each postcode centroid over the study period based on all available measurements from monitoring stations within a 40km radius.

Exposure – outcome relationships were assessed with case-crossover analysis [32]. This has become the standard for analysing acute events and short-term pollutant exposure (considered as a continuous variable). In this method, subjects serve as their own controls, reducing the effect of stable individual covariates.

Strata (one for each ICU episode) were formed by matching the day of hospital admission (case day) with up to 4 control days, where matching was by postcode, day of the week, month and year. The data were then analysed using conditional logistic regression in STATA [33]. Models were run for each pollutant separately with the pollution data included as 3 separate variables on the admission day, on the day prior and two days prior (lag 0, lag 1 and lag 2). By combining the coefficients for the 3 exposure days we obtained a summary relative risk and 95% confidence interval estimating the effect on ICU admission of a 10-unit (10ppb for NO_2 and 10μg/m^3 for particulates) increase in short-term exposure. This representation of the pollutant is referred to as an unconstrained distributed lag model, lags 0-2 (UDLM 0-2). Analyses were conducted both with and without covariate adjustment. In the latter we adjusted for temperature and humidity lags 0-2 and 3-6 days (modelled as four natural cubic splines with 3 knots) (S2), influenza-like illness and public holidays.

We investigated the associations between short-term pollutant exposure and ICU admission by APACHE diagnosis categories; cardiovascular, respiratory, stroke and sepsis. We then excluded patients admitted to ICU for palliative care or organ donation and investigated the effect of pollutant exposure on three measures of adverse outcome: death in ICU within 30 days; acute renal failure on admission to ICU (creatinine >133μmol/L and 24-hour urine output < 410ml); and invasive ventilation occurring within the first 24 hours of ICU admission.

Further prespecified subgroup analyses were also performed: age divided into two groups (<65, ≥65); admission APACHE III score (0-49, 50-99, ≥100), ICU length of stay (<7 days, 7-14 days, >14 days) and season of admission. Missing clinical data were not used in analyses. Length of stay and APACHE III score were set to missing for palliative or organ donation admissions, and length of stay was additionally set to missing if the patient died in ICU. For 30-day ICU mortality only age and season were considered. Conditional logistic regression models were run with and without the inclusion of a potential effect modifier and any improvement in fit tested for using a likelihood ratio test.

Sensitivity analyses

Sensitivity to residual seasonality was investigated by re-running analyses with the inclusion of a simple sine cosine annual cycle. We investigated whether any relationship between pollutant exposure and the log odds of ICU admission might be non-linear by modelling pollutant means (i.e.

the average concentration over lag days 0-2) using 3 knot natural cubic spline. Lastly, we repeated analyses excluding inter-hospital transfers.

Results

Pollutant data were obtained from 62 monitoring stations (Figure 1). Of the study period, pollution data were available for 75% of days for NO_2, 72% for PM_{10} and 40% for $PM_{2.5}$. Seasonal trends in daily mean air quality for PM_{10} and $PM_{2.5}$, categorised according to Australian National Environment Protection Council Ambient Air Quality Measure (AAQ NEPM) index [34] are shown in Figure 2.

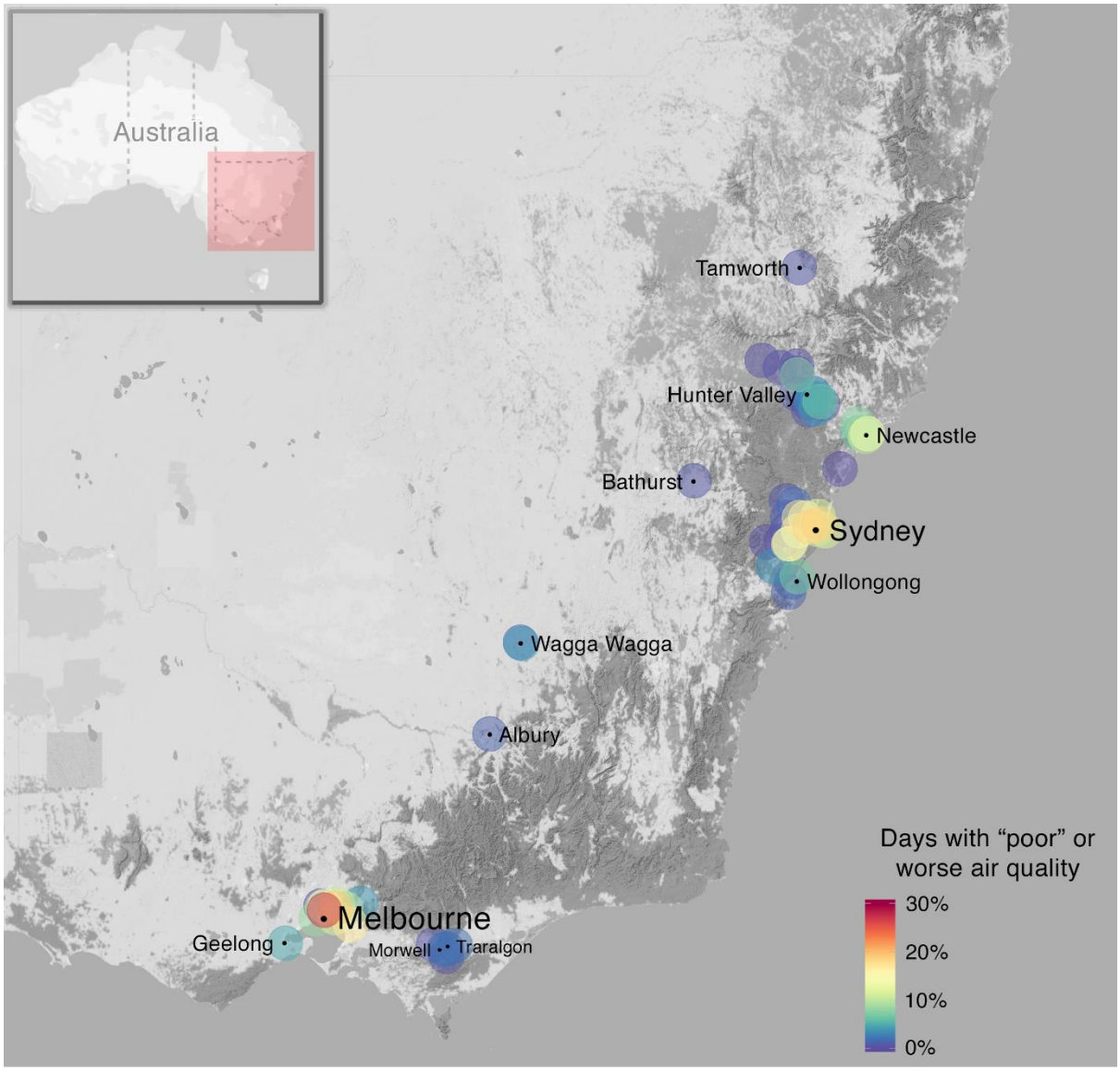

Figure 1. Location of the included 62 pollution monitoring stations and associated air quality over the duration of the study. Each point represents the location of a single station. The fill colour represents the proportion of days with a 24 hour mean level of PM_{10}, $PM_{2.5}$ or NO_2 classifed as "poor" or "very poor" according to the AAQ NEPM index[34]

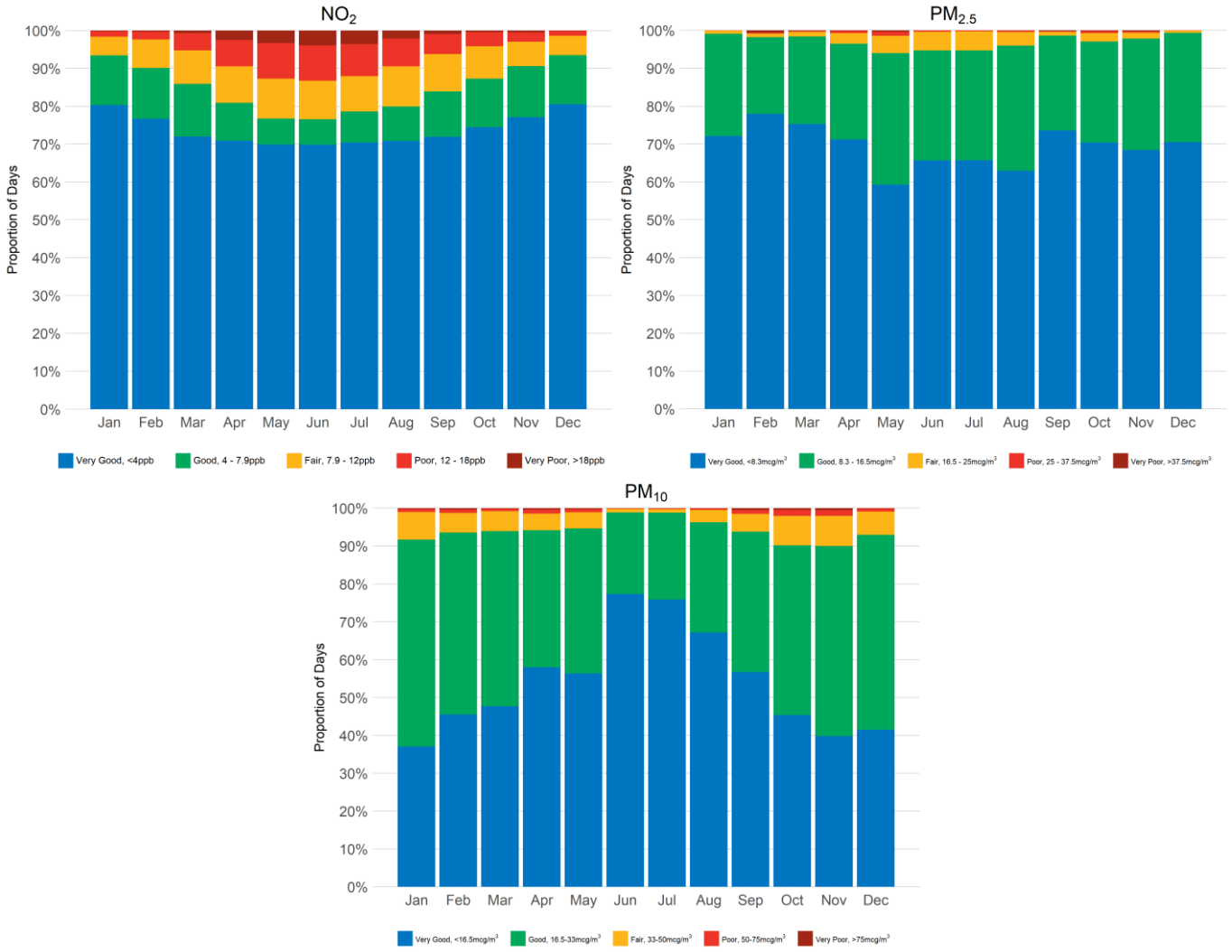

Figure 2. Seasonal trends observed in pollutant levels. The proportion of days per month classified by AAQ NEPM index at all stations, aggregated across the study duration.

46,965 episodes in 87 separate ICUs satisfied inclusion criteria for the study. These patients were residents of 419 different postcodes. Data from 45 pollutant monitoring stations were used. The medians of daily mean pollutant concentrations were: 8 ppb (inter-quartile range (IQR) 5 to 12) for NO_2, 6.2 µg/m^3 (IQR: 4.3 to 8.8) for $PM_{2.5}$ and 15.8 µg/m^3 (IQR: 11.7 to 21.1) for PM_{10}. Average within postcode Pearson correlation coefficients ($\bar{\rho}$) suggested that while daily mean concentrations of PM_{10} and $PM_{2.5}$ were strongly positively correlated ($\bar{\rho}$= 0.694, N=291), correlations of PM_{10} and $PM_{2.5}$ with NO_2 concentrations, though still positive, were weaker ($\bar{\rho}$= 0.111, N=404 and $\bar{\rho}$= 0.349, N=291, respectively) (S3). Complete data with at least one control day was available for 36,510 ICU episodes for NO_2, 39,039 for PM_{10} and 18,357 for $PM_{2.5}$ (S4). In total, 40,775 individual ICU episodes were used in the analyses.

For each analysis we only included episodes with complete data on the pollutant of interest and all covariates (i.e. the climate variables, influenza like illness activity, and public holidays) on the admission day and at least one control day.

Patient characteristics

Patient characteristics from all episodes used in analyses are summarised in Table 1.

Characteristic	n (%) or Median (IQR)
Total ICU Episodes	40,775
Respiratory	16,863 (41.4%)
Cardiovascular	11,636 (28.5%)
Sepsis	10,725 (26.3%)
Stroke	1,551 (3.8%)
Mortality in ICU	5,661 (13.9%)
30-day ICU mortality	5,608 (13.8%)
Mortality in hospital	8,093 (19.9%)
Age (years)	67 (54 to 78)
Male gender	22,812 (56%)
ICU length of stay (days)	3 (1 to 5)
Acute renal failure in first 24 hours ICU	4,127 (10.1%)
Invasive ventilation in first 24 hours ICU	13,907 (34.2%)
Admission APACHE III score	62 (45 to 84)

Table 1. Patient characteristics

Main findings

We found $PM_{2.5}$ was significantly associated with increased 30-day ICU mortality (RR 1.18, 95% CI 1.02 – 1.37, per 10µg/m^3) after adjustment for covariates (Table 2). This association was strongest with $PM_{2.5}$ concentrations on the day of admission (S5). No significant association was found between mortality and PM_{10} or NO_2.

We found no evidence of an association between short-term exposure to NO_2, $PM_{2.5}$ or PM_{10} and ICU admissions (all cause or by disease subgroup), invasive ventilation or acute renal failure (Table 2).

	NO_2			$PM_{2.5}$			PM_{10}		
	No. cases	**Unadjusted RR[§] (95% CI) per 10ppb**	**Adjusted RR[§¶] (95% CI) per 10ppb**	**No. cases**	**Unadjusted RR[§] (95% CI) per 10μg/m³**	**Adjusted RR[§¶] (95% CI) per 10μg/m³**	**No. cases**	**Unadjusted RR[§] (95% CI) per 10μg/m³**	**Adjusted RR[§¶] (95% CI) per 10μg/m³**
ICU Admissions (total)	36,510	1.015 (0.970, 1.062)	0.998 (0.950, 1.047)	18,357	1.020 (0.976, 1.066)	1.017 (0.970, 1.065)	39,039	1.002 (0.994, 1.011)	1.001 (0.992, 1.009)
Respiratory	15,054	0.977 (0.910, 1.048)	0.975 (0.902, 1.053)	7,716	1.030 (0.965, 1.099)	1.027 (0.959, 1.099)	16,114	1.004 (0.994, 1.015)	1.003 (0.992, 1.014)
Cardiovascular	10,466	1.063 (0.978, 1.154)	1.022 (0.934, 1.118)	4,870	1.048 (0.956, 1.148)	1.051 (0.954, 1.157)	11,162	1.003 (0.983, 1.023)	0.999 (0.979, 1.020)
Stroke	1,376	1.123 (0.886, 1.422)	1.176 (0.910, 1.519)	777	1.183 (0.916, 1.527)	1.287 (0.975, 1.699)	1,476	1.004 (0.902,1.118)	1.012 (0.898, 1.141)
Sepsis	9,614	1.008 (0.923, 1.100)	0.984 (0.895, 1.081)	4,994	0.935 (0.851, 1.027)	0.910 (0.822, 1.008)	10,287	0.986 (0.962, 1.012)	0.982 (0.954, 1.011)
30-day ICU mortality	4,843	1.027 (0.910, 1.160)	1.003 (0.879, 1.145)	2332	1.198** (1.046, 1.371)	1.182* (1.023, 1.366)	5,178	1.026 (0.994, 1.060)	1.027 (0.991, 1.063)
Acute renal failure[†]	3,681	0.966 (0.840, 1.111)	0.912 (0.786, 1.059)	1,798	1.015 (0.894, 1.151)	1.008 (0.883, 1.151)	3,917	0.978 (0.938, 1.019)	0.979 (0.937, 1.022)
Invasive ventilation within 24 hours of admission	12,445	1.011 (0.938, 1.090)	0.980 (0.904, 1.064)	6,057	1.041 (0.964, 1.125)	1.048 (0.966, 1.137)	13,262	1.001 (0.985, 1.018)	0.996 (0.978, 1.015)

All P values >0.05 except: **p=0.009 and *p=0.023

§ Relative risks based on an unconstrained distributed lag model lags 0-2 days prior in the pollutant of interest.

¶ Adjusted for temperature 0-2 days and 3-6 days (modelled as two natural cubic splines with 3 knots); humidity 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots), flu activity score and public holidays.

† Creatinine >133μmol/L and first 24-hour urine output < 410ml

Table 2. Relative risks of ICU admission categorised by admission diagnosis, and ICU admission with adverse outcome

	Modifying Factor	Level	NO_2		$PM_{2.5}$		PM_{10}	
			Adjusted RR[§¶] (95% CI) per 10ppb	Test for modifying effect P value	Adjusted RR[§¶] (95% CI) per 10µg/m³	Test for modifying effect P value	Adjusted RR[§¶] (95% CI) per10 µg/m³	Test for modifying effect P value
Total ICU admissions	**APACHE III Score**	**0-49**	1.023 (0.942, 1.112)	0.655	0.987 (0.913, 1.068)	0.832	0.994 (0.979, 1.010)	0.217
		50-99	0.969 (0.908, 1.035)		1.034 (0.970, 1.101)		1.008 (0.997, 1.019)	
		≥100	1.050 (0.938, 1.175)		1.033 (0.907, 1.178)		0.971 (0.938, 1.006)	
	Length of stay in ICU[‡]	**<7 days**	1.017 (0.961, 1.077)	0.443	0.992 (0.938, 1.049)	0.999	0.996 (0.985, 1.007)	0.594
		7-14 days	0.920 (0.802, 1.054)		0.981 (0.842, 1.143)		0.999 (0.967, 1.031)	
		>14 days	0.840 (0.652, 1.082)		0.931 (0.703, 1.234)		1.034 (0.936, 1.143)	
	Age	**<65 years**	1.025 (0.955, 1.100)	0.759	0.940 (0.872, 1.014)	0.001	0.984 (0.967, 1.002)	0.005
		≥65 years	0.977 (0.918, 1.040)		1.052 (0.988, 1.121)		1.006 (0.994, 1.018)	
30-day ICU mortality	**Age**	**<65 years**	0.999 (0.809, 1.234)	0.846	0.923 (0.712, 1.197)	0.023	0.956 (0.877, 1.042)	0.005
		≥65 years	1.007 (0.858, 1.182)		1.326 (1.113, 1.579)		1.070 (1.007, 1.138)	

§ Relative risks based on an unconstrained distributed lag model lags 0-2 days

¶ Adjusted for temperature 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots); humidity 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots), flu activity score and public holidays.

‡ Patients that died in ICU excluded from analyses.

Table 3. Subgroup analysis – relative risk of ICU admission and 30-day ICU mortality stratified by admission APACHE III score, ICU length of stay and age

Subgroup analyses

The positive relationship between $PM_{2.5}$ and 30-day ICU mortality was stronger in those aged 65 and over (RR 1.33, 95% CI 1.11 – 1.58, per 10μg/m^3), whereas no association was found in under 65s. PM_{10} was also significantly associated with increased 30-day ICU mortality (RR 1.07, 95% CI 1.01 – 1.14, per 10μg/m^3) in the over 65s only.

There was no modifying effect of APACHE III score or length of stay on relationships between ICU admission and pollutants (Table 3). We found no modifying effect of season on admission or mortality (S6).

Sensitivity analyses

Results in Table 2 were little changed by addition of a simple sine cosine annual cycle (S7), with no improvement in fit over a simple log-linear model for either NO_2 (p=0.354), $PM_{2.5}$ (p=0.261) or PM_{10} (p=0.381). Lastly, we repeated analyses shown in Table 2 excluding inter-hospital transfers (S8). The positive association between $PM_{2.5}$ and 30-day ICU mortality persisted (RR 1.19, 95% CI 1.01 – 1.41, per 10μg/m^3), which was again driven by exposure on the day of admission. The previously observed negative association between risk of admission for sepsis with $PM_{2.5}$ became even more negative, attaining statistical significance.

Discussion

This study is the first to investigate the relationship between air pollution, ICU admissions and outcome. Short-term exposure to pollution has been associated with mortality in general hospital populations, with additional high-risk groups identified [35]. Our study population has high mortality (approximately 10 to 15% [36]) and widespread organ dysfunction, the pathophysiology of which overlaps that described in air pollution exposure, providing a possible mechanism for interaction. Our results support the hypothesis that the ICU population is affected by $PM_{2.5}$ and warrants further study.

Our study design was informed by the strong association between pollution, cardio-respiratory disease and stroke. We also included sepsis based on its ubiquity in ICU, shared biological pathways and nascent associations with pollution [25,37]. As little is known about the effect of pollution on ICU population specifically, we studied only ICU admission and mortality and did not include post-ICU hospital mortality. Previous associations have been greatest over the first few days following exposure, with risk returning to baseline within a week [38,39]. Our study design reflects this and aims to mitigate the effect of hospital-acquired pathology by including only ICU admissions within 24 hours of hospital admission and death (in ICU) within 30 days.

We found a statistically significant increase in 30-day ICU mortality with higher exposure to $PM_{2.5}$, a species particularly associated with harm when co-pollutant levels are controlled for [7]. However, there were no statistically significant associations between pollutants and the number of ICU admissions, both overall and within diagnostic groups. Point estimates for $PM_{2.5}$ and ICU admission were positive except for sepsis (Table 2), suggesting it is possible that an association exists but we failed to detect it as statistically significant. Larger studies are required to investigate this relationship further. Another possible explanation for the increased mortality without increases in

ICU admission is that $PM_{2.5}$ may exert an effect on a vulnerable cohort of ICU patients, without increasing ICU admission for other individuals. Increases in cardiovascular mortality without excess hospital admissions have been observed elsewhere [40].

The effect estimate on ICU admission and dying in ICU within 30 days was an 18% (95% CI 2.3% - 36.6%) increase per 10μg/m^3 increase in $PM_{2.5}$. This is considerably larger than observed in general population studies [8,9] and may be due to the high-risk cohort we studied. This is supported by prespecified subgroup analysis of over 65s, in whom frailty is more common, and ICU prognosis is worse [41]. In this group, larger relative risk increases were found with exposure to both PM_{10} and $PM_{2.5}$. This is consistent with other studies, which have shown the elderly to be particularly vulnerable to particulates [8,16,17].

$PM_{2.5}$ and NO_2 levels were highest in the winter months (May – August), with PM_{10} levels highest in the spring and summer (September – February), a trend observed elsewhere [42,43]. Winter is associated with increases in ICU mortality, traditionally ascribed to influenza and cold weather (both of which were controlled for in this study). Our results suggest increased $PM_{2.5}$ may also contribute. We conducted seasonal analyses to see if outcomes were affected by annual trends (e.g. summer bushfires) but did not detect significant differences.

We present relative risks per 10-unit increase in pollutant, as is standard in air pollution literature. Pollutant distributions were positively skewed, with low levels on most days ($PM_{2.5}$ 5%, 25%, 50%, 75%, 95% percentiles: 2.3μg/m^3, 4.3μg/m^3, 6.2μg/m^3, 8.8μg/m^3, 14.4μg/m^3). Toxic levels for pollutants are unknown, and harm has been observed even with low levels [44]. The unprecedented 2019-20 bushfires in eastern Australia led to very high PM levels, presenting an opportunity to assess its impact on ICU patients.

<u>Weaknesses</u>

Short-term pollutant exposure is difficult to model, with significant variation over small areas. We used background monitoring station data, with a 10km allowable distance from residential postcode, based on similar studies [45]. Individual exposure within this radius will vary with time spent outdoors, proximity to pollutant sources and accumulation or dispersion due to meteorological and topographical factors. Our study assumes subjects have been present at their residential postcode prior to admission. Additionally, postcode areas are often large and eccentrically shaped, making centroids imprecise for matching.

21% of our ICU episodes were inter-hospital transfers. As the time of admission to the antecedent hospital is not collected by the APD, transfer arrival time was used, thus exposure modelling may be inaccurate in these cases. They were included as most represent transfers from small rural bases to regional ICUs occurring within hours of presentation, but this represents a weakness in the study. In sensitivity analyses, when these hospital transfers were excluded, the association between $PM_{2.5}$ and 30-day mortality persisted, again driven by exposure on the day of admission.

APD clinical data is taken only from the first 24 hours of ICU admission, hence our study was not able to identify outcomes after this. Furthermore, only one admission diagnosis is provided, which does not reflect the complexity of most ICU admissions.

Conclusions

We observed an association between short-term $PM_{2.5}$ exposure and mortality in a large and heterogeneous intensive care population. This adds to observational evidence that exposure to particulate matter is hazardous, and that critically ill patients may have increased sensitivity to outdoor air pollution. Further studies are required to determine if the number of ICU admissions increase with higher air pollution.

(Word count, excluding abstract, figures and references = 2,739)

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Electronic Supplementary Material

Cardiovascular	101.01	Shock; cardiogenic
	101.02	Papillary muscle rupture
	102.01	Cardiac arrest with or without respiratory arrest; for respiratory arrest see Respiratory System
	103.01	Aneurysm, dissecting aortic
	104.01	Congestive heart failure
	105.01	Aneurysm/Pseudoaneurysm, other
	105.02	Thrombus, arterial
	106.01	Rhythm disturbance (primary, e.g. tachyarrhythmias, bradyarrhythymias)
	106.02	rhythm disturbance (conduction defect)
	106.03	Rhythm disturbance (atrial, supraventricular)
	106.04	Rhythm disturbance (ventricular)
	107.01	Infarction, acute myocardial (MI)
	107.02	Infarction, acute myocardial (MI), ANTERIOR
	107.03	Infarction, acute myocardial (MI), INFEROLATERAL
	107.04	Infarction, acute myocardial (MI), NON Q Wave
	107.05	Infarction, acute myocardial (MI), none of the above

	108.01	Hypertension, uncontrolled (for cerebrovascular accident see Neurological System)
	109.01	Anaphylaxis
	109.02	Angina, stable (asymptomatic or stable pattern of symptoms with meds)
	109.03	Cardiovascular medical, other
	109.04	Chest pain, atypical (non-cardiac chest pain)
	109.05	Effusion, pericardial
	109.06	Endocarditis
	109.08	Haemorrhage (for gastrointestinal bleeding see GI system, for trauma see Trauma)
	109.09	Hypovolemia (including dehydration). Do NOT include shock states
	109.10	MI admitted > 24 hr after onset of ischemia
	109.12	Pericarditis
	109.13	Tamponade, pericardial
	109.14	Thrombosis, vascular (deep vein)
	109.16	Vascular medical, other
	110.01	Cardiomyopathy
	111.01	Angina, unstable (angina interferes with quality of life or meds are tolerated poorly)
Respiratory	201.01	Pneumonia, aspiration, toxic, chemical pneumonitis
	203.01	Arrest, respiratory (without cardiac arrest)
	204.01	ARDS-adult respiratory distress syndrome, non-cardiogenic pulmonary edema
	206.01	Emphysema/Bronchitis
	207.01	Embolus, pulmonary
	208.01	Obstruction-airway (e.g. acute epiglottitis, post-extubation edema, foreign body, *etc*.)
	209.01	Asthma
	210.01	Pneumonia, fungal
	210.02	Pneumonia, parasitic (e.g. Pneumocystis pneumonia)
	211.01	Apnea, sleep
	211.02	Atelectasis
	211.03	Effusions, pleural
	211.04	Hemorrhage/Haemoptysis, pulmonary
	211.05	Hemothorax
	211.06	Hypertension-pulmonary, primary/idiopathic
	211.08	Pneumothorax
	211.09	Respiratory-medical, other
	211.10	Restrictive lung diseases (e.g. sarcoidosis, pulmonary fibrosis)
	212.01	Pneumonia, bacterial
	212.02	Pneumonia, other
	213.01	Pneumonia, viral
Stroke	403.01	CVA, Cerebrovascular accident/Stroke
Sepsis	501.01	Sepsis, cutaneous/soft tissue
	501.02	Sepsis, GI
	501.03	Sepsis, gynaecologic
	501.04	Sepsis, other
	501.05	Sepsis, pulmonary
	501.06	Sepsis, unknown
	502.01	Sepsis, renal/UTI (including bladder)
	503.01	Sepsis with shock, not urinary tract
	504.01	Sepsis with shock, urinary tract

APACHE III-J Diagnosis inclusions:

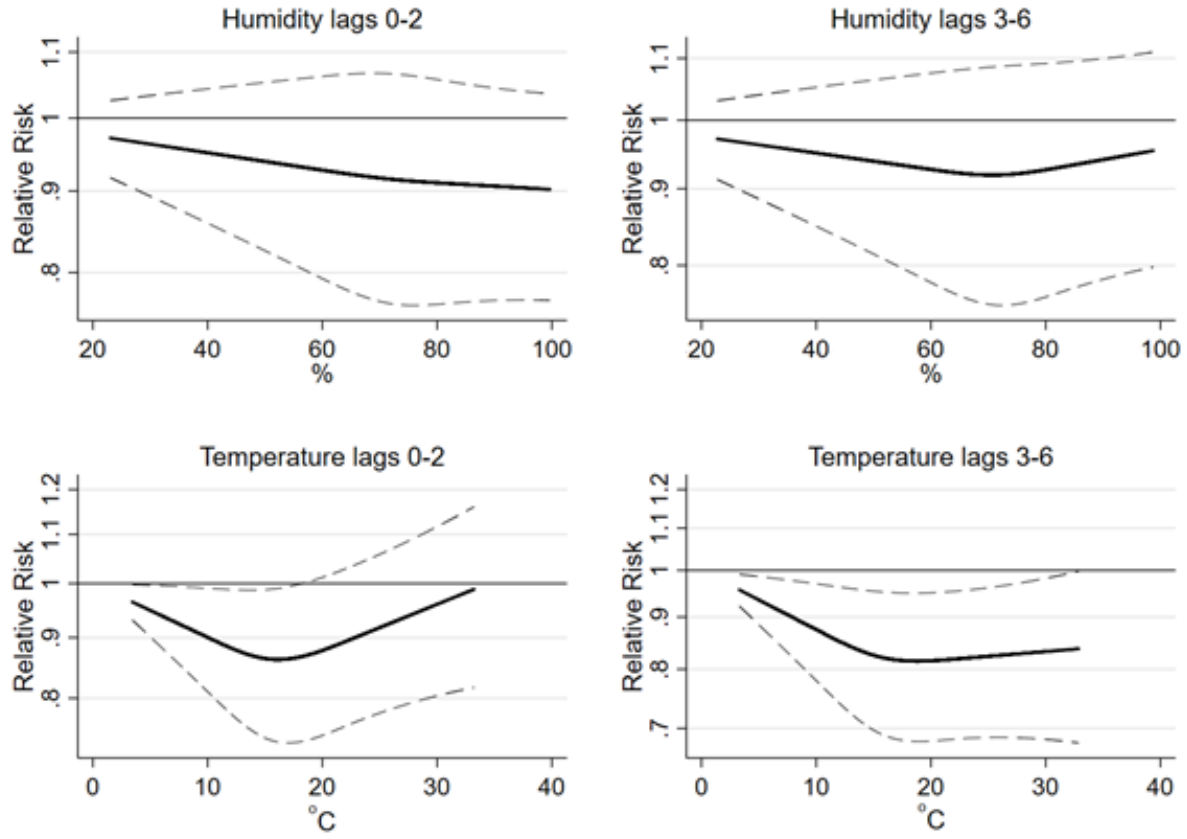
Cardiovascular	101	Cardiogenic shock
	102	Cardiac arrest
	103	Aneurysm, dissecting aortic
	104	Congestive heart failure
	105	Aneurysm/pseudoaneurysm, other Thrombus, arterial
	106	Rhythm disturbance
	107	Acute myocardial infarction
	108	Hypertension
	109	Other cardiovascular disease
	110	Cardiomyopathy
	111	Unstable angina
Respiratory	201	Pneumonia, aspiration, toxic, chemical pneumonitis
	203	Respiratory arrest
	204	Pulmonary oedema – non-cardiac
	206	Chronic obstructive pulmonary disease
	207	Pulmonary embolism
	208	Mechanical airway obstruction
	209	Asthma
	210	Parasitic pneumonia
	211	Other respiratory diseases
	212	Bacterial pneumonia
	213	Viral pneumonia
Stroke	403	Stroke
Sepsis	501	Sepsis, other than urinary
	502	Sepsis of urinary tract origin
	503	Sepsis with shock, other than urinary
	504	Sepsis of urinary tract origin with shock

APACHE II Diagnosis inclusions:

Respiratory	101	Asthma/Allergy
	102	COPD
	103	Pulmonary oedema (non-cardiogenic)
	105	Pulmonary embolus
	106	Respiratory infection
	108	Post respiratory arrest (only)
	303	Respiratory undefined (non-op)
Cardiovascular	109	Hypertension
	110	Congestive cardiac failure
	112	Coronary artery disease
	114	Post cardiac arrest (only)
	115	Cardiogenic shock
	117	Rhythm disturbance

	302	Cardiovascular undefined (non-op)
Sepsis	113	Sepsis (any aetiology)

S1. APACHE diagnostic category inclusion criteria



S2. The association between ICU admission and climate variables using 3 knot cubic splines. Dotted lines are 95% confidence intervals. Tests for improvement in fit over a simple log-linear model: top left p=0.739; top right p=0.263; bottom left p=0.009; bottom right p=0.057

	NO_2 (ppb)	$PM_{2.5}$ (µg/m^3)	PM_{10} (µg/m^3)	Temperature (◦C)	Relative Humidity (%)
Daily mean pollutant concentrations:					
No. of days (n)	1,198,528	624,775	1,265,669	1,360,010	1,354,050
Median	8	6.2	15.8	16.25	71.70
IQR	5 to 12	4.3 to 8.8	11.7 to 21.1	12.66 to 20.30	63.83 to 79.19
Within post-code means:					
No. of postcodes (N)	407	301	416	415	413
Mean	8.84	7.25	17.6	16.56	70.84
Range	1.79 – 12.94	5.85 – 9.05	12.8 - 22.7	12.97 – 20.03	62.69 – 82.42
Average within-postcode correlation coefficients:					
$PM_{2.5}$	0.349 (N=291)				
PM_{10}	0.111 (N=404)	0.694 (N=291)			
Temperature	-0.355 (N=403)	0.068 (N=300)	0.241 (N=411)		
Humidity	0.168	0.038	-0.211	-0.278	

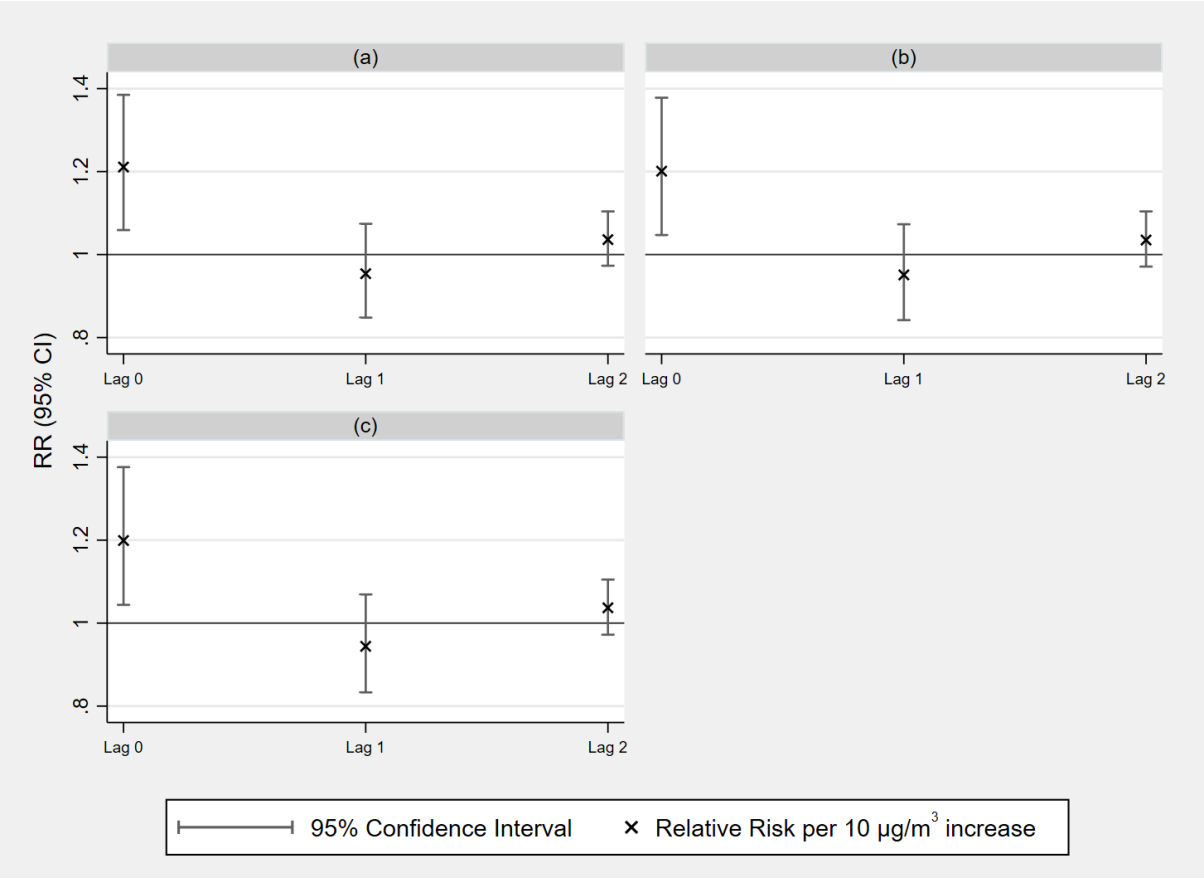
	(N=402)	(N=300)	(N=410)	(N=413)	

N=Total number of postcodes with available data (maximum: 419); n=total number of days with available data (maximum: 419x3288=1,377,672).

S3. Summary statistics based on pollutant and climate data for 2008-2016 from 419 postcodes.

	Pollutant	No. of episodes	Control days with complete data			
			1	2	3	4
Total ICU admissions	**NO_2**	36,510	890	5,369	19,714	10,537
	PM_{10}	39,039	489	4,280	21,881	12,389
	$PM_{2.5}$	18,357	620	2,995	9,821	4,921
Cardiovascular admissions	**NO_2**	10,466	231	1,490	5,662	3,083
	PM_{10}	11,162	130	1,183	6,241	3,608
	$PM_{2.5}$	4,870	146	782	2,616	1,326
Respiratory admissions	**NO_2**	15,054	364	2,189	8,141	4,360
	PM_{10}	16,114	185	1,689	9,055	5,185
	$PM_{2.5}$	7,716	262	1,230	4,114	2,110
Stroke admissions	**NO_2**	1,376	45	223	737	371
	PM_{10}	1,476	31	178	835	432
	$PM_{2.5}$	777	26	113	456	182
Sepsis admissions	**NO_2**	9,614	250	1,467	5,174	2,723
	PM_{10}	10,287	143	1,230	5,750	3,164
	$PM_{2.5}$	4,994	186	870	2,635	1,303

S4. Number of episodes available for each pollutant and admission diagnosis category



S5. The association between 30-day ICU mortality and exposure to $PM_{2.5}$ on the day of hospital admission (lag 0), one day prior (lag 1) and two days prior (lag 2). (a) Unadjusted; (b) adjusted for temperature 0-2 days and 3-6 days prior (modelled

as two natural cubic splines with 3 knots); humidity 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots), flu activity score and public holidays; (c) as in (b) with additional adjustment for sine cosine annual cycle.

	Season	NO_2		$PM_{2.5}$		PM_{10}	
		Adjusted RR[§¶] (95% CI) per 10 ppb	**Test for modifying effect P value**	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**	**Test for modifying effect P value**	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**	**Test for modifying effect P value**
All ICU admissions	**Summer**	1.016 (0.905, 1.140)	0.668	0.975 (0.845, 1.125)	0.687	0.993 (0.953, 1.036)	0.104
	Autumn	0.957 (0.868, 1.054)		0.976 (0.882, 1.080)		0.980 (0.942, 1.019)	
	Winter	0.992 (0.920, 1.070)		1.022 (0.923, 1.130)		1.025 (0.975, 1.077)	
	Spring	1.042 (0.940, 1.154)		1.034 (0.969, 1.104)		1.000 (0.991, 1.010)	
30-day ICU mortality	**Summer**	0.935 (0.681, 1.285)	0.924	1.261 (0.840, 1.892)	0.372	1.026 (0.918, 1.148)	0.945
	Autumn	0.913 (0.706, 1.180)		1.262 (0.967, 1.648)		1.019 (0.918, 1.131)	
	Winter	1.000 (0.816, 1.226)		1.138 (0.852, 1.521)		1.084 (0.946, 1.243)	
	Spring	1.200 (0.905, 1.589)		1.168 (0.888, 1.538)		1.025 (0.985, 1.067)	

[§] Relative risks based on an unconstrained distributed lag model lags 0-2 days prior

[¶]Adjusted for temperature 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots); humidity 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots), flu activity score and public holidays.

S6. The effect of season on pollution and ICU admission and 30-day ICU mortality. Summer: December – March, Autumn: April – May, Winter: June – August, Spring: September – November.

	NO_2		$PM_{2.5}$		PM_{10}	
	No. cases	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**	**No. cases**	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**	**No. cases**	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**
Admissions (total)	36,510	0.987 (0.939, 1.037)	18,357	1.014 (0.967, 1.062)	39,039	1.001 (0.992, 1.010)
Respiratory	15,054	0.961 (0.889, 1.039)	7,716	1.026 (0.958, 1.098)	16,114	1.003 (0.992, 1.015)
Cardiovascular	10,466	1.015 (0.926, 1.111)	4,870	1.046 (0.949, 1.152)	11,162	1.000 (0.979, 1.021)
Stroke	1,376	1.154 (0.890, 1.495)	777	1.268 (0.960, 1.676)	1,476	1.012 (0.898, 1.142)
Sepsis	9,614	0.975 (0.886, 1.073)	4,994	0.903 (0.815, 1.001)	10,287	0.982 (0.954, 1.012)
30-day ICU mortality	4,843	0.985 (0.861, 1.126)	2,332	1.172* (1.014, 1.356)	5,178	1.027 (0.992, 1.064)
Acute renal failure	3,681	0.900 (0.773, 1.047)	1,798	1.002 (0.875, 1.147)	3,917	0.979 (0.937, 1.022)
Invasive ventilation within 24 hours of admission	12,445	0.969 (0.892, 1.052)	6,057	1.043 (0.961, 1.132)	13,262	0.997 (0.978, 1.016)

[§] Relative risks based on an unconstrained distributed lag model lags 0-2 days prior in the pollutant of interest.

[¶] Adjusted for temperature 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots); humidity 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots), flu activity score, public holidays and a sine cosine annual cycle.

All P values>=0.05 except: *p=0.032

S7. Sensitivity analysis: Investigating the association between ICU admission categorised by admission diagnosis, and admission with adverse outcome after additional adjustment for seasonality with a sine cosine annual cycle.

	NO_2		$PM_{2.5}$		PM_{10}	
	No. cases	**Adjusted RR[§¶] (95% CI) per 10 ppb**	**No. cases**	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**	**No. cases**	**Adjusted RR[§¶] (95% CI) per 10 µg/m³**
Admissions (total)	28,840	0.983 (0.930,1.038)	14,547	0.969 (0.913,1.028)	30,968	0.995 (0.984,1.006)
Respiratory	11,891	0.953 (0.874,1.040)	6,170	1.015 (0.929,1.108)	12,805	1.001 (0.987, 1.015)
Cardiovascular	8,278	1.020 (0.922,1.128)	3,798	0.964 (0.855, 1.087)	8,851	0.988 (0.962, 1.015)
Stroke	1,141	1.141 (0.862, 1.509)	659	1.337 (0.978, 1.828)	1,228	1.023 (0.895, 1.169)
Sepsis	7,530	0.965 (0.867, 1.075)	3,920	0.861* (0.762, 0.973)	8,084	0.972 (0.937, 1.009)
30-day ICU mortality	3,788	0.980 (0.844, 1.138)	1,740	1.192* (1.011, 1.406)	4,070	1.025 (0.973, 1.081)
Acute renal failure†	2,565	0.925 (0.774, 1.105)	1,089	0.951 (0.782,1.156)	2,738	0.942 (0.879, 1.009)
Invasive ventilation within 24 hours of admission	9,085	0.986 (0.897, 1.085)	4,131	0.957 (0.859,1.066)	9,710	0.984 (0.959, 1.011)

All P values >0.05 except: * p≤0.037

§ Relative risks based on an unconstrained distributed lag model lags 0-2 days prior in the pollutant of interest.

¶ Adjusted for temperature 0-2 days and 3-6 days (modelled as two natural cubic splines with 3 knots); humidity 0-2 days and 3-6 days prior (modelled as two natural cubic splines with 3 knots), flu activity score and public holidays.

† Creatinine >133µmol/L and first 24-hour urine output < 410ml

S8. Sensitivity analysis: relative risks of ICU admission and ICU admission with adverse outcome with inter-hospital transfers removed

Albury Wodonga Health ICU, Alfred Hospital ICU, Austin Hospital ICU, Ballarat Health Services ICU, Bankstown-Lidcombe Hospital ICU, Bathurst Base Hospital ICU, Bendigo Health Care Group ICU, Blacktown Hospital ICU, Box Hill Hospital ICU, Cabrini Hospital ICU, Calvary Mater Newcastle ICU, Campbelltown Hospital ICU, Central Gippsland Health Service (Sale) ICU, Coffs Harbour Health Campus ICU, Concord Hospital (Sydney) ICU, Dandenong Hospital ICU, Epworth Eastern Private Hospital ICU, Epworth Freemasons Hospital ICU, Epworth Hospital (Richmond) ICU, Figtree Private Hospital ICU, Footscray Hospital ICU, Frankston Hospital ICU, Gosford Hospital ICU, Gosford Private Hospital ICU, Goulburn Base Hospital ICU, Goulburn Valley Health ICU, Grafton Base Hospital ICU, Griffith Base Hospital ICU, Hornsby Ku-ring-gai Hospital ICU, John Fawkner Hospital ICU, John Hunter Hospital ICU, Kareena Private Hospital ICU, Knox Private Hospital ICU, Latrobe Regional Hospital ICU, Lismore Base Hospital ICU, Liverpool Hospital ICU, Macquarie University Private Hospital ICU, Manly Hospital & Community Health ICU, Manning Rural Referral Hospital ICU, Maroondah Hospital ICU, Mater Private Hospital (Sydney) ICU, Melbourne Private Hospital ICU, Mildura Base Hospital ICU, Monash Medical Centre-Clayton Campus ICU, Mulgrave Private Hospital ICU, Nepean Hospital ICU, Newcastle Private Hospital ICU, North Shore Private Hospital ICU, Northeast Health Wangaratta ICU, Norwest Private Hospital ICU, Orange Base Hospital ICU, Peninsula Private Hospital ICU, Peter MacCallum Cancer Institute ICU, Port Macquarie Base Hospital ICU, Prince of Wales Hospital Sydney) ICU, Prince of Wales Private Hospital (Sydney) ICU, Royal Melbourne Hospital ICU, Royal Prince Alfred Hospital ICU, Shoalhaven Hospital ICU, South West Healthcare (Warrnambool) ICU, St George Hospital (Sydney) CICU, St George Hospital (Sydney) ICU, St George Hospital (Sydney) ICU2, St George Private Hospital (Sydney) ICU, St John of God Hospital (Bendigo) ICU, St John Of God Hospital (Geelong) ICU, St Vincent's Hospital (Melbourne) ICU, St Vincent's Hospital (Sydney) ICU, St Vincent's Private Hospital (Sydney) ICU, St Vincent's Private Hospital Fitzroy ICU, Sunshine Hospital ICU, Sutherland Hospital & Community Health Services ICU, Sydney Adventist Hospital ICU, Sydney Southwest Private Hospital ICU, Tamworth Base Hospital ICU, The Northern Hospital ICU, Tweed Heads District Hospital ICU, University Hospital Geelong ICU, Wagga Wagga Base Hospital & District Health ICU, Warringal Private Hospital ICU, Western District Health Service (Hamilton) ICU, Westmead Hospital ICU, Westmead Private Hospital ICU, Wimmera Health Care Group (Horsham) ICU, Wollongong Hospital ICU, Wollongong Private Hospital ICU, Wyong Hospital ICU

S9. Contributing sites

PM10 was measured using a Tapered Element Oscillating Microbalance (TEOM). PM2.5 was measured using Beta Attenuation Monitoring (BAM).