Environment International 121 (2018) 415–420

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Long-term exposure to low concentrations of air pollutants and hospitalisation for respiratory diseases: A prospective cohort study in Australia

Farhad Salimi[a,b,c], Geoffrey Morgan[a,c,*], Margaret Rolfe[a], Evangelia Samoli[d], Christine T. Cowie[c,e,f], Ivan Hanigan[a,c,g], Luke Knibbs[c,h], Martin Cope[c,i], Fay H. Johnston[b,c], Yuming Guo[c,j], Guy B. Marks[c,e,f], Jane Heyworth[c,k], Bin Jalaludin[c,l]

[a] University Centre for Rural Health – North Coast, School of Public Health, University of Sydney, Australia
[b] Menzies Institute for Medical Research, University of Tasmania, Australia
[c] Centre for Air Pollution, Energy and Health, Glebe, NSW 2037, Australia
[d] Department of Hygiene and Epidemiology, University of Athens Medical School, Greece
[e] South West Sydney Clinical School, University of New South Wales, Sydney, Australia
[f] Woolcock Institute of Medical Research, University of Sydney, Australia
[g] Centre for Research and Action in Public Health, University of Canberra, Australia
[h] School of Public Health, The University of Queensland, Australia
[i] CSIRO Oceans & Atmosphere, PMB1, Aspendale, VIC, Australia
[j] Department of Epidemiology and Preventive Medicine, Monash University, Australia
[k] School of Population and Global Health, The University of Western Australia, Australia
[l] School of Public Health and Community Medicine and Ingham, Institute for Applied Medical Research, University of New South Wales, Australia

ARTICLE INFO

Handling Editor: Xavier Querol

Keywords:
Air pollution
Particulate matter
Hospitalisation
Respiratory
Low concentration
Cohort study

ABSTRACT

Background: Short- and long-term spatiotemporal variation in exposure to air pollution is associated with respiratory morbidity in areas with moderate-to-high level of air pollution, but very few studies have examined whether these associations also exist in areas with low level exposure.

Objectives: We assessed the association between spatial variation in long-term exposure to $PM_{2.5}$ and NO_2 and hospitalisation for all respiratory diseases, asthma, chronic obstructive pulmonary disease (COPD), and pneumonia, in older adults residing in Sydney, Australia, a city with low-level concentrations.

Methods: We recorded data on hospitalisations for 100,084 participants, who were aged > 45 years at entry in 2006–2009 until June 2014. Annual NO_2 and $PM_{2.5}$ concentrations were estimated for the participants' residential addresses and Cox proportional hazards regression was used to model the association between exposure to air pollutants and first episode of hospitalisation, controlling for personal and area level covariates. We further investigated the shape of the exposure-response association and potential effect modification by age, sex, education level, smoking status, and BMI.

Results: NO_2 and $PM_{2.5}$ annual mean exposure estimates were 17.5 $\mu g \cdot m^{-3}$ and 4.5 $\mu g \cdot m^{-3}$ respectively. NO_2 and $PM_{2.5}$ was positively, although not significantly, associated with asthma. The adjusted hazard ratio for a 1 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ was 1.08, 95% confidence interval 0.89–1.30. The adjusted hazard ratio for a 5 $\mu g \cdot m^{-3}$ increase in NO_2 was 1.03, 95% confidence interval 0.88–1.19. We found no positive statistically significant associations with hospitalisation for all respiratory diseases, and pneumonia while negative associations were observed with COPD.

Conclusions: We found weak positive associations of exposure to air pollution with hospitalisation for asthma while there was no evidence of an association for all respiratory diseases.

* Corresponding author.
E-mail address: Geoff.Morgan@sydney.edu.au (G. Morgan).

https://doi.org/10.1016/j.envint.2018.08.050
Received 17 April 2018; Received in revised form 13 August 2018; Accepted 23 August 2018
Available online 25 September 2018

1. Introduction

Epidemiological studies consistently find associations between short-term temporal variation and long-term spatial variation in exposure to air pollution and mortality or morbidity (WHO 2013). Globally, ambient particulate matter pollution was the fifth-ranking risk factor for premature death in 2015. Exposure to particulate matter (PM) with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) was estimated to cause 4.2 million premature deaths representing 7.6% of total global premature deaths (Cohen et al. 2017).

Over the last decades, ambient air pollutant concentrations have decreased significantly in developed countries (Brauer et al. 2016). Nevertheless, an epidemiological study found adverse health effects of exposure to air pollution at levels well below current WHO air pollution standards (Crouse et al. 2012). To date, due to the very limited number of epidemiological studies of long term exposure to air pollution at low concentrations, little evidence is available on whether there is any specific threshold below which the adverse health effects of air pollution do not occur (Burnett et al. 2014). In order to inform future risk assessments and regulation, it is important to know whether adverse effects continue to be observed at lower concentrations of air pollution.

The prevalence of respiratory diseases has significantly increased worldwide (Eder et al. 2006; Gibson et al. 2010; Murray et al. 2013; Sunyer 2001). In adults, tobacco smoking is established as the main risk factor, however, the increasing prevalence of respiratory diseases suggests a possible role of environmental factors such as air pollution (Eder et al. 2006; Kim et al. 2015; Sunyer 2001; WHO 2013). Exposure to air pollution has adverse acute respiratory effects (Künzli et al. 2010), including short-term decreases in lung function, respiratory symptoms, and increases in hospitalisation and death due to respiratory causes (Brunekreef and Holgate 2002; Zanobetti et al. 2008). The extent to which long-term exposure to air pollution contributes to respiratory disease is less clear (Schikowski et al. 2014b).

A cross-sectional European study of around 650,000 participants aged ≥20 years (Cai et al. 2017) found that 10 $\mu g \cdot m^{-3}$ increases in nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameter < 10 μm (PM_{10}) were associated with 1.9 and 2.8% higher lifetime asthma prevalence respectively. Previous cohort studies have found associations between long-term exposure to air pollution with first hospitalisation, self-reported diagnosis/symptoms, development and persistence of asthma and chronic obstructive pulmonary disease (COPD) in Europe, US, and Australia (Andersen et al. 2011; Andersen et al. 2012; Bowatte et al. 2018; Fisher et al. 2016; Jacquemin et al. 2015; Young et al. 2014), while others did not observe any associations (Atkinson et al. 2015; Schikowski et al. 2014a; Weichenthal et al. 2017).

As summarised above, several studies have studied the associations between exposure to air pollution and respiratory diseases, however, evidence on the effects of long-term exposure to air pollution on respiratory health is inconsistent. Furthermore, most of these studies have been conducted in areas with relatively high levels of air pollution, with mean annual $PM_{2.5}$ concentrations > 10 $\mu g \cdot m^{-3}$, while annual average $PM_{2.5}$ in Sydney, Australia's largest city, was around 5.5 $\mu g \cdot m^{-3}$ in 2011 (source: New South Wales Government air pollution data).

Despite the need for studies of exposure-response relationships at lower pollutant concentrations, to our knowledge, there have been very few studies conducted on the long-term effects of exposure to low-levels of air pollution on respiratory morbidity. To address this gap in knowledge we investigated the associations between long-term exposure to low levels of air pollution and hospitalisation for respiratory diseases in an Australian cohort of adults over 45 years of age.

2. Methods

2.1. Design and health outcome

We obtained data on 266,969 adults aged above 45 years and over, living in the state of New South Wales (NSW), who were recruited to the Sax Institute's 45 and Up Study. The prospective participants were sampled from the Department of Human Services enrolment database. Each participant joined the study by completing a questionnaire at baseline (2006–2009) and giving signed consent for follow-up and linkage of their information to routine health databases. Questionnaire included information on demographic and social characteristics, personal health behaviours, and general health-related data (45 and Up Study Collaborators 2008). The data were linked by the Centre for Health Record Linkage to hospitalisation data (NSW Admitted Patient Data Collection) and mortality data (NSW Registry of Births Deaths and Marriages (RBMD)). Study participants for this analysis comprised participants who resided in a 100 km × 100 km grid centred on Sydney Airport (Sydney Metropolitan Region), due to availability of pollutant exposure estimates, resulting in a sample size of 99,317 participants. 45 and Up Study has ethical approval from the University of NSW Human Research Ethics Committee (HREC) and we have also obtained ethical approval from University of Sydney HREC for this study.

Only unscheduled hospitalisations were included in the analyses. Primary diagnosis was used to identify hospitalisation for all respiratory diseases (International Classification of Diseases, 10th revision (ICD-10): J00–J99 excluding J95.4 to J95.9, R09.1, R09.8), asthma (ICD-10: J45–J46), COPD (ICD-10: J40–J44), and pneumonia (ICD-10: J12–J18). Participants with a record of hospitalisation for the same diagnosis before the baseline were removed from the primary analysis. The first hospitalisation between baseline and 30 June 2014 was defined as the main outcome.

2.2. Exposure assessment

Ambient concentrations of NO_2 were estimated using a validated satellite-based land use regression (LUR) model that has been described in detail elsewhere (Knibbs et al. 2014; Knibbs et al. 2016). Briefly, the satellite-based LUR uses satellite observations of NO_2 and land-use variables to predict the annual average NO_2. This model explained around 80% (RMSE = 1.4 ppb) of spatial variation in annual ambient NO_2 concentrations during 2006–2011.We used this model to estimate annual average NO_2 concentration at mesh blocks across Sydney in 2007. Mesh blocks are the smallest geographical area defined by Australian Bureau of Statistics and contains around 30–60 dwellings. Participants' exposure to annual average NO_2 in 2007 was calculated at the mesh block centroid closest to their residential addresses.

Ambient $PM_{2.5}$ concentrations were estimated using a chemical transport model blended with fixed site monitor data (Physick et al. 2007). Using elliptical influence functions, this model blends computed air pollutant fields from a meteorological and air quality model with observations from the air quality network. This model estimated the 07/2010–07/2011 annual average $PM_{2.5}$ concentrations across Sydney at 1 km^2 resolution and has been described elsewhere (Broome et al. 2016). Estimated $PM_{2.5}$ and NO_2 concentrations were assumed to reflect the concentrations at baseline.

2.3. Statistical analyses

Cox proportional hazards models were used to assess the association between exposure to NO_2 and $PM_{2.5}$ and first hospitalisation for respiratory disease. Age was treated as underlying time and was left truncated at the age at recruitment and right censored at the first admission post recruitment, death or end of follow-up (30 June 2014), whichever came first. Following an approach similar to the ESCAPE study (Beelen et al. 2014), the effects of exposure to NO_2 and $PM_{2.5}$

were adjusted for defined confounders, determined a priori, in three steps: Model 1) age (underlying time in years), sex and year of enrolment (continuous in years); Model 2) Model 1 plus adjustment for marital status (categorical variable: married/partnered or single/divorced/widowed), education (categorical variable: below high school, high school or university), employment status (categorical variable: employed or unemployed/retired), smoking status (categorical variable: current, previous or non-smoker), smoking duration (for current/past smokers in years), smoking intensity (for current smokers in cigs/day) and body mass index (BMI) (categorical variable: underweight (BMI $< 18.5\,kg/m^2$), normal ($18.5\,kg/m^2 <$ BMI $< 25\,kg/m^2$), overweight ($25\,kg/m^2 <$ BMI $< 30\,kg/m^2$), obese (BMI $> 30\,kg/m^2$); Model 3 (Main model) Model 2 plus further adjustment for area level socioeconomic status (SES) indicator. All models (1–3) were performed using the dataset with no missing covariates in model 3.

We used the Index of Relative Socioeconomic Disadvantage (IRSD) from the 2006 Census as the measure of area level SES. This index summarises a range of information (e.g. income, education, and unemployment) for individuals and households within a Census Collection District (CCD), the smallest geographical spatial unit, with on average 220 dwellings in urban areas (ABS 2006). Low score indicates relatively greater disadvantage (ABS 2008). We ranked the IRSD score in Sydney Metropolitan Region and grouped these into quartiles where category 1 (lower SES) is the most disadvantaged and category 4 (higher SES) is the least disadvantaged.

All models were tested for proportional hazard assumptions. To allow comparison across pollutants and ease of comparison with other studies, the effects of exposure to $PM_{2.5}$ and NO_2 were estimated for either 1, 5, or $10\,\mu g{\cdot}m^{-3}$ changes in each pollutant, whichever was closest to the interquartile range (IQR). When the model 3 (main model) results suggested an association with air pollution we further examined the exposure-response relation using splines and threshold modelling. A 3rd degree penalised p-spline (Eilers and Marx 1996) was used to estimate non-linear associations. Optimal number of degrees of freedom for the splines was chosen based on corrected Akaike Information Criterion (AIC) (Hurvich et al. 1998). Significance of non-linear trends was assessed by the likelihood ratio test. Model 3 s were also developed with $PM_{2.5}$ and NO_2 effect assumed null below certain threshold levels. Thresholds ranged from $1\,\mu g{\cdot}m^{-3}$ and increased by a step of $1\,\mu g{\cdot}m^{-3}$ to the 90th percentile. Performances of threshold models were assessed by any decrease in the AIC and Bayesian Information Criterion (BIC). Potential effect modification by age group (< 60 years, 60–74 years, > 75 years), sex, education level, smoking status, and BMI category was evaluated by introducing interaction term in the main model. These covariates have been identified as potential effect modifiers (Beelen et al. 2014; Stafoggia et al. 2014).

We also applied several sensitivity analyses to test the robustness of our effect estimates 1) Model 3 was further adjusted for additional covariates including physical activity and alcohol consumption; 2) as participants residing in the same area may share similar characteristics and exposure to similar environmental conditions, we applied multilevel random effects (frailty) models to account for the potential spatial correlation. Random effects in our models were represented by one level of spatial cluster defined by Statistical Area Level 2 (SA2). SA2s have an average population of about 10,000 persons; 3) we also applied frailty models by including area level SES as a random effect; 4) since some individuals may have repeat admissions, we included multiple admissions for individuals in a negative binomial regression model with each person-year at risk as the denominator; 5) participants with a record of hospitalisation for the same diagnosis before the baseline were included in the analysis; 6) since COPD is sometimes misdiagnosed as asthma and vice versa, we combined these two outcomes in the analysis; 6) participants with a self-reported asthma diagnosis at baseline were analysed separately. Covariates of the model 3 were included in all the sensitivity models.

The results are presented as Hazard Ratios (HRs) with 95% confidence intervals (CIs) per 1 and $5\,\mu g{\cdot}m^{-3}$ increase in NO_2 and $PM_{2.5}$ concentrations, respectively, using Survival package version 2.38–1 in R version 3.2.0.

Table 1
Number of hospitalisations pre- and post-baseline for different respiratory outcomes, 45 and Up cohort.

Outcome	Pre-baseline hospitalisation	First post-baseline hospitalisation
All respiratory diseases	2162	3530
Asthma	900	218
COPD	467	748
Pneumonia	940	1762

3. Results

Of the 99,317 cohort participants who resided in the Sydney Metropolitan Region, 12,870 were excluded due to missing information on covariates and/or exposure estimates and 2162 had an admission for respiratory diseases before baseline. Of the 84,285 (85%) remaining participants, 3530 were hospitalised for the first time post-baseline for respiratory diseases (Table 1).

Average pollutant concentrations were $17.5\,\mu g{\cdot}m^{-3}$ for NO_2 and $4.5\,\mu g{\cdot}m^{-3}$ for $PM_{2.5}$ (Table 2). Areas with a lower SES were associated with higher concentrations for both NO_2 and $PM_{2.5}$. Annual concentrations of $PM_{2.5}$ were strongly correlated with NO_2 ($r = 0.8$).

The prevalence of hospitalisation on one or more occasions during the study period due to respiratory diseases increased with age and with decreasing area-level and individual SES characteristics (Table 3). It was greater in men than women and in underweight and obese individuals, compared with normal weight individuals.

The associations between 1 and $5\,\mu g{\cdot}m^{-3}$ increase in $PM_{2.5}$ and NO_2 concentrations, respectively, and time to first hospitalisations are shown in Table 4. All models satisfied the proportional hazards assumption test. Exposure to $PM_{2.5}$ and NO_2 displayed positive but not statistically significant associations with hospitalisation for asthma (HRs and 95% CIs: 1.10 (0.89–1.37), and 1.03 (0.88–1.19) for $PM_{2.5}$ and NO_2, respectively). Exposure to $PM_{2.5}$ and NO_2 was negatively associated with hospitalisation for COPD (HRs and 95% CIs: 0.89 (0.79–1.01), and 0.90 (0.82–0.98) for $PM_{2.5}$ and NO_2, respectively). No associations were observed for all respiratory diseases and pneumonia. Inclusion of area level SES in all the models attenuated the estimated HRs.

Application of the frailty models as well as negative binomial model did not significantly alter the effect estimates (Table S1, 4 and7).

Table 2
Summary of assigned NO_2 (2007) and $PM_{2.5}$ (2010 − 11) concentrations estimated in 2007 and 2010–2011, respectively, at enrolment for the 45 and Up study participants residing in the Sydney Metropolitan Region.

	$PM_{2.5}$ ($\mu g{\cdot}m^{-3}$)	NO_2 ($\mu g{\cdot}m^{-3}$)
Mean (SD)	4.5 (0.6)	17.5 (4.7)
Median (IQR)	4.5 (0.8)	17.0 (5.9)
Minimum	2.8	8.3
Maximum	13.8	71.2
Pollution levels by quartiles of SES		
Mean (SD)		
1 (most disadvantaged)	4.6 (0.6)	18.3 (4.4)
2	4.5 (0.7)	17.5 (4.9)
3	4.4 (0.6)	17.7 (5.1)
4 (least disadvantaged)	4.4 (0.4)	16.6 (4.0)
Test for pollutant trend[a]	$p < 0.001$	$p < 0.001$
Correlation[b] between pollutants		
NO_2	0.81	–

[a] Analysis of variance.
[b] Spearman's rank correlation coefficient.

Table 3
Sample characteristics and hospitalisation percentages of asthma by sex, age, smoking status, education, employment status, BMI category and socio-economic status indicator.

Covariate	Category	Total (N (%)) 84,285	Hospitalisation on one or more occasions during the study period for any respiratory diseases (N (%)) 3530 (4.2%)
Sex	Male	40,276 (47.8%)	1988 (4.9%)
	Female	44,009 (52.2%)	1542 (3.5%)
Age-groups (years)	45–54	27,061 (32.1%)	303 (1.1%)
	55–64	27,168 (32.2%)	587 (2.2%)
	65–74	15,341 (18.2%)	745 (4.9%)
	75–84	11,794 (14.0%)	1352 (11.5%)
	> 85	32,918 (3.5%)	543 (18.6%)
Smoking	Current	5138 (6.1%)	280 (5.4%)
	Previous	27,370 (32.5%)	1455 (5.3%)
	Never	51,777 (61.4%)	1795 (3.5%)
Education	Below high school	22,294 (26.5%)	1446 (6.5%)
	High school	35,134 (41.7%)	1411 (4.0%)
	University	26,857 (31.9%)	673 (2.5%)
Employment status	Unemployed/ retired	44,333 (53.3%)	2936 (6.6%)
	Employed	39,952 (46.7%)	594 (1.5%)
Marital status	Single	21,460 (25.5%)	1304 (6.1%)
	Married	62,852 (74.5%)	2226 (3.5%)
BMI	Underweight	1186 (1.4%)	118 (9.9%)
	Normal	34,054(40.4%)	1418 (4.2%)
	Overweight	32,595(38.7%)	1280 (3.9%)
	Obese	16,450 (19.5%)	714 (4.3%)
Area level SES	1 (lowest SES)	20,902(24.8%)	1238 (5.9%)
	2	21,028 (24.9%)	894 (4.3%)
	3	21,133 (25.1%)	760 (3.6%)
	4 (highest SES)	21,222 (25.2%)	638 (3.0%)

The associations were slightly more positive for all outcomes when we included the subjects with previous hospitalisations (Table S2), and more positive associations were observed when we limited the analyses to individuals with prior asthma hospitalisation (Table S3) which showed borderline statistical significance for the association of exposure to NO_2 and hospitalisation for asthma (HR's and 95% CI's: 1.42 (1.00–2.02)). Associations with COPD was no longer negative when we limited the analyses to individuals with prior COPD hospitalisation (HRs and 95% CIs: 1.12 (0.89–1.42), and 1.10 (0.93–1.29) for $PM_{2.5}$ and NO_2, respectively).

None of the interaction terms were statistically significant. The nonlinear associations of the exposure-response relationship modelled by a 3rd degree p-spline with 2 degrees of freedom were not statistically different from linear model. None of the threshold models were materially different from the linear model.

4. Discussion

This is one of the few studies that assesses the effects of long-term exposure to $PM_{2.5}$ and NO_2 on hospital admission for different respiratory diseases at low-level concentrations. We found positive associations for asthma while no such associations were found for all respiratory diseases, COPD and pneumonia.

The observed associations of NO_2 exposure and asthma hospitalisation are generally in agreement with a study conducted in Denmark with similar NO_2 levels (Andersen et al. 2012). Similar to Andersen et al. (2012), we found higher effects of exposure to air pollution on asthma hospitalisation for subjects with prior asthma hospitalisation, compared with those without history of asthma hospitalisation before baseline. This indicates that air pollution probably affects individual with severe asthma (as defined by a previous hospitalisation) to a greater extent compared to people with less severe asthma.

A US study assessed the associations between long-term exposure to $PM_{2.5}$ and self-reported asthma diagnosis (Young et al. 2014) and reported an odds ratio (OR) of 1.20 (95% CI: 0.99–1.46) per an IQR increase ($3.6\,\mu g{\cdot}m^{-3}$) in $PM_{2.5}$. A multi-cohort prospective study (Jacquemin et al. 2015) found a non-significant positive association between $PM_{2.5}$ and adult-onset asthma (OR and 95% CI per $5\,\mu g.m^{-3}$ = 1.04 (0.93–1.30)). The magnitude of the associations with $PM_{2.5}$ we found in Sydney (HR = 1.10 per $1\,\mu g{\cdot}m^{-3}$) with generally lower $PM_{2.5}$ concentration (median annual average $PM_{2.5} = 4.5\,\mu g.m^{-3}$) was substantially higher than the magnitude found in the US study (OR = 1.20 per $3.6\,\mu g{\cdot}m^{-3}$) and multi-cohort European study (OR = 1.04 per $5\,\mu g{\cdot}m^{-3}$).

In our study, mean pollutant concentrations were $17.5\,\mu g.m^{-3}$ for NO_2 and $4.5\,\mu g{\cdot}m^{-3}$ for $PM_{2.5}$. The median $PM_{2.5}$ concentration in the US study (Young et al. 2014) was $10.8\,\mu g{\cdot}m^{-3}$ and in the European multi-cohort study (Jacquemin et al. 2015), the cohort with the lowest exposure levels had mean concentrations of $22\,\mu g{\cdot}m^{-3}$ for NO_2 and $10\,\mu g{\cdot}m^{-3}$ for $PM_{2.5}$.

Neupane et al. (2010) found positive associations between exposure to air pollution and hospitalisation for pneumonia, while we did not find such associations in our study. In contrast to a Danish study (Andersen et al. 2011) where they found positive associations between exposure to air pollution and COPD hospitalisation, we found negative associations which were statistically significant for NO_2. These inconsistent results could be due to higher NO_2 mean concentrations in the study by Neupane et al. (2010) (~$30\,\mu g{\cdot}m^{-3}$ vs $17.5\,\mu g{\cdot}m^{-3}$) and longer follow up period in the study by Andersen et al. (2011) (~13 years vs ~7 years).

Our results provide some evidence of the effects of exposure to

Table 4
Hazard Ratios and 95% Confidence Intervals from Cox Proportional Hazards Models with increasing covariate adjustment for the association between an IQR increase in $PM_{2.5}$/NO2 and hospitalisation for respiratory diseases.

Outcome	Pollutant	Hazard ratios and 95% confidence intervals		
		Model 1	Model 2	Model 3
All respiratory diseases	$PM_{2.5}$ ($\mu g{\cdot}m^{-3}$)	1.04 (0.98–1.10)	1.02 (0.96–1.08)	0.98 (0.92–1.04)
	NO_2 ($\mu g{\cdot}m^{-3}$)	1.01 (0.98–1.05)	1.01 (0.97–1.04)	0.99 (0.95–1.03)
Asthma	$PM_{2.5}$ ($\mu g{\cdot}m^{-3}$)	1.16 (0.94–1.44)	1.15 (0.93–1.42)	1.10 (0.89–1.37)
	NO_2 ($\mu g{\cdot}m^{-3}$)	1.04 (0.90–1.20)	1.05 (0.91–1.22)	1.03 (0.88–1.19)
COPD	$PM_{2.5}$ ($\mu g{\cdot}m^{-3}$)	1.01 (0.89–1.15)	0.94 (0.83–1.06)	0.89 (0.79–1.01)
	NO_2 ($\mu g{\cdot}m^{-3}$)	0.96 (0.88–1.04)	0.91 (0.84–0.99)	0.90 (0.82–0.98)
Pneumonia	$PM_{2.5}$ ($\mu g{\cdot}m^{-3}$)	1.00 (0.92–1.09)	0.99 (0.91–1.07)	0.96 (0.88–1.05)
	NO_2 ($\mu g{\cdot}m^{-3}$)	0.99 (0.94–1.05)	0.99 (0.93–1.04)	0.97 (0.92–1.03)

Hazard ratios are for 1 and $5\,\mu g{\cdot}m^{-3}$ changes in $PM_{2.5}$ and NO_2 levels, respectively.
Model 1: adjusted for age (time variable), year of enrolment and sex.
Model 2: model 1 plus marital status, education, employment status, and smoking status/during/intensity, and BMI.
Model 3: model2 plus area level socio-economic status.

$PM_{2.5}$ and asthma in lower concentrations. This highlights that more studies in countries and regions with low-level concentrations should be conducted in order to further our understanding of the effects of air pollution at low levels. In addition, our study would help future estimations in the Global Burden of Disease (GBD) study as asthma will be considered in future updates of GBD estimates (Cohen et al. 2017).

Particulate matter can trigger inflammation and induce oxidative stress (Hogg and Van Eeden 2009). Exposure to particulate matter can cause bronchial inflammatory changes and increased airway resistance (McCreanor et al. 2007; Salvi et al. 2000). Part of these observed physiological effects of exposure to particulate matter could perhaps be short-term, therefore, some asthma hospitalisation observed in our study could possibly be attributed to the increases of particulate matter in the days before the admission. Understanding and discerning short-term exposure effects from long-term exposure effects of air pollution can help to form a better understanding of the underlying mechanisms. Therefore, cohort studies analysing simultaneously health effects due to long-term and short-term exposure to air pollution need to be conducted. We plan to analyse simultaneously long-term and short-term health effects of exposure to air pollution in future studies. One recent time series study examined the joint effects of short and long term exposure to air pollution (Yitshak-Sade et al. 2018), but to our knowledge, this approach has not yet been implemented in cohort studies.

It is known that SES is associated with many health outcomes (Adler and Stewart 2010), in addition, individual and area level SES have both been found to be associated with air pollution concentrations (Hajat et al. 2013). In recent studies such as ESCAPE, it has been a common approach to adjust for area level SES due to potential residual confounding. Therefore, we also included the area level SES in our analyses. We found that this extra adjustment attenuated the HRs estimates. Lower estimates resulted in models including area level SES (HR = 1.10 and 1.03 for $PM_{2.5}$ and NO_2, respectively) compared to the ones without (HR = 1.15 and 1.05 for $PM_{2.5}$ and NO_2, respectively). Similar attenuating effects of area level SES inclusion have been observed in other studies (Atkinson et al. 2013; Cesaroni et al. 2014). We found that increasing area level SES was associated with lower levels of air pollution, therefore, there is a possibility that the adjustment for area level SES is removing effects of air pollution. Attenuating effects of area level SES were more pronounced in studies where a composite measure of socioeconomic status was used (Atkinson et al. 2015) compared with studies in which a single measure of area level socioeconomic status such as mean income of the neighbourhood were used (Cesaroni et al. 2014).

This study is a large prospective cohort with detailed individual level information collected at baseline. Very few studies have investigated the long-term effects of low-level exposure to $PM_{2.5}$ and NO_2 on respiratory morbidity. This may be due to lack of relevant data sources (i.e. cohort studies and air pollution exposure estimates) and/or significant costs of these types of studies. However, studies at these low levels of exposure can help to better understand the exposure-response relationship at the lower end of the exposure-response curve. This study was conducted in Sydney, Australia where the level of air pollution is generally low and the low-level concentrations in Sydney are indicative of major cities in Australia.

Despite plausible biological mechanisms, the role of ambient air pollution in the development of respiratory diseases in adults is not clear due to inconsistencies in the results of epidemiological studies. Some studies have found positive associations (Andersen et al. 2011; Andersen et al. 2012; Bowatte et al. 2018; Fisher et al. 2016; Jacquemin et al. 2015; Young et al. 2014) while others did not observe any associations (Atkinson et al. 2015; Schikowski et al. 2014a; Weichenthal et al. 2017). In addition, studies with hospitalisation or mortality as the main outcome cannot clearly distinguish the role of air pollution in exacerbating pre-existing disease from its contribution to the development of the disease (Künzli 2012; Schikowski et al. 2014b). Therefore, whether and to what extent respiratory diseases in adults were caused or exacerbated by long-term exposure to air pollution is not clear.

A limitation of our study is that it had limited follow up of around seven years which resulted in a small number of events. The spatial resolution of $PM_{2.5}$ was 1 km^2 and this may have resulted in exposure misclassification that would likely attenuate the estimated HRs. Moreover, hospitalisation for respiratory diseases does not represent the overall prevalence of those diseases, but rather, may only indicate the prevalence of moderate to severe disease or milder disease in which the person is at risk of exacerbations.

5. Conclusions

In summary, we found weak positive association between long-term exposure to fine particulate matter and NO_2 with hospitalisation for asthma in a large Australian cohort at concentrations well below the current standards. There was no evidence of positive associations for all respiratory diseases, COPD and pneumonia.

Acknowledgments

This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Ageing, Carers and the Disability Council NSW; and the Australian Red Cross Blood Service. We thank the many thousands of people participating in the 45 and Up Study.

This project was funded by Centre for Air Pollution, Energy and Health (CAR) and the Clean Air and Urban Landscapes (CAUL) hub of the Australian Government's National and Environmental Science Programme (NESP). This study is part of the “Understanding the impact of the social, economic and environmental factors on the health of Australians in mid - later life; where are the opportunities for prevention?” study (National Health & Medical Research Council (NHMRC) Grant 402810) and we wish to acknowledge Philayrath Phongsavan for her tireless and effective coordination of the project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.08.050.

References

45 and Up Study Collaborators, 2008. Cohort profile: the 45 and up study. Int. J. Epidemiol. 37, 941–947.
ABS, 2006. 2006 Census Data. Australian Bureau of Statistics. Statistical Geography Volume 1: Australian Standard Geographical Classification (asgc).
ABS, 2008. Information Paper: An Introduction to Socio-economic Indexes for Areas (seifa), 2006 Australian Bureau of Statistics.
Adler, N.E., Stewart, J., 2010. Health disparities across the lifespan: meaning, methods, and mechanisms. Ann. N. Y. Acad. Sci. 1186, 5–23.
Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Loft, S., Sørensen, M., et al., 2011. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution. Am. J. Respir. Crit. Care Med. 183, 455–461.
Andersen, Z.J., Bønnelykke, K., Hvidberg, M., Jensen, S.S., Ketzel, M., Loft, S., et al., 2012. Long-term exposure to air pollution and asthma hospitalisations in older adults: a cohort study. Thorax 67, 6–11.
Atkinson, R.W., Carey, I.M., Kent, A.J., van Staa, T.P., Anderson, H.R., Cook, D.G., 2013. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24, 44–53.
Atkinson, R.W., Carey, I.M., Kent, A.J., van Staa, T.P., Anderson, H.R., Cook, D.G., 2015. Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occup. Environ. Med. 72, 42–48.
Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., et al., 2014. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre escape project. Lancet 383, 785–795.
Bowatte, G., Lodge, C.J., Knibbs, L.D., Erbas, B., Perret, J.L., Jalaludin, B., et al., 2018.

Traffic related air pollution and development and persistence of asthma and low lung function. Environ. Int. 113, 170–176.
Brauer, M., Freedman, G., Frostad, J., van Donkelaar, A., Martin, R.V., Dentener, F., et al., 2016. Ambient air pollution exposure estimation for the global burden of disease 2013. Environ. Sci. Technol. 50, 79–88.
Broome, R.A., Cope, M.E., Goldsworthy, B., Goldsworthy, L., Emmerson, K., Jegasothy, E., et al., 2016. The mortality effect of ship-related fine particulate matter in the Sydney greater metropolitan region of nsw, Australia. Environ. Int. 87, 85–93.
Brunekreef, B., Holgate, S.T., 2002. Air pollution and health. Lancet 360, 1233–1242.
Burnett, R.T., Pope, C.A., Ezzati, M., Olives, C., Lim, S.S., Mehta, S., et al., 2014. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. Environ. Health Perspect. 122, 397–403.
Cai, Y., Zijlema, W.L., Doiron, D., Blangiardo, M., Burton, P.R., Fortier, I., et al., 2017. Ambient air pollution, traffic noise and adult asthma prevalence: a bioshare approach. Eur. Respir. J. 49.
Cesaroni, G., Forastiere, F., Stafoggia, M., Andersen, Z.J., Badaloni, C., Beelen, R., et al., 2014. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the escape project. BMJ 348.
Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., Estep, K., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the global burden of diseases study 2015. Lancet 389 (10082), 1907–1918.
Crouse, D.L., Peters, P.A., van Donkelaar, A., Goldberg, M.S., Villeneuve, P.J., Brion, O., et al., 2012. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ. Health Perspect. 120, 708.
Eder, W., Ege, M.J., von Mutius, E., 2006. The asthma epidemic. N. Engl. J. Med. 355, 2226–2235.
Eilers, P.H., Marx, B.D., 1996. Flexible smoothing with b-splines and penalties. Stat. Sci. 89–102.
Fisher, J.E., Loft, S., Ulrik, C.S., Raaschou-Nielsen, O., Hertel, O., Tjønneland, A., et al., 2016. Physical activity, air pollution, and the risk of asthma and chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 194, 855–865.
Gibson, P.G., McDonald, V.M., Marks, G.B., 2010. Asthma in older adults. Lancet 376, 803–813.
Hajat, A., Diez-Roux, A.V., Adar, S.D., Auchincloss, A.H., Lovasi, G.S., O'Neill, M.S., et al., 2013. Air pollution and individual and neighborhood socioeconomic status: evidence from the multi-ethnic study of atherosclerosis (mesa). Environ. Health Perspect. 121, 1325–1333.
Hogg, J.C., Van Eeden, S., 2009. Pulmonary and systemic response to atmospheric pollution. Respirology 14, 336–346.
Hurvich, C.M., Simonoff, J.S., Tsai, C.L., 1998. Smoothing parameter selection in non-parametric regression using an improved akaike information criterion. J. R. Stat. Soc. Ser. B (Stat Methodol.) 60, 271–293.
Jacquemin, B., Siroux, V., Sanchez, M., Carsin, A.-E., Schikowski, T., Adam, M., et al., 2015. Ambient air pollution and adult asthma incidence in six European cohorts (escape). Environ. Health Perspect. 123, 613.
Kim, K.-H., Kabir, E., Kabir, S., 2015. A review on the human health impact of airborne particulate matter. Environ. Int. 74, 136–143.
Knibbs, L.D., Hewson, M.G., Bechle, M.J., Marshall, J.D., Barnett, A.G., 2014. A national satellite-based land-use regression model for air pollution exposure assessment in Australia. Environ. Res. 135, 204–211.
Knibbs, L.D., Coorey, C.P., Bechle, M.J., Cowie, C.T., Dirgawati, M., Heyworth, J.S., et al., 2016. Independent validation of national satellite-based land-use regression models for nitrogen dioxide using passive samplers. Environ. Sci. Technol. 50, 12331–12338.
Künzli, N., 2012. Is air pollution of the 20th century a cause of current asthma hospitalisations? Thorax 67, 2–3.
Künzli, N., Perez, L., Rapp, R., 2010. Air Quality and Health: European Respiratory Society.
McCreanor, J., Cullinan, P., Nieuwenhuijsen, M.J., Stewart-Evans, J., Malliarou, E., Jarup, L., et al., 2007. Respiratory effects of exposure to diesel traffic in persons with asthma. N. Engl. J. Med. 357, 2348–2358.
Murray, C.J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A.D., Michaud, C., et al., 2013. Disability-adjusted life years (dalys) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. Lancet 380, 2197–2223.
Neupane, B., Jerrett, M., Burnett, R.T., Marrie, T., Arain, A., Loeb, M., 2010. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. Am. J. Respir. Crit. Care Med. 181, 47–53.
Physick, W.L., Cope, M.E., Lee, S., Hurley, P.J., 2007. An approach for estimating exposure to ambient concentrations. J. Expo. Sci. Environ. Epidemiol. 17, 76–83.
Salvi, S.S., Nordenhall, C., Blomberg, A., Rudell, B., Pourazar, J., Kelly, F.J., et al., 2000. Acute exposure to diesel exhaust increases il-8 and gro-α production in healthy human airways. Am. J. Respir. Crit. Care Med. 161, 550–557.
Schikowski, T., Adam, M., Marcon, A., Cai, Y., Vierkötter, A., Carsin, A.E., et al., 2014a. Association of ambient air pollution with the prevalence and incidence of copd. Eur. Respir. J. 44, 614–626.
Schikowski, T., Mills, I.C., Anderson, H.R., Cohen, A., Hansell, A., Kauffmann, F., et al., 2014b. Ambient air pollution: a cause of copd? Eur. Respir. J. 43, 250–263.
Stafoggia, M., Cesaroni, G., Peters, A., Andersen, Z.J., Badaloni, C., Beelen, R., et al., 2014. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the escape project. Environ. Health Perspect. 122, 919–925.
Sunyer, J., 2001. Urban air pollution and chronic obstructive pulmonary disease: a review. Eur. Respir. J. 17, 1024–1033.
Weichenthal, S., Bai, L., Hatzopoulou, M., Van Ryswyk, K., Kwong, J.C., Jerrett, M., et al., 2017. Long-term exposure to ambient ultrafine particles and respiratory disease incidence in Toronto, Canada: a cohort study. Environ. Health 16, 64.
WHO, 2013. Review of Evidence on Health Aspects of Air Pollution–revihaap Project.
Yitshak-Sade, M., Bobb, J.F., Schwartz, J.D., Kloog, I., Zanobetti, A., 2018. The association between short and long-term exposure to pm2.5 and temperature and hospital admissions in New England and the synergistic effect of the short-term exposures. Sci. Total Environ. 639, 868–875.
Young, M.T., Sandler, D.P., DeRoo, L.A., Vedal, S., Kaufman, J.D., London, S.J., 2014. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of us women. Am. J. Respir. Crit. Care Med. 190, 914–921.
Zanobetti, A., Bind, M.-A.C., Schwartz, J., 2008. Particulate air pollution and survival in a copd cohort. Environ. Health 7, 48.