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


University Centre for Rural Health – North Coast, School of Public Health, University of Sydney, Australia
Menzies Institute for Medical Research, University of Tasmania, Australia
Centre for Air Pollution, Energy and Health, Glebe, NSW 2037, Australia
Department of Hygiene and Epidemiology, University of Athens Medical School, Greece
South West Sydney Clinical School, University of New South Wales, Sydney, Australia
Woolcock Institute of Medical Research, University of Sydney, Australia
Centre for Research and Action in Public Health, University of Canberra, Australia
School of Public Health, The University of Queensland, Australia
CSIRO Oceans & Atmosphere, PMB1, Aspendale, VIC, Australia
Department of Epidemiology and Preventive Medicine, Monash University, Australia
School of Population and Global Health, The University of Western Australia, Australia
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 μg·m$^{-3}$ and 4.5 μg·m$^{-3}$ respectively. NO$_2$ and PM$_{2.5}$ was positively, although not significantly, associated with asthma. The adjusted hazard ratio for a 1 μg·m$^{-3}$ increase in PM$_{2.5}$ was 1.08, 95% confidence interval 0.89–1.30. The adjusted hazard ratio for a 5 μg·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.

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
0160-4120/ © 2018 Published by Elsevier Ltd.
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 μg·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 μg·m$^{-3}$, while annual average PM$_{2.5}$ in Sydney, Australia’s largest city, was around 5.5 μg·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/m²), normal (18.5 kg/m² ≤ BMI < 25 kg/m²), overweight (25 kg/m² ≤ BMI < 30 kg/m²), obese (BMI > 30 kg/m²); 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 (least disadvantaged) is the most disadvantaged and category 4 (higher SES) is the most advantaged 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 μg·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 μg·m⁻³ and increased by a step of 1 μg·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 multi-level 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 μg·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.

### 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 μg·m⁻³ for NO_{2} and 4.5 μg·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 μg·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 and 7).

### Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-baseline hospitalisation</th>
<th>First post-baseline hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respiratory diseases</td>
<td>2162</td>
<td>3530</td>
</tr>
<tr>
<td>Asthma</td>
<td>900</td>
<td>218</td>
</tr>
<tr>
<td>COPD</td>
<td>467</td>
<td>748</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>940</td>
<td>1762</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>PM_{2.5} (μg·m⁻³)</th>
<th>NO_{2} (μg·m⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most disadvantaged)</td>
<td>4.6 (0.6)</td>
<td>18.3 (4.4)</td>
</tr>
<tr>
<td>2</td>
<td>4.5 (0.7)</td>
<td>17.5 (4.9)</td>
</tr>
<tr>
<td>3</td>
<td>4.4 (0.6)</td>
<td>17.7 (5.1)</td>
</tr>
<tr>
<td>4 (least disadvantaged)</td>
<td>4.4 (0.4)</td>
<td>16.6 (4.0)</td>
</tr>
<tr>
<td>Test for pollutant trenda</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Correlationb between pollutants NO_{2}</td>
<td>0.81</td>
<td></td>
</tr>
</tbody>
</table>

a Analysis of variance.

b Spearman’s rank correlation coefficient.
The associations were slightly more positive for all outcomes when we included the subjects with previous hospitalisations (Table S3), and we included the subjects with previous hospitalisations (Table S2), and showed borderline statistical significance for the association between PM2.5 and hospitalisation for respiratory diseases, COPD and pneumonia.

The observed associations of NO2 exposure and asthma hospitalisation in general are in agreement with a study conducted in Denmark with similar NO2 levels (Andersen et al. 2012). The US study (Young et al. 2014) was 10.8 μg·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 μg·m⁻³ for NO2 and 10 μg·m⁻³ for PM2.5.

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 NO2. These inconsistent results could be due to higher NO2 mean concentrations in the study by Neupane et al. (2010) (~30 μg·m⁻³ vs 17.5 μg·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 PM2.5 and NO2 on hospital admission for different respiratory diseases at low-concentration levels. We found positive associations for asthma while no such associations were found for all respiratory diseases, COPD and pneumonia.
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 (Kümzli 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 Pholyathong 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


