Long term exposure to low air pollutant concentrations and the relationship with all-cause mortality and stroke in older men.

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Abstract

Long term air pollution exposure has been associated with increased risk of mortality and stroke. Less is known about the risk at lower air pollutant concentrations. The association of long term exposure to low concentrations of $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x with all-cause mortality, fatal and non-fatal stroke was investigated in a cohort of older men in Perth.
Land use regression models were used to estimate long term exposure to air pollutants at participant's home address over 16 years. Different time metrics of exposure were assigned: exposure in the baseline year; in the year prior the outcome event; and average exposure across the follow-up period. Hazard ratios were estimated using Cox proportional hazard regression models.
$PM_{2.5}$Absorbance baseline exposure and average exposure across the follow-up increased the risk of all-cause mortality. Excess risks of all-cause mortality was seen for $PM_{2.5}$, NO_2, and NO_x baseline exposures, and NO_2 exposure across the follow-up period, although the associations were not statistically significant. No associations between long term exposure to $PM_{2.5}$Absorbance, $PM_{2.5}$, NO_2, and NO_x and non-fatal stroke. Exposure to all pollutants during the preceding year, and $PM_{2.5}$ exposure across the follow-up period were associated with a reduced risk of all-cause mortality and fatal stroke, with the strongest association observed between $PM_{2.5}$ and fatal stroke.
Longer term exposure to $PM_{2.5}$Absorbance was a risk factor for all-cause mortality among older men exposed to low concentrations, and exposure to $PM_{2.5}$Absorbance, $PM_{2.5}$, NO_2, and NO_x in the preceding year was associated with reduced risk of fatal stroke.

Keywords: Air pollution, mortality, stroke, long term exposures, low concentrations.

Introduction

Adverse effects of ambient air pollution are responsible for three million deaths in 2012[1] and 29% of stroke burden globally.[2] A large body of work has provided evidence for the association between long-term exposure to air pollution and mortality.[3,4] Studies on stroke have reported inconsistent results,[5] but more recent studies have observed significant associations between risk of stroke and

long term exposure to $PM_{2.5}$,[6] NO_2,[7] and NO_x.[8] The existing evidence for effects is predominantly based on annual average concentrations above or near the limit values of ambient air quality guidelines (40μg/m^3 for NO_2, and 20μg/m^3 for $PM_{2.5}$).[9] However, several studies with air pollutant concentrations below WHO guideline values have also reported positive associations for both mortality and stroke morbidity,[10,11]

With annual average concentrations of 4.7μg/m^3 for $PM_{2.5}$, 0.7x$10^{-5}$$m^{-1}$ for $PM_{2.5}$Absorbance, 10.1μg/m^3 for NO_2, and 18.7μg/m^3 for NO_x,[12,13] Perth is a city with relatively low air pollutant concentrations compared with international locations. Despite these relatively low air pollutant concentrations, emerging evidence suggests that every 1 ppb increase in NO_2 concentration in Perth is associated with a 1% increase in the risk of hospitalizations.[14]

This study aimed to investigate the association of long term exposure to low concentrations of $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x with all-cause mortality, fatal stroke and hospitalized stroke, in a cohort of older men in Perth, Western Australia. Different time metrics of exposure such as baseline, past-year, and average-exposures across the follow-up period were analysed.

Methods

Study Population

The study population comprised men aged 65 years and above who were recruited in a population–based cohort study in Perth, the Health in Men Study (HIMS).[15] HIMS commenced as a randomized controlled trial of screening for abdominal aortic aneurysm in Perth, Western Australia.[15] Among the 19,352 men invited to participate in the randomized controlled trial, 12,203 men were recruited between 15 April 1996 and 29 January 1999. These men became the cohort members of HIMS and completed physical and health assessments, and self-reported questionnaires at baseline as well as every two to four years.[15] These 12,203 men are able to be followed up using linked hospitalization and mortality data from the Western Australia Data Linkage System.

Participants who lived outside the Metropolitan Perth region (n=476), or who had missing data on the key baseline variables (education level, history of smoking, daily tobacco consumption, weight, and height) were excluded (n=100), leaving 11,627 (96%) eligible participants for study. Among initial HIMS participants, 1,152 (9.8%) participants had moved during study period, providing a final non-mover population of 10,483 (87%) men. These men comprised the study population in the analyses for all-cause mortality.

For fatal and hospitalized stroke analyses, participants with a history of stroke prior to the baseline examination were excluded from the analyses. These participants were those who reported a history of stroke in the baseline questionnaire (n=902) or had experienced a hospital admission for stroke in the twenty years prior the recruitment date, based on hospital admission records from the Western Australia Data Linkage System (n=834). Participants who had missing information on history of hypertension at baseline (n=394) were also excluded, leaving a total of 10,126 all participants and 9,099 non-movers participants for stroke analyses.

All participants provided written consent to participate, and this study was approved by the Human Research Ethics Committee of The University of Western Australia.

Assessment of exposure

Land use regression (LUR) models were used to estimate long term exposure to $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x at each participant's home address/es. The LUR models are outlined in detail elsewhere[12,13] and briefly outlined here.

Following the European Study of Cohort for Air Pollution Effects (ESCAPE) protocol (http://www.escapeproject.eu/manuals/), the annual average concentrations of air pollutants were derived from a three-season (summer, autumn, and winter), two-week air monitoring campaign across the metropolitan area of Perth, from January 31 to September 5, 2012, with adjustment for temporal variations. $PM_{2.5}$ samples were collected on a Teflon filter using a Harvard Impactor at 20 sites, while

the oxides of nitrogen samples were collected onto Ogawa passive samplers at 43 sites. The spatial distribution of HIMS participants' home addresses and monitoring sites throughout the metropolitan area of Perth can be seen in Supplementary Figure S1.

Manual stepwise-selection regression procedure was used to select the best predictors of each air pollutant, and the LOOCV method was used to evaluate the models. The LUR models for NO_2 and NO_x included nearby traffic intensity and length of roads, housing density and industrial area within a 5 km buffer. The $PM_{2.5}$ model included traffic variables, the proportion of water within a 5km buffer, proximity to water, proportion of green space within 1000m, and population densities within 100m. The performance of LUR models for $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x demonstrated adjusted R^2 of both model and LOOCV above 60%.[12,13] The LUR models were used to estimate air pollution concentrations at the participants' baseline addresses.

Exposures to air pollution between baseline (1996–1999) and the end of the follow-up period (2012) were obtained by back extrapolating the predicted concentrations of the LUR model, based on annual concentrations from one year before the recruitment year (1995) until 2012, sourced from the fixed air monitoring network from the Western Australia Department of Environment Regulation. Back-extrapolation was done by the standardized procedure in the ESCAPE study (http://www.escapeproject.eu/manuals/) (Supplementary Information SI1).

Fixed air monitoring data for ambient $PM_{2.5}$Absorbance were not available during follow-up period, and so it was not possible to estimate past exposures to $PM_{2.5}$Absorbance using the above method. As the concentrations of $PM_{2.5}$Absorbance were correlated with NO_2 (r=0.7), we used temporal NO_2 concentrations as proxy for temporal change in $PM_{2.5}$Absorbance concentrations. That is measured concentrations of NO_2, derived from the fixed monitoring network over follow-up period were used to predict changes in concentrations of $PM_{2.5}$Absorbance (Supplementary Information SI1).

The resulting annual mean air pollutant concentrations between 1996 and 2012 were then assigned as long term exposure for each participant, using different time metrics of exposure: (1) baseline exposure; (2) past-year exposure; and (3) average exposure. The predicted annual average concentrations of $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x in 1996, 1997, and 1998 were assigned as baseline exposures for participants who were recruited in 1996 (n=1,644), 1997 (n=6144), 1998 (n=3,846) and January 1999 (n=6), respectively. For $PM_{2.5}$, NO_2, and NO_x, time-varying annual concentrations were used to assign past-year exposure. The average exposure, was the mean of annual air pollutant concentrations from the time of recruitment until the date of an outcome event.

Assessment of outcomes

Data from two core datasets of the Western Australia Data Linkage System: the Mortality Register and the Hospital Morbidity Data System were linked to the HIMS cohort dataset using a unique identifier. Mortality and hospitalization data were recorded using the clinical modification of the ninth revision of the International Statistical Classification of Diseases (ICD-9 CM) prior to July 1, 1999, and the Australian modification of the tenth revision (ICD-10-AM) subsequent to July 1, 1999.

All-cause mortality was defined as deaths from any cause. Fatal and hospitalized strokes included haemorrhagic, ischaemic and unspecified strokes (ICD-9 430, 431, 433.x1, 434.x1, 436; ICD-10-AM I60, I61, I63, I64), transient ischaemic attacks (TIA) (435, G45), and other cerebrovascular diseases, including retinal infarction (362.3, H34.1) and neurologically asymptomatic cerebrovascular disease (433.x0, 434.x1; I66). Patients who died within 28 days after hospitalization for a hospitalized stroke were also recorded as fatal stroke cases. Fatal and hospitalized stroke, and all-cause mortality were identified as outcomes if occurring between baseline/recruitment data and December 31, 2012.

Statistical Analyses

Cox proportional hazard regression models were used to estimate the associations between baseline, past-year, and average exposures to $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x, and all-cause mortality,

fatal stroke and hospitalized stroke. Age (in years) of each participant was calculated as the difference between the date of recruitment and date of birth and was used as the time scale to obtain the hazard ratio (HRs) and their ninety-five percent confidence intervals (95% CI) for all outcomes. The survival time for all-cause mortality was calculated from the date of recruitment until: (i) date of death, or (ii) end of the follow up (December 31, 2012), whichever occurred first. For fatal stroke, until: (i) date of death due to stroke, (ii) date of death due to another cause, or (iii) December 31, 2012, whichever occurred first. For hospitalized stroke, until: (i) date of hospitalized hospitalized stroke, (ii) date of death, or (ii) December 31, 2012, whichever occurred first. We also considered composite outcome of fatal or hospitalized stroke, whichever occurred first.

Multivariable-adjusted models included potential confounding variables that were measured at baseline. These variables were initially determined *a priori* from the literature[3-5,16] and available data: smoking, education level, body mass index (BMI), waist to hips ratio, diabetes, physical inactivity, a high-fat diet, alcohol consumption, and hypertension. Each variable was added separately to a model adjusted for age, and each had little impact on the hazard ratio of the age-adjusted model (<2%), except for education level (5%). For all-cause mortality, multivariable adjusted models included smoking, education level, and continuous measures of BMI. For the stroke outcomes, the multivariable adjusted models included all variables controlled for in all-cause mortality analyses plus history of hypertension.

Smoking was classified into: never, former-smokers who had quit ≥10 years before the baseline, former-smoker who had quit <10 years before the baseline, and current-smokers. The highest education level was classified as completed university, completed high school, completed less than five years of high schools, and completed some primary school or never attended school. BMI was calculated by dividing the baseline weight (in kilograms) by baseline height (in metre squared) (kg/m^2). Hypertension was identified from the self-reported history of hypertension.

The same analyses were conducted for non-movers to determine if misclassification of exposure due to residential mobility impacted on results.

Spearman correlation coefficients for each pair of pollutants were calculated to check potential correlation between the pollutants. If the correlation coefficient was below 0.5, then two-pollutant models were developed by including both pollutants in the models to investigate potential confounding between pollutants. These analyses were only undertaken in fully adjusted models.

The linearity relationship between baseline exposure to each air pollutant and each outcome was assessed by generating the curve of cubic spline function with exposures that were plotted in three equally spaced knots. The hazard ratio and the associated 95% confidence interval were reported per 5μg/m^3 increase in $PM_{2.5}$, and 10μg/m^3 increase in NO_2 and NO_x to allow direct comparison with other studies. The *P*-value of 0.05 was used to determine statistical significance. All data were managed and analysed with STATA statistical package software V12.0 and V13.1 (StataCorp, College Station, TX).

Results

Characteristics of study population

The mean baseline age of all participants was 72 years. A majority of participants were former-smokers reporting they had quit smoking more than one decade prior to the baseline examination. Just over 10% of the participants were current-smokers at baseline with tobacco consumption of approximately 14 grams/day. Forty percent of the participants had an education level of at least high school. A similar pattern was observed for the baseline characteristics among the non-movers (Table 1).

Table 1 Baseline characteristics of the study population across various confounders and estimates of exposures to air pollutants.

Individual – level variable	All participants (n = 11,627)	Non – movers (n = 10,483)
Baseline age (years), mean ± SD	72.1 ±4.4	72.1 ±4.4
% total population based on recruitment year, n (%)		
1996	1,664 (14.3)	1,518 (14.5)
1997	6,114 (52.6)	5,490 (52.4)
1998[a]	3,852 (33.1)	3,477 (33.1)
Smoking status, n (%)		
Never-smokers	3,491 (30.0)	3,149 (30.0)
Former smokers who had quit smoking ≥10 years before the baseline	5,411 (46.5)	4,899 (46.7)
Former smokers who had quit smoking <10 years before the baseline	1,478 (12.7)	1,327 (12.7)
Current-smokers	1,250 (10.8)	1,110 (10.6)
Daily tobacco consumptions among current smokers (grams/day)	13.6 ± 9.9	13.6 ± 9.9
BMI (kg/m^2)[d]	26.9 ± 3.7	26.9 ± 3.7
Education level, n (%)		
Completed university	1,854 (15.9)	1,661 (15.8)
Completed high school	2,813 (24.2)	2,506 (23.9)
Completed some high school	4,344 (37.4)	3,885 (37.1)
Completed primary school or never attended school	2,619 (22.5)	2,433 (24.2)
Baseline exposures, mean ± sd		
$PM_{2.5}$ Absorbance ($10^{-5}m^{-1}$)	0.9 ± 0.3	0.9 ± 0.3
$PM_{2.5}$ ($\mu g/m^3$)	5.1 ± 1.7	5.1 ± 1.7
NO_2 ($\mu g/m^3$)	13.4 ± 4.1	13.4 ± 4.1
NO_x ($\mu g/m^3$)	32.3 ± 11.6	32.4 ± 11.6

[a]The six participants who were recruited in January 1999 were included in the year 1998

Distribution of exposure to air pollution

The means of all pollutant concentrations at baseline among the non-movers were similar to all participants (Table 1). There were larger positive correlations between the predicted exposure to

$PM_{2.5}$Absorbance and NO_2 and NO_x concentrations (r>0.7), and lower correlations between $PM_{2.5}$ and NO_2 and NO_x (r<0.4) (data not shown).

The spatial distribution for each air pollutant in 2012 and baseline years in 1996-99 are shown in Supplementary Figure S2. The predicted air pollutant concentrations exhibit similar spatial distribution patterns at baseline and in 2012, noting that concentrations for all air pollutants, in particular NO_x have reduced over time. By the end of study period, the predicted exposure concentrations at baseline decreased by 13% for $PM_{2.5}$, 7% for NO_2, and 21% for NO_x (Supplementary Figure S3).

Associations between air pollution and all-cause mortality, fatal and hospitalized stroke

During the study period, 54% of participants died, 3% suffered a fatal stroke, and 14% were hospitalized stroke cases. The number of cases recorded among the non-movers was similar to those recorded among all-participants (Table 2).

Table 2 shows the fully adjusted models hazard ratios and 95% confidence intervals per unit increase in $10^{-5}m^{-1}$ $PM_{2.5}$Absorbance, $5\mu g/m^3$ $PM_{2.5}$, $10\mu g/m^3$ NO_2, and $10\mu g/m^3$ NO_x for all-cause mortality, fatal-stroke, and hospitalized stroke. The age-adjusted models are presented in Supplementary Table S1.

A significant association was observed between baseline exposure to $PM_{2.5}$Absorbance and all-cause mortality among all participants. For every $10^{-5}m^{-1}$ increase in baseline exposure to $PM_{2.5}$Absorbance, the risk of all-cause mortality increased by 22% adjusted for age only, and 13% adjusted for history of smoking, smoking intensity among current smokers, education level, and BMI. Restricting analyses to non-movers attenuated the effect estimate slightly (by 1%), but the association remained statistically significant. Average exposure to $PM_{2.5}$Absorbance was significantly associated with an 11% increased risk of all-cause mortality in both all-participants and non-movers. However, exposure to $PM_{2.5}$Absorbance in the past-year was associated with a 12% reduced risk of mortality.

For all-participants, baseline and average exposures to $PM_{2.5}$, or NO_2 concentrations were associated with an increased risk in all-cause mortality, but these were significant only in the age-adjusted models. Among non-movers, non-significant associations with all-cause mortality were observed in both the age- and fully-adjusted models.

For baseline, average, and past-year exposures to $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2, and NO_x, no associations with hospitalized stroke were observed. Restricting the analyses to non-movers yielded similar hazard ratios. However, for $PM_{2.5}$, there were significantly reduced risks for fatal stroke based upon the past-year and average exposures in both all-participants and non-movers. A reduced risk for baseline exposure was also observed, albeit not reaching statistical significance. $PM_{2.5}$Absorbance, NO_2 and NO_x exposures in the past-year were also associated with reduced risk of stroke mortality. Baseline and average $PM_{2.5}$Absorbance exposure were also associated with a non-significant reduced risk for fatal stroke. A total of 1,637 composite stroke cases were identified among all participants, and 1,452 cases among the non-movers. Similar to hospitalized stroke, non-significant associations were seen for all air pollutant exposures and the composite stroke measure (Supplementary Table S3).

Including $PM_{2.5}$ and NO_2, or $PM_{2.5}$ and NO_x in the same model together did not alter the observed associations with all-cause mortality, fatal and hospitalized stroke in both all-participants and non-movers (Table 2). For $PM_{2.5}$ and $PM_{2.5}$Absorbance, the cubic spline curves showed a linear relationship with all-cause mortality, while for NO_2, and NO_x–all-cause mortality associations, a steep rise is observed at low concentrations and a plateau is evident at higher concentrations (Supplementary Figure S3).

Table 2. Adjusted Hazard Ratio and 95% Confidence Intervals per $10^{-5}m^{-1}$ $PM_{2.5}$Absorbance, 5µg/m^3 $PM_{2.5}$, 10µg/m^3 NO_2, and 10µg/m^3 NO_x baseline exposures for all-cause mortality, fatal stroke and hospitalized stroke among all-participants and non-movers.

	All-cause death		Fatal stroke		Hospitalized stroke	
Exposure	**All Participants**	**Non Movers**	**All participants**	**Non Movers**	**All participants**	**Non movers**
N cohort	**11,627**	**10,483**	**10,126**	**9,099**	**10,126**	**9099**

	All-cause death		Fatal stroke		Hospitalized stroke	
Exposure	**All Participants**	**Non Movers**	**All participants**	**Non Movers**	**All participants**	**Non movers**
N cases	**6284**	**5,763**	**321**	**290**	**1453**	**1280**
Per 10^{-5} µg/m^3 $PM_{2.5}$Absorbance						
Baseline	**1.13 (1.02 – 1.23)**	**1.12 (1.00 – 1.22)**	0.68 (0.45 – 1.02)	0.67 (0.43 – 1.03)	0.88 (0.72 – 1.07)	0.91 (0.74 – 1.12)
Average	**1.11 (1.02 – 1.22)**	**1.11 (1.01 – 1.21)**	0.68 (0.46 – 1.00)	0.68 (0.45 – 1.03)	0.91 (0.76 – 1.10)	0.95 (0.78 – 1.16)
Past-year	**0.88 (0.81 – 0.96)**	**0.89 (0.81 – 0.98)**	**0.50 (0.34 – 0.74)**	**0.53 (0.35 – 0.80)**	0.94 (0.78 – 1.13)	0.99 (0.80 – 1.19)
Per 5µg/m^3 $PM_{2.5}$						
Baseline	1.06 (0.98 – 1.15)	1.04 (0.96 – 1.13)	0.73 (0.52 – 1.02)	0.68 (0.47 – 0.97)	0.96 (0.81 – 1.13)	0.93 (0.77 – 1.11)
Average	0.95 (0.87 – 1.03)	0.93 (0.86 – 1.02)	**0.62 (0.43 – 0.88)**	**0.58 (0.39 – 0.84)**	0.95 (0.79 – 1.12)	0.92 (0.76 – 1.11)
Past-year	**0.915 (0.84 – 0.99)**	**0.90 (0.83 – 0.98)**	**0.59 (0.41 – 0.85)**	**0.56 (0.37 – 0.81)**	0.93 (0.78 – 1.11)	0.91 (0.75 – 1.09)
Per 10µg/m^3 NO_2						
Baseline	**1.06 (1.00 – 1.13)**	1.06 (0.99 – 1.12)	0.92 (0.70 – 1.19)	0.93 (0.71 – 1.24)	0.97 (0.85 – 1.10)	0.99 (0.86 – 1.13)
Average	1.05 (0.99 – 1.11)	1.05 (0.99 – 1.11)	0.90 (0.70 – 1.16)	0.92 (0.71 – 1.20)	0.98 (0.86 – 1.10)	0.99 (0.87 – 1.13)
Past-year	**0.92 (0.87 – 0.98)**	**0.92 (0.87 - 0.98)**	**0.75 (0.58 – 0.97)**	0.79 (0.61 – 1.03)	0.99 (0.88 – 1.11)	1.01 (0.89 – 1.15)
Per 10µg/m^3 NO_x						
Baseline	1.02 (0.99 – 1.04)	1.02 (0.99 – 1.04)	0.96 (0.88– 1.05)	0.97 (0.87 – 1.07)	0.99 (0.95 – 1.04)	0.99 (0.95 – 1.04)
Average	**0.95 (0.93 – 0.98)**	0.99 (0.97 – 1.02)	0.93 (0.85 – 1.03)	0.94 (0.85 – 1.04)	0.99 (0.95 – 1.04)	1.00 (0.96 – 1.05)
Past-year	**0.93 (0.91 – 0.95)**	**0.94 (0.92 – 0.96)**	**0.85 (0.77 – 0.93)**	**0.87 (0.79 – 0.96)**	0.99 (0.95 – 1.04)	0.99 (0.97 – 1.04)

Adjusted models for all-cause mortality were included for age, smoking history (never-smokers, former-smokers who had quit ≥10 years, former-smokers who had quit <10years, current-smokers), and smoking intensity among current smokers (gr/day), and BMI; Adjusted model for fatal stroke and hospitalized stroke included age, smoking history (never-smokers, former-smokers who had quit ≥10 years, former-smokers who had quit <10years, current-smokers), and smoking intensity among current smokers (gr/day), BMI, and past history of hypertension.

Discussion

We found a significant association between long term residential exposure to $PM_{2.5}$Absorbance and an increased risk of all-cause mortality. The association was similar for mean baseline $PM_{2.5}$Absorbance and for the mean $PM_{2.5}$Absorbance exposure during follow-up. There was an excess risk of all-cause mortality associated with exposure to $PM_{2.5}$, NO_2, and NO_x, and mean NO_2 exposure with longer-term follow-up, although the association was not statistically significant.

Exposure to $PM_{2.5}$Absorbance, $PM_{2.5}$, NO_2, and NO_x during the preceding year, and average $PM_{2.5}$ exposure however, were unexpectedly associated with a reduced risk of all-cause mortality and fatal

stroke, with the strongest association between $PM_{2.5}$ and fatal stroke. There was no evidence of an association between long term exposure to $PM_{2.5}$Absorbance, $PM_{2.5}$, NO_2, and NO_x and hospitalized stroke.

The finding of a significant association between $PM_{2.5}$ and $PM_{2.5}$Absorbance at baseline, and $PM_{2.5}$Absorbance mean exposure during follow-up with all-cause mortality, support the growing evidence from a relatively small body of literature of the health risks associated with long term exposure to $PM_{2.5}$, and $PM_{2.5}$Absorbance, a surrogate for black carbon or products of combustion.[17]

The spatial variation (measured as range per mean) of $PM_{2.5}$Absorbance was larger than that of $PM_{2.5}$, and this led to greater power to detect within-area associations with all-cause mortality.[3,18,19] The magnitude of the hazard ratio for $PM_{2.5}$Absorbance was comparable with the adjusted hazard ratio in a cohort study of male US military veterans that reported an 18% increased risk of all-cause mortality associated with 1-$\mu g/m^3$ increase in elemental carbon (another surrogate of black carbon particles),[20] equivalent to the unit change of $10^{-5}m^{-1}$ $PM_{2.5}$Absorbance (https://www.iso.org/obp/ui/#iso:std:iso:9835). Our results were also consistent with those in France,[21] the US,[22] and a meta-analyses of four cohorts in North America and Europe regions, reporting an approximate 6% increase in all-cause mortality per 1$\mu g/m^3$ increase in elemental carbon concentration.[19]

There has been limited evidence in toxicological studies on the specific mechanisms and biological pathway for the effect of $PM_{2.5}$Absorbance on mortality. A recent review of experimental studies suggested that black carbon may not cause toxicity directly, but possibly acts as a universal carrier of various combustion-derived components that are harmful for the human‘s organs, major defence cells and systemic blood circulation.[19]

While the effects of $PM_{2.5}$ on all-cause mortality were non-significant (Table 2), possibly due to a lack of power, the hazard ratio was consistent with findings from European study. A meta-analysis of a subset of nine cohorts in the ESCAPE study with mean $PM_{2.5}$ concentrations below the limit of WHO

guideline (6 – 10µg/m^3) have a pooled adjusted hazard ratio of 6% increased risk in natural mortality per 5µg/m^3 $PM_{2.5}$.[10] The magnitude was also comparable with other studies reporting higher mean concentration of $PM_{2.5}$ than that concentration in Perth.[3,7,23]

The Diet, Cancer, and Health (DCH) study in Denmark, and Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) cohort study also reported non-significant increased risk between NO_2 and NO_x where mean concentrations were also comparable with our study (<17µg/m^3 for NO_2, and <35µg/m^3 for NO_x).[10] The Gazel cohort study followed 20,327 participants in metropolitan France for 25-years and reported non-significant increased risks between NO_2 and all-cause mortality, but with a slightly higher adjusted hazard ratio (8–9% increases in all-cause mortality per IQR increase in NO_2 concentrations).[24]

Canadian studies have reported significant associations with all-cause mortality, with increased risk of between 4 and 26% per 10µg/m^3 increase in $PM_{2.5}$ concentrations, with baseline exposure concentrations between 6.3 and 8.9µg/m^3.[25-27] Significant associations between NO_2 and NO_x and all-cause mortality were also observed in other studies with percent increases in all-cause mortality risks ranging from 2% to 14% per 10µg/m^3 NO_2,[21,28,29] and from 2 to 8% per 10 µg/m^3 NOx concentrations.[8,30]

The lack of significant associations between $PM_{2.5}$Absorbance, NO_2, NO_x and hospitalized stroke in our study are in agreement with those by Stafoggia et al.,[31] and another meta-analysis of eight European cohorts.[5] The results for $PM_{2.5}$ contrast with another study conducted in regions with low concentrations of $PM_{2.5}$,[25] but are consistent with other studies for NO_2[32] and NO_x.[33-35]

Prior studies reporting significant associations between $PM_{2.5}$, NO_2, or NO_x and mortality and stroke had larger case numbers[7,25,27] relative to our study. The absence of significant associations with stroke in this cohort of older men may be attributable to a low number of stroke cases in our study (3% for fatal stroke and 14% for hospitalized stroke). The incidence of stroke has been steadily declining in

many regions, including Western Australia.[36] Much of this trend relates to the increased treatment and the high medication use of hypertension amongst other things such as smoking, blood pressure, and cholesterol, and thus people are now receiving better primary and secondary prevention of stroke. In addition, stroke is often under recorded on death certificates as a cause of death. In the beginning of our study, 5% of total participants were exposed to $PM_{2.5}$ concentrations above the Australian ambient air quality standard,[37] and the WHO ambient air quality guidelines.[9] At the end of study, only 2% of participants were exposed to NO_2 and none of participants were exposed to $PM_{2.5}$ concentrations above the limit. A Canadian study has reported that $PM_{2.5}$ may not have detectable effect on incident stroke at concentrations ranging from 4.4–5.1μg/m^3,[38] which was comparable with the exposure concentrations of $PM_{2.5}$ (5.1μg/m^3 for baseline exposure, 4.6μg/m^3 for average-exposure, and 4.5 μg/m^3 for past-year exposure). Collectively, the increased treatment and the use of medications possibly affected or outweighed the effect of $PM_{2.5}$ on stroke at these low concentrations.

The indication of negative association between $PM_{2.5}$, NO_2, and NO_x exposures during the most recent year and fatal stroke is unlikely given recent reviews have shown the weight of evidence for long term exposure to these pollutants would suggest an increased risk of stroke mortality and morbidity.[3-5,39] In this present study, competing risks possibly have influenced the estimated risks. Approximately 50% of the total participants died of any cause during the follow-up period, and hence decreased susceptible participants in the recent years of follow-up. Furthermore, individual several confounders such as smoking and BMI may have changed over the sixteen year period. However, the changes over time in these confounders were unable to be accounted for because information on confounders was only obtained at the time of recruitment. This may introduce some error in the recent years and potentially altered the estimated risks toward the null.[40]

However, the findings for past-year exposure were consistent with two studies that reported the diminishing effect of air pollution on mortality over time.[41,42] NO_2 exposure during baseline periods (1960–1969) was associated with the increased attributable risk of mortality, whereas in the most

recent period (1995–1997) NO_2 was significantly associated with the reduced risk of mortality, among older people aged ≥65 years resided in the United States (except Alaska).[42] In a cohort of American veterans with baseline age ≥70 years, a significant negative association between $PM_{2.5}$ and mortality was observed in both earlier (1979–1981) and recent period (1982–1984).[41] A high total mortality rate over a long follow-up period (>10 years) has been suggested as the leading cause of findings.[41,42] Finally, long term NO_x exposure was associated with the reduced risk of incident stroke in rural areas of Sweden.[43]

The proportion of men who did not move during the follow-up was high (90%), and the analyses restricted to these non-movers had little impact on the effect estimates (<10%), suggesting the residential changes did not influence the estimated effect sizes. We cannot exclude the possibility of residual confounding by other risk factors for stroke such as hypercholesterolemia, and diabetes. However, we noted that these factors had little impact (<2%) on the estimated hazard ratio (data not shown).

Time spent away from home was not recorded, thus may be prone to exposure misclassification. Nevertheless, men aged above 64years spending as much as 85% of their time at home daily (http://www.aihw.gov.au/ageing/older-australia-at-a-glance/). Therefore, the effects of ambient air pollutants were less likely influenced by air pollution exposures at other places besides home. Some studies observed strong correlations between residential outdoor and indoor air pollutant concentrations of $PM_{2.5}$, $PM_{2.5}$Absorbance, NO_2 and NO_x, and suggest residential outdoor measures may be adequate to estimate individual exposure to air pollution for those who stay at home with low activity levels such as the elderly.[44-46] Nevertheless, the observed associations should be interpreted with caution, as individual exposure to air pollution was estimated solely based on residential outdoor concentrations.

The LUR models had a good performance with adjusted R^2 and the LOOCV above 60%.[12,13] While other studies have demonstrated that LOOCV tends to overestimate the predictive power,[47,48] our

model evaluation using hold out validation, and cross-hold out validation resulted in comparable results with the LOOCV,[12,13] supporting the validity of our LUR models to predict air pollutant concentrations. The back-extrapolation of LUR models to approximately 15 years prior assumed that the spatial variations were minimal over the study period. However, there has been good agreement in the estimates of exposure between the specific year of which LUR model was developed and the back-extrapolation year over a fifteen-year period.[49-52]

Conclusions

Baseline exposure to $PM_{2.5}$Absorbance, likely to be from traffic emissions is a risk factor for all-cause mortality in older men in Perth, Western Australia. Longer term exposures to $PM_{2.5}$, NO_2, and NO_x at low concentrations were not associated with the increase risk of hospitalized stroke. Exposure to $PM_{2.5}$Absorbance, $PM_{2.5}$, NO_2, and NO_x in the preceding year was associated with reduced risk of fatal stroke.

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