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Long-term Exposure to Low Air Pollutant Concentrations and the Relationship with All-Cause Mortality and Stroke in Older Men

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Background: Long-term air pollution exposure has been associated with increased risk of mortality and stroke. Less is known about the risk at lower concentrations. The association of long-term exposure to $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2, and NO_x with all-cause mortality and stroke was investigated in a cohort of men aged ≥ 65 years who lived in metropolitan Perth, Western Australia.

Methods: Land use regression models were used to estimate long-term exposure to air pollutants at participant's home address (n = 11,627) over 16 years. Different metrics of exposure were assigned: baseline; year before the outcome event; and average exposure across follow-up period. The Mortality Register and Hospital Morbidity Data from the Western Australia Data Linkage System were used to ascertain mortality and stroke cases. Hazard ratios (HRs) and 95% confidence intervals were estimated using Cox proportional hazard models, adjusting for age, smoking, education, and body mass index for all-cause mortality. For fatal and hospitalized stroke, the models included variables controlled for all-cause mortality plus hypertension.

Results: Fifty-four percent of all-participants died, 3% suffered a fatal stroke, and 14% were hospitalized stroke cases. $PM_{2.5}$ absorbance increased the risk of all-cause mortality with adjusted HR of 1.12 (1.02–1.23) for baseline and average exposures, and 1.14 (1.02–1.24) for past-year exposure. There were no associations between $PM_{2.5}$ absorbance, NO_2, and NO_x and stroke outcomes. However, $PM_{2.5}$ was associated with reduced risks of fatal stroke.

Conclusion: Long-term exposure to $PM_{2.5}$ absorbance was associated with all-cause mortality among older men exposed to low concentrations; and exposure to $PM_{2.5}$ was associated with reduced risk of fatal stroke.

Keywords: Air pollution; Long-term exposures; Low concentrations; Mortality; Stroke

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The data are not available for replication due to the ethics requirement. All data sourced from Western Australia Data Linkage should be accessed and analyzed at The University of Western Australia.

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Adverse effects of ambient air pollution were responsible for an estimated 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] and few studies have reported the mortality effects at low concentrations.[5–11]

Studies on stroke have reported inconsistent results,[12] but more recent studies have observed significant associations between risk of stroke and long-term exposure to particulate matter ≤2.5 μm in diameter ($PM_{2.5}$),[13] nitrogen dioxide (NO_2),[14] and nitrogen oxides (NO_x).[15] The existing evidence for effects is predominantly based on the annual average concentrations above or near the limit values of ambient air quality guidelines (40 μg/m^3 for NO_2, and 10 μg/m^3 for $PM_{2.5}$).[16] However, several studies with air pollutant concentrations below WHO guideline values have also reported positive associations for both mortality and stroke morbidity.[5,17]

There is also growing evidence that long-term exposure to $PM_{2.5}$ absorbance, is a surrogate measure of black carbon and is associated with all-cause mortality. It has been used as a specific marker for nearby primary combustion emissions

such as traffic and exhibits higher spatial variability within urban areas than for NO_2 and $PM_{2.5}$.[18] Nonetheless, the evidence of an association between $PM_{2.5}$ absorbance exposure and stroke is less developed.

With annual average concentrations of 4.7 μg/m^3 for $PM_{2.5}$, $0.7 \times 10^{-5} m^{-1}$ for $PM_{2.5}$ absorbance, 10.1 μg/m^3 for NO_2, and 18.7 μg/m^3 for NO_x,[19,20] Perth is a city with relatively low air pollutant concentrations compared with international locations. Despite these low concentrations, evidence suggests that daily increases in NO_2 concentrations of 1 ppb (2.1 μg/m^3) are associated with an 1% increase in the risk of hospitalization.[21] Long-term exposures, however, may pose greater risks to human health than short-term exposures.

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 metrics of exposure such as baseline, past-year, and average-exposures across the follow-up period were analyzed.

METHODS

Study Population

The study population comprised men aged ≥65 years who were recruited in a population-based cohort study in Perth, the Health in Men Study (HIMS).[22] HIMS commenced as a randomized controlled trial of screening for abdominal aortic aneurysm in Perth, Western Australia.[22] Among the 19,352 men invited to participate in the randomized controlled trial, 12,203 were recruited between April 1996 and January 1999 and became the HIMS cohort members. These men completed physical and health assessments, self-reported questionnaires at baseline and every 2 to 4 years, and are followed up using linked hospitalization and mortality data from the Western Australia Data Linkage System.[22]

Participants who lived outside the Metropolitan Perth region (n = 476) or had missing data on the key baseline variables (education level, smoking status, daily tobacco consumption, weight, and height) were excluded (n = 100), leaving 11,627 (96%) eligible participants for study. Among initial HIMS participants, 1152 (9.8%) participants had moved to another address (movers) mainly in the Perth area, providing l1,483 (87%) nonmovers. These men comprised the study population for all-cause mortality analyses.

For stroke, participants who reported a history of stroke in the baseline questionnaire (n = 902) or had a stroke hospitalization in the 20 years before the recruitment date (n = 834) were excluded from the analyses. 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 9099 nonmovers 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 residential long-term exposure to $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2, and NO_x, which in our study is the sum of NO and NO_2. The LUR models are outlined in detail elsewhere[19,20] and briefly outlined here.

Following the European Study of Cohorts 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), 2-weeks air monitoring campaign across the metropolitan area of Perth, from 31 January 2012 to 5 September 2012, with adjustment for temporal variations. Oxides of nitrogen samples were collected onto Ogawa passive samplers at 43 sites, while $PM_{2.5}$ samples were collected on a Teflon filter using a Harvard Impactor at 20 sites. Reflectance of $PM_{2.5}$ samples was measured using a Smoke Stain Reflectometer to obtain $PM_{2.5}$ absorbance concentrations. The spatial distribution of HIMS participants' home addresses and monitoring sites throughout the metropolitan area of Perth can be seen in eFigure 1; http://links.lww.com/EDE/B527.

A manual stepwise-selection regression procedure was used to select the best predictors of each air pollutant. A series of evaluation methods were applied to assess the models' performance. The methods included were as follows: leave-one-out-cross validation (LOOCV), leave-ten-out-cross validation, and hold-out validation for NO_x and NO_2 models, while LOOCV, hold-out validation, and cross-hold-out validation were used to evaluate $PM_{2.5}$ and $PM_{2.5}$ absorbance models.[19,20]

NO_2 and NO_x models included nearby traffic intensity and road length, housing density, and industrial area. The $PM_{2.5}$ model comprised nearby traffic intensity, traffic load, proximity to water, population density, water body area, and green space. Predictors for $PM_{2.5}$ absorbance were heavy vehicle traffic load, industrial area, population density, water body area, and proximity to water. The performance of LUR models for each air pollutant, demonstrated by adjusted R^2 of both final and validation models, were >60%.[19,20]

Exposures between baseline (1996–1999) and the end of the follow-up (2012) were obtained by back extrapolating the LUR-predicted concentrations, based on the annual concentrations from one year before the recruitment (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 (http://www.escapeproject.eu/manuals/) (eInformation 1).

Data from fixed monitoring network for $PM_{2.5}$ absorbance during the follow-up period were not available, so it was not possible to estimate previous exposures using the above method. As $PM_{2.5}$ absorbance concentrations were correlated with NO_2 (r = 0.7), temporal NO_2 concentrations were used as proxy for temporal change in $PM_{2.5}$ absorbance

concentrations. In other words, concentrations of NO_2 derived from the monitoring network over follow-up period were used to predict changes in concentrations of $PM_{2.5}$ absorbance (eInformation 1).

The resulting annual mean air pollutant concentrations during 1996–2012 were assigned as long-term exposure for each participant, using different metrics of exposure: baseline, past-year, and average. The predicted annual average concentrations in 1996, 1997, and 1998 were assigned as baseline exposures for participants who were recruited in 1996 (n = 1,664), 1997 (n = 6,111), 1998 (n = 3,846), and January 1999 (n = 6), respectively. Time-varying annual concentrations were used to assign past-year exposure. The average exposure was the mean of annual concentrations from the time of recruitment until the date of 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 for completeness of case ascertainment. Mortality and hospitalization data were recorded using the clinical modification of the ninth revision of the International Statistical Classification of Diseases (ICD-9-CM) before 1 July 1999, and the Australian modification of the tenth revision (ICD-10-AM) subsequent to 1 July 1999.

All-cause mortality was defined as death from any cause. Fatal and hospitalized stroke included hemorrhagic, ischemic, and unspecified strokes (ICD-9 430, 431, 433.x1, 434.x1, 436; ICD-10-AM I60, I61, I63, I64), transient ischemic 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; I69). Patients who died within 28 days after stroke hospitalization were also recorded as fatal stroke cases. Fatal and hospitalized stroke, and all-cause mortality were identified as outcomes if occurring between recruitment date and 31 December 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 each outcome. Attained age (in years) was used as the time scale to obtain the HRs[23] and their 95% confidence intervals (CIs). The survival time for all-cause mortality, fatal stroke, and hospitalized stroke were defined as the time from the date of recruitment until: date of death, or end of the follow up (31 December 2012), whichever occurred first (all-cause mortality), date of death due to stroke, date of death due to another cause, or 31 December 2012, whichever occurred first (fatal stroke), and date of hospitalized stroke, date of death, or 31 December 2012, whichever occurred first (hospitalized stroke). We also considered composite outcome of fatal or hospitalized stroke, whichever occurred first.

Variables that potentially confound the relationship between air pollution and mortality and stroke were hypothesized a priori from the literature[3,4,12,24] and available data: smoking status, daily tobacco consumption, education level, body mass index (BMI), waist to hip ratio, diabetes, physical inactivity, a high-fat diet, alcohol consumption, and hypertension. Each was added separately to a model adjusted for age to decide whether these variables should be included in the multivariable models, and each had little impact on the HR of the age-adjusted model (<2%), except for education level (5%). Accordingly, multivariable models for all-cause mortality included smoking status (never, former-smokers who had quit ≥ 10 years before the baseline, former-smoker who had quit <10 years before the baseline, and current-smokers), tobacco consumption among current-smokers (g/day), education level (completed university, completed high school, completed <5 years of high schools, and completed some primary school or never attended school), and continuous measures of BMI (kg/m^2). The stroke models included all variables controlled for in all-cause mortality analyses plus self-reported history of hypertension. The same analyses were conducted for nonmovers to determine whether misclassification of exposure due to residential mobility impacted results.

The independent effect of two pollutants was investigated by adjusting for different pollutants in the single model. This two-pollutant model was developed if the Pearson correlation coefficient between the pair was <0.7. These analyses were only undertaken in fully-adjusted models.

The linearity relationship between baseline exposure and each outcome was assessed by generating the curve of cubic spline function with exposures that were plotted in three equally spaced knots. Schoenfeld residuals tests were used to evaluate the proportional-hazard assumption and the model was stratified for the covariates that violate the assumption. The HRs and the associated 95% CI were reported per 5 $\mu g/m^3$ increase in $PM_{2.5}$, and 10 $\mu g/m^3$ increase in NO_2 and NO_x to allow direct comparison with other studies. All data were managed and analyzed with STATA statistical package software V12.0 and V13.1 (Stata Corp, College Station, TX).

RESULTS

Characteristics of Study Population

The mean baseline age of all-participants was 72 years. The majority of participants were former-smokers reporting they had quit smoking >10 years before the baseline examination. Just over 10% of the participants were current-smokers at baseline with tobacco consumption of approximately 14 g/day, and 40% had an education level of at least high school. A similar pattern was observed for the baseline characteristics among the nonmovers (Table 1).

Distribution of Exposure to Air Pollution

The means of baseline pollutant concentrations among the nonmovers were similar to all-participants (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)	Nonmovers (n = 10,483)
Baseline age[a] (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	6,111 (52.6)	5,490 (52.4)
1998[b]	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 (g/day)	13.6 ± 9.9	13.6 ± 9.9
BMI (kg/m^2)	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[c]		
$PM_{2.5}$ 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]Age during the baseline, determined as the differences between the date of recruitment and date of birth.
[b]There were six participants who were recruited in January 1999 were included in the year 1998.
[c]Exposure concentrations did not vary across individual-level variables.

The predicted NO_2 concentrations exhibited strong correlations with NO_x (r = 0.98). Positive correlations were observed between the $PM_{2.5}$ absorbance and NO_2 and NO_x (r > 0.7), and lower correlations between $PM_{2.5}$ and NO_2 and NO_x (r < 0.4).

The spatial distribution for each pollutant in 2012 and baseline years in 1996–1999 are shown in eFigure 2; http://links.lww.com/EDE/B527. The predicted concentrations exhibit similar spatial distribution patterns at baseline and in 2012, noting that by the end of study period, concentrations for all air pollutants reduced over time (decreased by 13% for $PM_{2.5}$, 7% for NO_2, and 21% for NO_x) (eFigure 3; http://links.lww.com/EDE/B527).

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 nonmovers was similar to those recorded among all-participants (Table 2).

Table 2 shows the fully-adjusted models HRs and 95% CI 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 and fatal and hospitalized stroke. The age-adjusted models are presented in eTable 1; http://links.lww.com/EDE/B527.

An association was observed between $PM_{2.5}$ absorbance baseline exposure and all-cause mortality among all-participants. For every $10^{-5}m^{-1}$ increase in baseline and average exposures to $PM_{2.5}$ absorbance, the risk of all-cause mortality increased by 22% adjusted for age only, and 12% adjusted for smoking, tobacco consumption, education level, and BMI. Past-year exposure to $PM_{2.5}$ was associated with a 14% reduced risk of mortality. Restricting analyses to nonmovers attenuated the effect estimate slightly (by 1%). For all-participants, baseline, average, or past-year exposures to $PM_{2.5}$ concentrations were strongly associated with an increased risk in all-cause mortality only in the age-adjusted models. For nonmovers, weak associations with all-cause mortality were observed in the age- and fully-adjusted models. Baseline, average, and past-year exposures to NO_2 and NO_x among all-participants and nonmovers were associated with an increased risk in all-cause mortality.

Albeit not strong, a reduced risk for fatal and nonfatal stroke based on baseline and average exposures to $PM_{2.5}$ absorbance, NO_2, and NO_x were observed in both all-participants and nonmovers. Similar results were found for $PM_{2.5}$ and stroke outcomes among all-participants. Among nonmovers, however, all metrics of $PM_{2.5}$ exposures were associated with reduced risk of fatal stroke. A total of 1637 composite stroke cases were identified among all-participants, and 1452 cases among the nonmovers. No associations were seen for all air pollutant exposures and the composite stroke measure (eTable 2; http://links.lww.com/EDE/B527).

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 each outcome in all-participants and nonmovers (eTable 2; http://links.lww.com/EDE/B527). For $PM_{2.5}$ and $PM_{2.5}$ absorbance, the cubic spline curves showed a linear relation 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 (eFigure 3; http://links.lww.com/EDE/B527). All models met the proportional hazard assumption.

DISCUSSION

We found an association between $PM_{2.5}$ absorbance and an increased risk of all-cause mortality. There was an excess risk of all-cause mortality associated with $PM_{2.5}$, NO_2, and NO_x exposures. Although there was no evidence of an association between $PM_{2.5}$ absorbance, NO_2, and NO_x and fatal and hospitalized stroke, $PM_{2.5}$ was unexpectedly associated with a reduced risk of fatal stroke.

TABLE 2. Adjusted Hazard Ratio and 95% Confidence Intervals per $10^{-5}m^{-1}$ $PM_{2.5}$ Absorbance, 5 μg/m³ $PM_{2.5}$, 10 μg/m³ NO_2, and 10 μg/m³ NO_x Exposures for All-Cause Mortality, Fatal Stroke, and Hospitalized Stroke Among All-Participants and Nonmovers

	All-Cause Death		Fatal Stroke		Hospitalized Stroke	
Exposure	**All Participants**	**Nonmovers**	**All Participants**	**Nonmovers**	**All Participants**	**Nonmovers**
N cohort	11,627	10,483	10,126	9,099	10,126	9099
N cases	6,284	5,763	325	294	1,453	1,280
Per 10^{-5} m^{-1} $PM_{2.5}$ absorbance						
Baseline	1.12 (1.02–1.23)	1.11 (1.00–1.22)	0.69 (0.45–1.03)	0.68 (0.44–1.05)	0.85 (0.70–1.03)	0.88 (0.71–1.08)
Average	1.12 (1.02–1.22)	1.11 (1.01–1.21)	0.70 (0.47–1.03)	0.70 (0.46–1.04)	0.86 (0.71–1.03)	0.88 (0.72–1.08)
Past-year	1.14 (1.03–1.24)	1.13 (1.03–1.24)	0.71 (0.48–1.06)	0.72 (0.47–1.09)	1.00 (0.83–1.20)	1.03 (0.84–1.26)
Per 5 μg/m³ $PM_{2.5}$ absorbance						
Baseline	1.06 (0.98–1.15)	1.04 (0.96–1.13)	0.73 (0.52–1.02)	0.68 (0.48–0.97)	0.95 (0.81–1.12)	0.92 (0.77–1.10)
Average	1.07 (0.98–1.16)	1.05 (0.96–1.14)	0.71 (0.49–1.02)	0.67 (0.46–0.98)	1.01 (0.84–1.21)	1.00 (0.83–1.21)
Past-year	1.06 (0.98–1.16)	1.05 (0.96–1.14)	0.78 (0.55–1.12)	0.67 (0.45–0.99)	1.03 (0.86–1.24)	0.98 (0.81–1.18)
Per 10 μg/m³ NO_2						
Baseline	1.06 (1.00–1.13)	1.06 (0.99–1.12)	0.92 (0.70–1.19)	0.93 (0.70–1.24)	0.96 (0.84–1.09)	0.97 (0.85–1.11)
Average	1.06 (1.00–1.13)	1.06 (1.00–1.12)	0.93 (0.72–1.19)	0.94 (0.72–1.23)	0.96 (0.85–1.08)	0.97 (0.86–0.11)
Past-year	1.07 (1.01–1.13)	1.06 (1.00–1.13)	0.93 (0.72–1.21)	0.96 (0.73–1.25)	1.04 (0.92–1.17)	1.05 (0.93–1.19)
Per 10 μg/m3 NO_x						
Baseline	1.02 (1.00–1.04)	1.02 (0.99–1.04)	0.96 (0.88–1.06)	0.96 (0.87–1.07)	0.98 (0.94–1.03)	0.99 (0.94–1.04)
Average	1.02 (1.00–1.04)	1.02 (1.00–1.04)	0.97 (0.88–1.07)	0.97 (0.88–1.07)	1.00 (0.95–1.04)	1.00 (0.95–1.05)
Past-year	1.02 (1.00–1.05)	1.02 (1.00–1.05)	0.97 (0.88–1.06)	0.97 (0.88–1.08)	1.00 (0.99–1.01)	1.04 (0.99–1.09)

Fully 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 tobacco consumption among current smokers (g/day), and BMI; Adjusted model for fatal 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 tobacco consumption among current smokers (g/day), BMI, and history of hypertension.

The finding of $PM_{2.5}$ absorbance and all-cause mortality association supports the evidence from a relatively small body of literature on the health risks associated with long-term exposure to $PM_{2.5}$ absorbance, a surrogate for black carbon or combustion products.[25] The spatial variation (measured as range per mean) of $PM_{2.5}$ absorbance was larger than that of $PM_{2.5}$, which led to greater power to detect within-area associations with all-cause mortality.[3,18,26] The HR magnitude for $PM_{2.5}$ absorbance was comparable with the adjusted HR in a cohort study of male US military veterans that reported an 18% increased risk of all-cause mortality associated with 1 μg/m³ increase in elemental carbon (another surrogate of black carbon particles),[27] 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,[28] the US,[29] and meta-analyses of four cohorts in North America and European regions, reporting an approximate 6% increase in all-cause mortality per 1 μg/m³ increase in elemental carbon concentration.[18]

Black carbon may not cause toxicity directly, but rather it is hypothesized that it acts as a carrier of various combustion-derived components that have varying toxicity to humans' organs, major defense cells, and systemic blood circulation.[18]

While $PM_{2.5}$ effects on all-cause mortality were not significant (Table 2), the HR was consistent with findings from a 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 (6–10 μg/m³), have a pooled adjusted HR of 6% increased risk in natural mortality per 5 μg/m³ $PM_{2.5}$.[17] The magnitude was also comparable with other studies reporting higher mean concentration of $PM_{2.5}$ than the concentration in Perth.[3,7,14] Our findings are consistent with results from a recent US study that did not find evidence of an increased risk in all-cause mortality at $PM_{2.5}$ exposure concentrations <8 μg/m³ and 8–12 μg/m³.[10]

The Diet, Cancer, and Health (DCH) study in Denmark and the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) cohort study have reported weak associations between mortality and NO_2 or NO_x, where the mean concentrations were also comparable with our study (<17 μg/m³ for NO_2; <35 μg/m³ for NO_x).[17] The Gazel cohort study followed 20,327 participants in metropolitan France for 25 years also reported a weak association between NO_2 and all-cause mortality, but with a slightly higher adjusted HR (8–9% increases in all-cause mortality risks per IQR increase in NO_2 concentrations).[30]

Canadian studies have reported associations with all-cause mortality, with increased risk of 4–26% per 10 μg/m³ increase in $PM_{2.5}$ concentrations, with baseline exposure concentrations of 6.3–8.9 μg/m³.[5,8,31] 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: 2–14% per 10 μg/m^3 NO_2,[28,32,33] and 2–8% per 10 μg/m^3 NO_x concentrations.[15,34]

The lack of 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[35] and another meta-analysis of eight European cohorts.[12] The results for $PM_{2.5}$ are contrast with another study conducted in regions with low concentrations of $PM_{2.5}$,[10,31] but are consistent with other studies for NO_2[36] and NO_x.[37,38]

Studies reporting associations between $PM_{2.5}$, NO_2, or NO_x and mortality and stroke had larger case numbers[8,14,31] relative to our study. The absence of association 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 stroke incidence has been steadily declining in many regions, including Western Australia.[39] Much of this trend relates to the increased treatment for hypertension amongst other things such as smoking, blood pressure, and cholesterol; and thus people are now receiving better primary and secondary prevention for stroke. Moreover, 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,[40] and the WHO ambient air quality guidelines.[16] At the end of study, only 2% of participants were exposed to NO_2 and none of the participants were exposed to $PM_{2.5}$ concentrations above the limit. A Canadian study has reported that $PM_{2.5}$ may not have a detectable effect on incident stroke at concentrations of 4.4–5.1 μg/m^3,[41] which was comparable with the $PM_{2.5}$ exposure concentrations (5.1 μg/m^3 for baseline, 4.6 μg/m^3 for average, and 4.5 μg/m^3 for past-year exposures). Collectively, the increased treatment and medications use possibly affected or outweighed the effect of $PM_{2.5}$ on stroke at these low concentrations.

The indication of a negative association between $PM_{2.5}$, NO_2, and NO_x and 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.[3,4,12,42] In this present study, competing risks possibly influenced the estimated risks. Approximately 50% of the total participants died of any cause during follow-up period, and hence decreased the susceptible participants in the recent years of follow-up. Furthermore, several individual confounders such as smoking and BMI may have changed over the 16-year period, but the changes over time were unable to be accounted for because the information 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.[43]

However, the findings for past-year exposure were consistent with two studies that reported the diminishing effect of air pollution on mortality over time.[44,45] NO_2 exposure during baseline periods (1960–1969) was associated with increased attributable risk of mortality, whereas in the most recent period (1995–1997), NO_2 was noticeably associated with the reduced risk of mortality among people ≥65-years-old in the United States (except Alaska).[45] In an American veterans cohort (age ≥ 70 years), a negative association between $PM_{2.5}$ and mortality was observed in both earlier (1979–1981) and recent periods (1982–1984).[44] A high total mortality rate over a long follow-up period (>10 years) has been suggested as the leading cause of findings.[44,45] Finally, long-term NO_x exposure was associated with the reduced risk of incident stroke in rural areas of Sweden.[37]

The proportion of men who did not move during the follow-up was high (90%), and the analyses restricted to nonmovers 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 HR.

Time spent away from home was not recorded, thus could be exposure misclassification. Nevertheless, men aged above 64 years spend 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 concentrations of $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2, and NO_x, suggesting residential outdoor measures may be adequate to estimate individual exposure for those who stay at home with low activity levels, as such for the elderly.[46–48] Nevertheless, the observed associations should be interpreted with caution, as individual exposure to air pollution was estimated solely based on residential outdoor concentrations. This study was limited to an elderly population of men and hence the findings of exposure–response relation may differ in women or those who are younger.

The performance of our LUR models supports the robustness of predicted air pollutant concentrations.[19,20] The back-extrapolation of LUR models to approximately 15 years prior assumed that the spatial variations were minimal over the study period, but there has been good agreement in the exposure estimates between the specific year of which the LUR model was developed and the back-extrapolation year over a 15-year period.[49–52]

CONCLUSIONS

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

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