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Long-term exposure to low-concentration $PM_{2.5}$ and heart disease in older men in Perth, Australia

The Health in Men Study

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Abstract

Background: Exposure to particulate matter with an aerodynamic diameter less than or equal to 2.5 µm ($PM_{2.5}$) is associated with increased risk of heart disease, but less is known about the relationship at low concentrations. This study aimed to determine the dose-response relationship between long-term $PM_{2.5}$ exposure and risk of incident ischemic heart disease (IHD), incident heart failure (HF), and incident atrial fibrillation (AF) in older men living in a region with relatively low ambient air pollution.

Methods: $PM_{2.5}$ exposure was estimated for 11,249 older adult males who resided in Perth, Western Australia and were recruited from 1996 to 1999. Participants were followed until 2018 for the HF and AF outcomes, and until 2017 for IHD. Cox-proportional hazards models, using age as the analysis time, and adjusting for demographic and lifestyle factors were used. $PM_{2.5}$ was entered as a restricted cubic spline to model nonlinearity.

Results: We observed a mean $PM_{2.5}$ concentration of 4.95 µg/m^3 (SD 1.68 µg/m^3) in the first year of recruitment. After excluding participants with preexisting disease and adjusting for demographic and lifestyle factors, $PM_{2.5}$ exposure was associated with a trend toward increased incidence of IHD, HF, and AF, but none were statistically significant. At a $PM_{2.5}$ concentration of 7 µg/m^3 the hazard ratio for incident IHD was 1.04 (95% confidence interval [CI] = 0.86, 1.25) compared with the reference category of 1 µg/m^3.

Conclusions: We did not observe a significant association between long-term exposure to low-concentration $PM_{2.5}$ air pollution and IHD, HF, or AF.

Keywords: Air pollution; Atrial fibrillation; Heart failure; Male; Myocardial ischemia; Particulate matter

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Introduction

Particulate matter with an aerodynamic diameter equal to or less than 2.5 µm ($PM_{2.5}$) is an air pollutant that is widely recognized as a risk factor for poor health outcomes.[1–7] It is composed of organic matter, elemental and organic carbon, sea salt, mineral dust, and other materials, and derived from vehicle exhaust, road dust, fuel and biomass combustion, industrial activities, and other sources.[8] The size distribution and chemical composition of $PM_{2.5}$ air pollution varies temporally and by geographical area, making study of its impact on health complex.[9]

Data from the Global Burden of Disease study suggests that in 2015, $PM_{2.5}$ exposure contributed to 7.6% (4.2 million) of global deaths making it the fifth greatest risk factor for death.[10] The majority of these deaths occurred in older adult males, and most were due to ischemic heart disease (IHD).[10,11] Bu et al[11] reported that ambient rather than household $PM_{2.5}$ exposure was the main contributor to these deaths.

There are few studies on the association between long-term $PM_{2.5}$ exposure and the incidence of IHD, heart failure (HF), or atrial fibrillation (AF) at low $PM_{2.5}$ concentrations,[6,12,13] which are important causes of morbidity and mortality in the community.[14] A Canadian study found a 5% increase in the risk of incident HF and myocardial infarction for each 3.5 µg/m^3 increase in $PM_{2.5}$ exposure and that the effect of a small increase in exposure on risk of HF is greater at lower than at high concentrations of $PM_{2.5}$.[12] Studies on $PM_{2.5}$ and HF conducted in the United Kingdom[13] and Sweden[15] reported

What this study adds

This study did not find a statistically significant association between long-term exposure to increasing concentrations of $PM_{2.5}$ and risk of IHD, HF, or AF among older men living in Perth, Australia, a city with relatively low $PM_{2.5}$ concentrations.

similar increases in risk but did not describe the shape of such a relationship. Research on the association between $PM_{2.5}$ exposure and the incidence of IHD has been more extensive and provides evidence of increased risk of IHD with higher concentrations of $PM_{2.5}$, but studies at lower $PM_{2.5}$ concentrations are lacking.[12,15–20] As for AF, there are also few studies of the effect of $PM_{2.5}$ exposure on the risk of incident AF at low concentrations,[15,21] and their results have been inconclusive regarding the shape of the concentration-response function. All populations in the above mentioned studies had annual average exposures higher than 5 μg/m^3[3,12,13,15,17–21] which is above the current upper limit of long-term $PM_{2.5}$ exposure recommended by the World Health Organization (WHO).[9] As such, their ability to elucidate the effect of $PM_{2.5}$ exposure on the risk of incident HF, IHD, and AF below this concentration was limited.

The effect of long-term exposure to low-concentration $PM_{2.5}$ on human health becomes more important as countries work toward reducing air pollution. The capital city of Western Australia, Perth, has a relatively low annual mean long-term $PM_{2.5}$ concentration making it a suitable location to further study the effect of very low concentrations of $PM_{2.5}$ on IHD, HF, and AF.[22] This study will thus provide evidence of the impact of changes in $PM_{2.5}$ concentrations on population health at $PM_{2.5}$ concentration ranges for which there are currently limited evidence. The aim of this study was to determine the relationship between long-term exposure to $PM_{2.5}$ and incident IHD, HF, and AF in a cohort of older adult males living in a region with a low concentration of ambient air pollution.

Methods

Study population

The study population comprised men ≥65 years old who were enrolled in the Health in Men Study (HIMS).[23] Between April 1996 and January 1999, 12,203 men were recruited by random selection from the electoral roll (voting is compulsory in Australia). These men completed baseline surveys and have been followed since then through follow-up surveys and electronic linkage to the Western Australia Data Linkage System (WADLS).[24] Further details about the study design and the various study waves have been reported elsewhere.[23] Participants were excluded from the current study if they lived outside the Perth metropolitan region (n = 476). Written informed consent was obtained from all participants. The collection and use of human data used in this study has been assessed and approved by the Human Research Ethics Committee of the University of Western Australia (approval number: RA/4/1/5765).

Exposure ascertainment

The study area of metropolitan Perth, Western Australia, was 6,418 km^2.[22] The exposure of interest was long-term average ambient $PM_{2.5}$ concentration. Individual participant annual $PM_{2.5}$ exposure was derived from land use regression (LUR) models. Details of this methodology and validation are published elsewhere and briefly outlined here.[22] The model was based on data collected at 20 ground-based air pollution monitoring sites across Perth in 2012. The monitoring systems had a lower limit of detection of 0.01 μg/m^3. The concentration of $PM_{2.5}$ was monitored over 2-week periods in three seasons at each monitoring site and at a continuously monitored reference site. Land use regression models were used to predict the measured $PM_{2.5}$ concentrations using a range of environmental predictors such as land use, population/household density, and nearby traffic measures. From this model, the annual concentration of $PM_{2.5}$ at each participant's home address was determined for 2012. The LUR model was validated using leave-one-out, hold-out validation, and cross-hold validation methods. The validation suggested this LUR model explained 67% of the variation in $PM_{2.5}$.[22] Back and forward extrapolation for the periods 1996 to 2011 and 2013 to 2018 using air monitoring data from the WA Department of Water and Environmental Regulation fixed air monitoring network were used to estimate annual average $PM_{2.5}$ exposure of individual participants for each year of follow-up using the method described in the European Study of Cohorts for Air Pollution Effects (ESCAPE) manual.[25] Extrapolated $PM_{2.5}$ concentrations were calculated by first determining ratios of $PM_{2.5}$ concentration between the reference year (2012) and each year of interest. The estimate of each participant's $PM_{2.5}$ exposure in 2012 was then multiplied by these ratios to estimate $PM_{2.5}$ exposures in each year of forward and back extrapolation. This method of back and forward extrapolation of air pollution data has been used and validated in other studies for other traffic-related pollutants.[20,26,27] In the analyses, exposure to $PM_{2.5}$ was considered in a time-varying manner, where the average annual exposure was allowed to vary for each year of follow-up (i.e., a 1-yearly moving average) from the year of recruitment to either the outcome of interest, death, or end of follow-up.

Outcomes

Three outcomes were investigated: incident HF, incident AF, and IHD incidence. IHD was identified using International Classification of Diseases, Ninth and Tenth Revision 410-414 or I20-I25, HF as 428 or I50, and AF as 427.31 or I48. Hospitalization and mortality outcome data were obtained from the WADLS. This system was established in 1995 and datasets include hospitalizations, emergency department presentations, and deaths within Western Australia from both public and private hospitals with high fidelity and completeness.[24,28,29] Mortality data were available to 31 December 2018, but detail on underlying cause of death was only available until 21 December 2017. The hospitalization data were used to identify incident HF and AF events while both the hospitalization and underlying cause of death data were used to identify incident IHD events. IHD deaths were included because they comprise a high proportion of incident IHD events.[30] Diagnoses for a person admitted to hospital in Western Australia can be categorized as either a principal or additional diagnosis. Principal diagnoses represent the main reason that a person was hospitalized, whereas additional diagnoses are other events that required additional management, procedures, or monitoring during the same admission. However, because AF is often an incidental finding, for this outcome, we ran two models: the first with only principal diagnoses of AF as an outcome event and the second with principal and additional diagnoses of AF. When excluding participants from analyses for preexisting medical conditions, we considered both principal and additional diagnoses that occurred at any time before study enrollment.

Covariates

Data on covariates were obtained from a baseline survey that was completed at recruitment and collected demographic, health, and lifestyle data. Potential confounding factors were selected based on previous literature. They included marital status, highest level of education achieved, smoking status, physical activity ("Sufficiently active" defined as ≥ 150 minutes of exercise each week, or "Insufficiently active" defined as < 150 minutes of exercise each week), occupation, body mass index (BMI) ("Healthy or underweight" defined as BMI < 25 kg/m^2, "Overweight" defined as BMI ≥ 25 kg/m^2 and < 30 kg/m^2, and "Obese" defined as BMI ≥ 30 kg/m^2), and years lived in Australia. These variables were collected at the first follow-up of HIMS. Additionally, socioeconomic status was measured by the Socio-Economic Index for Area (SEIFA) Index of Disadvantage,

collected in the linked datasets, and was categorized into quartiles for ease of analysis. This index is developed by the national Australian Bureau of Statistics which ranks areas within Australia according to their relative socioeconomic disadvantage in terms of people's access to resources, both social and material, and their ability to participate in society.[31]

Data analysis

Participants' demographic, lifestyle, and health data were summarized using means and respective standard deviations (SDs) for continuous variables, and frequency and percentages for categorical variables. Four Cox proportional hazards models, with age as the analysis time, were developed to assess the relationship between $PM_{2.5}$ exposure during follow-up and each of the study outcomes. The outcomes of interest for each model were (1) incident IHD, (2) incident HF, (3) incident AF with AF as a principal diagnosis, and (4) incident AF with AF as a principal or additional diagnosis. For IHD incidence, the follow-up period was from study enrollment to 21 December 2017 (end of available cause of death data). Participants who died where IHD was not included as a cause of death were censored at their date of death, and those who did not die nor have a recorded IHD hospitalization within the study period were censored at 21 December 2017. For the HF and AF models, participants were followed until 31 December 2018. For the analysis of these outcomes, participants who did not have a HF or AF diagnosis but died within the study period were censored at their date of death, and those that survived without a diagnosis were censored at 31 December 2018. Participants with a previous hospital diagnosis of IHD (n = 3,256), HF (n = 466), or AF (n = 751) before recruitment were excluded from the respective models. The proportional hazards assumption was assessed using Schoenfeld residuals and log-log plots. Variables that failed to meet this assumption were entered into the model with time-varying coefficients.

To allow for nonlinearity of the relationship between $PM_{2.5}$ and each outcome, we considered models where $PM_{2.5}$ was entered as a restricted cubic spline with three knots. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported for $PM_{2.5}$ concentrations of 3, 5, 6, and 7 $\mu g/m^3$, compared with a reference value of 1 $\mu g/m^3$. Results are presented for the unadjusted models, and the models adjusted for marital status, education, smoking status, physical activity, occupation, BMI category, years lived in Australia, and socioeconomic status. Four sets of sensitivity analyses were conducted for each study outcome. The first repeated the original analyses while excluding patients with history of any of IHD, HF, or AF, rather than excluding just the specific outcome of interest for each analyses. Secondly, as some men moved during the follow-up period, which could cause misclassification of $PM_{2.5}$ exposure, sensitivity analyses were performed considering only the nonmovers. Lastly, to assess the impact of different measurements of exposure, sensitivity analyses were performed using only the exposure measured at the year of recruitment (between 1996 and 1999; referred to as baseline henceforth), and using only the 2012 exposure. All analyses were conducted using STATA 17.0 (StataCorp LLC, College Station, TX).

Results

Of 12,203 participants available for inclusion, 476 lived outside of metropolitan Perth and a further 478 had incomplete data of important confounders, leaving 11,249 participants for analysis. Of these, 7,993 men were included in the IHD analysis, 10,783 in the HF analysis, and 10,498 in the AF analyses (Figure 1). Participant baseline characteristics are summarized in Table 1. Most participants were former smokers (59.2%), did not complete high school (59.9%), and were overweight (50.8%) or obese (18.1%). Tradepersons, laborers, and related workers made up 44.0% of the cohort. We observed a mean $PM_{2.5}$ concentration of 4.95 $\mu g/m^3$ (SD 1.68 $\mu g/m^3$) across all participant addresses in 1996, the starting year of recruitment and of 4.41 $\mu g/m^3$ (SD 1.49 $\mu g/m^3$) in 2018, and the end of the follow-up period (Figure 2). Across all years, $PM_{2.5}$ concentrations ranged from below the limit of detection of 0.01 to 10.02 $\mu g/m^3$.

Of 7,993 men, 2,291 (28.7%) were either hospitalized or died due to IHD during follow-up. In the unadjusted model, the risk of incident IHD began to increase at $PM_{2.5}$ concentrations

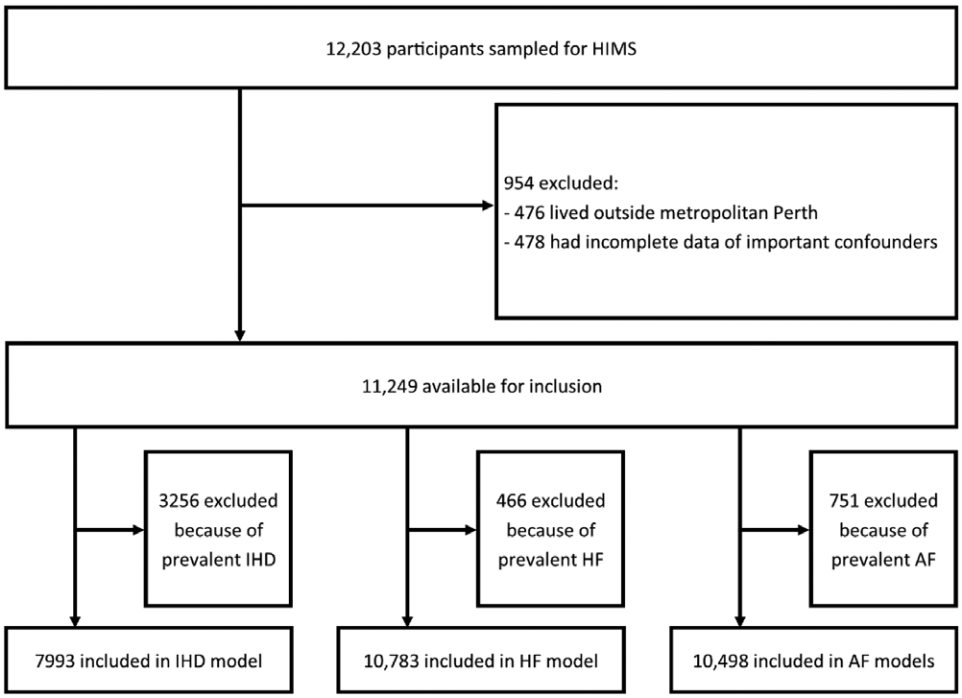

Figure 1. Included and excluded participant flowchart.

Table 1.

Participant baseline characteristics

Characteristic	All (N = 11,249)
Age, years	
Mean (SD)	72.1 (4.4)
Smoking status, n (%)	
Never smoker	3,357 (29.8)
Former smoker	6,662 (59.2)
Current smoker	1,230 (10.9)
Years lived in Australia	
Mean (SD)	56.4 (19.4)
Occupation, n (%)	
Tradespersons, laborers, and related workers	4,949 (44.0)
Nontrade-related work, nonlaborers, and all other worktypes	6,300 (56.0)
Education level, n (%)	
Did not complete high school	6,739 (59.9)
Completed high school (year 12 or equivalent)	2,704 (24.0)
Completed university or other tertiary degree	1,806 (16.1)
BMI category, n (%)	
Healthy or underweight	3,492 (31.0)
Overweight	5,720 (50.8)
Obese	2,037 (18.1)
Marital status, n (%)	
Never married	426 (3.8)
Now married or de facto	9,241 (82.1)
Separated, divorced, or widowed	1,582 (14.1)
Physical activity, n (%)	
Sufficiently active	6,892 (61.3)
Insufficiently active	4,357 (38.7)
Medical history, n (%)	
IHD	3,256 (28.9)
Heart failure	466 (4.1)
Atrial fibrillation	751 (6.7)
Hypertension	4,340 (38.6)
Stroke	827 (7.4)
High cholesterol	3,403 (30.3)
Diabetes	1,282 (11.4)
Regular aspirin	4,014 (35.7)

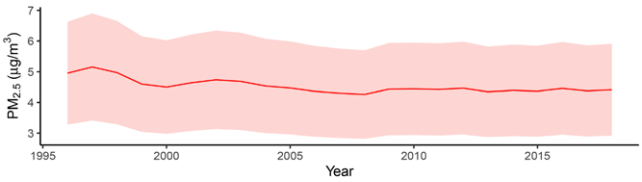

Figure 2. Average (±SD) concentration of $PM_{2.5}$ measured at participant addresses over time.

above 5 µg/m³; however, this was not statistically significant (7 vs. 1 µg/m³; HR = 1.08; 95% CI = 0.92, 1.27) (Figure 3A). After adjustment, the results were similar to the unadjusted model, again not statistically significant (7 vs. 1 µg/m³; HR = 1.04; 95% CI = 0.86, 1.25) (Table 2).

Incident HF occurred in 1,603 (14.9%) of the HF cohort. There was an increased risk of HF incidence for higher concentrations of $PM_{2.5}$ in the unadjusted model (7 vs. 1 µg/m³; HR = 1.28; 95% CI = 1.06, 1.55) (Table 2 and Figure 3B). However, this HR was attenuated after adjustment (7 vs. 1 µg/m³; HR = 1.03; 95% CI = 0.82, 1.28). The attenuation was predominantly driven by the adjustment of job group.

Of the 10,498 participants included in each of the AF models, incident hospitalization with a principal diagnosis of AF occurred in 1,022 (9.7%) participants while incident hospitalization with either a principal or additional diagnosis of AF occurred in 3,342 (31.8%) participants. There was a decreased risk of incident hospitalization with a principal diagnosis of AF with increasing concentrations of $PM_{2.5}$ for the unadjusted model, although this was associated with large confidence intervals, whereas the risk started to slightly increase at $PM_{2.5}$ concentrations greater than 6 µg/m³ in the adjusted model (7 vs. 1 µg/m³; unadjusted HR = 0.90; 95% CI = 0.71, 1.13 and adjusted HR = 1.02; 95% CI = 0.78, 1.33) (Table 2 and Figure 3C). When considering the event of incident principal or additional diagnosis of AF, unadjusted risk was elevated at concentrations of $PM_{2.5}$ greater than about 5 µg/m³ (Table 2 and Figure 3D); however, this did not reach statistical significance (7 vs. 1 µg/m³; HR = 1.08; 95% CI = 0.95, 1.23). After adjustment this risk was attenuated (7 vs. 1 µg/m³; HR = 1.02; 95% CI = 0.88, 1.19).

In the first set of sensitivity analyses, 3,533 (31.4%) participants with preexisting IHD, HF, or AF were excluded, leaving 7,716 men available for inclusion. Of these, 2,215 (28.7%) men had incident IHD, 903 (11.7%) had incident HF, 707 (9.2%) with incident principal diagnosis of AF, and 2,314 (30.0%) with incident principal or additional diagnosis of AF. The estimated risks were similar to the main analyses; however, these were associated with larger confidence intervals (Table S1; http://links.lww.com/EE/A230).

In the second set of sensitivity analyses, those who moved during the follow-up period were excluded. Of the total cohort of 11,249 men, 1,109 (9.86%) moved during the follow-up. The results of these analyses excluding those who moved are consistent with that when considering the full cohort (Table S2; http://links.lww.com/EE/A230).

In the third and fourth sets of sensitivity analyses, the exposure measure was considered as the $PM_{2.5}$ concentration at baseline and during 2012, respectively. The average baseline $PM_{2.5}$ concentration was 5.05 µg/m³ (SD 1.69 µg/m³) and the average $PM_{2.5}$ concentration in 2012 was 4.47 µg/m³ (SD 1.51 µg/m³). The results of these are shown in Tables S3 and S4 (http://links.lww.com/EE/A230). The results of the analysis considering the 2012 exposure were very similar to that of the main analysis and the results considering the baseline exposure were only slightly attenuated.

Discussion

This study builds on the limited evidence of the effect of long-term $PM_{2.5}$ exposure on cardiovascular health at low concentrations. We found that in a region with generally low concentrations of $PM_{2.5}$, higher long-term exposure to $PM_{2.5}$ was associated with a trend toward increased risk of incident IHD, HF and AF in older adult men, but the association did not reach statistical significance in adjusted models. We observed no evidence of elevated risk below $PM_{2.5}$ concentrations of 5 µg/m³.

Long-term exposure to $PM_{2.5}$ has been associated with respiratory tract inflammation and translocation of small particles or their soluble components into the systemic circulation.[6] This, coupled with release of proinflammatory mediators, has been associated with systemic inflammation, increased oxidative stress, elevation in blood pressure, vascular endothelial dysfunction, platelet activation, and hypercoagulability.[7] These changes seem to accelerate atherosclerosis and elevate the risk of IHD, HF, stroke, thromboembolic disease, cardiac arrhythmias, and mortality.[7]

The existing literature reports a positive association between long-term $PM_{2.5}$ exposure and HF.[12,13,15] The results of the current study provide evidence at lower concentrations than previously reported and suggests no association between $PM_{2.5}$ and HF incidence at concentrations at or below 6 µg/m³. Stockfelt et al[15] identified an association between $PM_{2.5}$ and increased risk of hospitalization or death due to HF in 5,850 older adult males in Sweden (HR = 1.49; 95% CI = 1.07, 2.10; per 5 µg/m³ increase). The authors found a near-linear relationship with no evidence of a safe level of exposure. However, the distribution of $PM_{2.5}$ concentrations had a median $PM_{2.5}$ exposure of 9.3 µg/m³ and a 5th percentile of 6.3 µg/m³. This distribution limits the power of

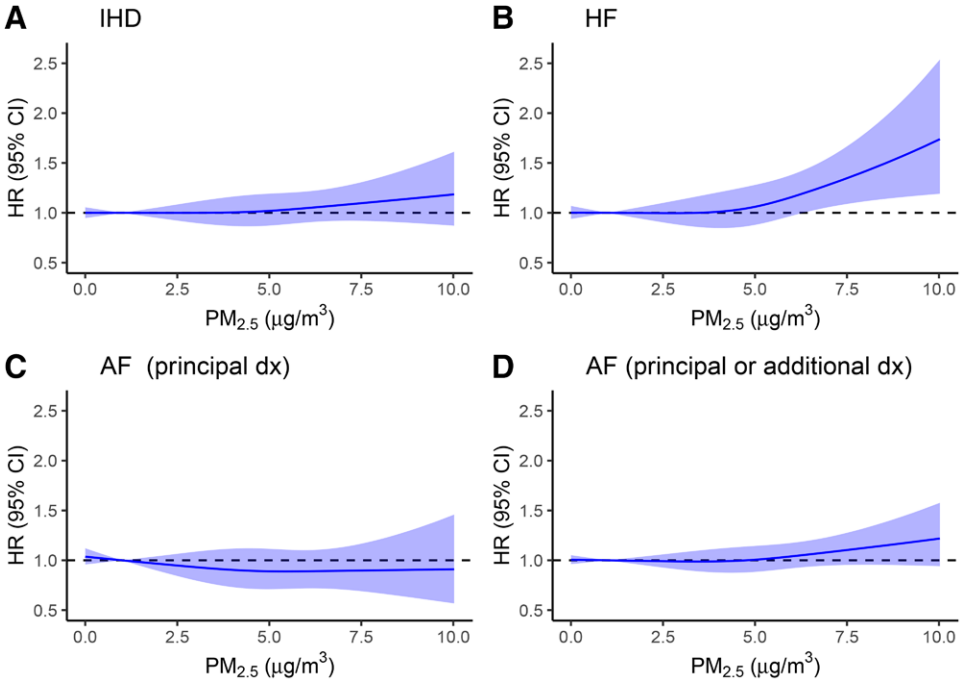

Figure 3. Relationships between $PM_{2.5}$ concentration and outcomes. Specifically, hazard ratios (HRs; solid blue line) and 95% confidence intervals (CIs; shaded blue area) are presented for a range of $PM_{2.5}$ concentrations compared to a reference of 1 μg/m³ $PM_{2.5}$ concentration for outcomes of IHD (A), HF (B), AF principal diagnosis (C) and AF principal or additional diagnosis (D). Note that dx indicates diagnosis.

Table 2.

Risk of IHD, HF and AF for increases in exposure to $PM_{2.5}$

Measure	$PM_{2.5}$ concentration (μg/m³)	IHD hospitalization/death	HF hospitalization	AF, principal	AF, principal and additional
Unadjusted HR (95% CI)	3	1.00 (0.90, 1.11)	1.00 (0.88, 1.13)	0.93 (0.80, 1.09)	0.99 (0.91, 1.08)
	5	1.02 (0.87, 1.19)	1.06 (0.88, 1.28)	0.89 (0.71, 1.11)	1.01 (0.88, 1.14)
	6	1.05 (0.90, 1.21)	1.16 (0.97, 1.38)	0.89 (0.72, 1.10)	1.04 (0.92, 1.17)
	7	1.08 (0.92, 1.27)	**1.28 (1.06, 1.55)**	0.90 (0.71, 1.13)	1.08 (0.95, 1.23)
Adjusted[a] HR (95% CI)	3	0.98 (0.87, 1.10)	0.89 (0.77, 1.02)	0.98 (0.83, 1.16)	0.96 (0.87, 1.06)
	5	0.99 (0.83, 1.17)	0.87 (0.70, 1.07)	0.98 (0.76, 1.27)	0.96 (0.83, 1.10)
	6	1.01 (0.85, 1.19)	0.93 (0.76, 1.14)	1.00 (0.78, 1.28)	0.98 (0.85, 1.13)
	7	1.04 (0.86, 1.25)	1.02 (0.82, 1.27)	1.02 (0.78, 1.33)	1.02 (0.88, 1.19)

Hazard ratios significant at the 5% level are represented in bold. Hazard ratios consider a $PM_{2.5}$ concentration of 1 μg/m³ as the reference value.
[a]Adjusted for marital status, education, smoking status, physical activity, occupation, BMI, years lived in Australia, and socioeconomic status.

the analysis at concentrations below 5 μg/m³, which is the $PM_{2.5}$ range that most of the participants in the current study were exposed to. Similarly, Bai et al[12] reported a supra-linear relationship between long-term $PM_{2.5}$ exposure and incident HF and no evidence of a safe threshold, but again the majority of participants were exposed to long-term $PM_{2.5}$ concentrations in excess of 5 μg/m³ (mean: 9.6 μg/m³, SD: 2.8 μg/m³). Other studies with higher mean concentrations of $PM_{2.5}$ generally report increased incidence of HF.[13,32,33] Perhaps at concentrations below 5 μg/m³ $PM_{2.5}$ exposure is not associated with increased risk of HF, as supported by the current study, but above this concentration an increased risk is observed, as evidenced by the trend toward increased risk in this study and the existing literature.

In the current study, there was a trend toward lower HF incidence at a $PM_{2.5}$ concentrations of 3 to 5 μg/m³. A negative association between $PM_{2.5}$ and incident HF has been previously observed in a study conducted in South Korea.[34] The authors report an adjusted HR for HF incidence of 0.84 (95% CI = 0.73, 0.96) per 10 μg/m³ increase in $PM_{2.5}$ but suggest that this might be partly due to differences in incident HF between metropolitan and nonmetropolitan areas. Metropolitan areas had a lower incidence of HF but also had higher $PM_{2.5}$ concentrations compared with nonmetropolitan areas. However, in our study, all participants were living in a metropolitan area. As the pathophysiology of $PM_{2.5}$ as a cause of cardiovascular disease is well established,[7] it seems unlikely that there would be a protective effect for HF at these concentrations and more likely that this is due to confounding from an unknown and unmeasured factor or factors.

While there was a slight trend toward increased risk of AF at the higher end of $PM_{2.5}$ distribution, this study did not find a statistically significantly increased risk of incident AF with higher concentrations of $PM_{2.5}$. The existing literature has varied findings on the relationship between $PM_{2.5}$ exposure and risk of developing AF. For example, a Canadian study with more than 5 million participants and a mean $PM_{2.5}$ exposure concentration of 9.8 μg/m³ reported a HR of 1.03 (95% CI = 1.01, 1.04) per 4.14 μg/m³ increase in $PM_{2.5}$ with a sublinear concentration-response curve and a threshold of 6 μg/m³.[21] In contrast, a Swedish study by Stockfelt et al[15] reported no relationship between $PM_{2.5}$ and incident AF in a cohort of 5,850 males. However, they reported a HR for risk of AF of 1.09 per 5 μg/m³ increase in $PM_{2.5}$ with a wide 95% confidence interval of 0.84 to 1.42. Rather than this being evidence of no relationship between $PM_{2.5}$ and AF it might suggest that the increased risk of AF

was small and that only the Canadian study with 5 million participants was sufficiently powered to detect it. Other studies at higher mean $PM_{2.5}$ concentrations also report increased risk of cardiac arrhythmias with increasing $PM_{2.5}$ exposure.[35,36] The results of the current study are consistent with the presence of a threshold effect at a concentration of about 6 μg/m^3 as there is a slight increase in the risk of AF at a concentration of 7 μg/m^3 but not below.

Increased risk of IHD has previously been demonstrated at $PM_{2.5}$ concentrations below 10 μg/m^3 and, in contrast to the current study, there has also been a report of an increase in risk of IHD mortality at $PM_{2.5}$ concentrations below 5 μg/m^3.[5,17] In a subgroup analysis of Canadians exposed to long-term average $PM_{2.5}$ concentrations of less than 5 μg/m^3, Pinault et al[17] reported a HR for IHD mortality of 2.06 (95% CI = 1.40, 3.04) per 10 μg/m^3 increase in long-term $PM_{2.5}$ exposure. This study included a larger proportion of participants living in nonmetropolitan areas and the outcome of interest was IHD death whereas the current study included IHD hospitalizations and deaths as the outcome measure. There is evidence to suggest that the composition of $PM_{2.5}$ influences its effect on IHD incidence,[37] and there may be differences in $PM_{2.5}$ composition between metropolitan and nonmetropolitan areas, for example, due to differences in the amount of road traffic.[38] Road traffic was the main source of $PM_{2.5}$ in Perth[22] and traffic-related $PM_{2.5}$ is not consistently associated with IHD mortality.[37] Traffic-related $PM_{2.5}$ has been associated with cardiovascular disease mortality elsewhere[39] but nonetheless differences in $PM_{2.5}$ composition may account for varied findings between studies.[22,37]

This study has several limitations. Firstly, unmeasured confounding may alter the effect of $PM_{2.5}$ on the study outcomes. For example, we did not have access to noise exposure data which when included as a confounder in previous studies has reduced the estimates of the effect of $PM_{2.5}$ exposure on cardiovascular mortality.[40] Air pollutants other than $PM_{2.5}$ and further unknown factors may also change the effect estimates. The included confounding factors were measured only at baseline. Therefore, changes in occupation, smoking status, or other variables are not included in the models. Secondly, although the WADLS captures all hospitalizations and deaths in WA, people with IHD, HF, and AF may be managed in the community by primary health providers and never present to hospital. In the United States, 38% of first HF diagnoses[41] and 41% of AF diagnoses occur in hospital.[42] Of the cases that initially present elsewhere, it remains unknown what proportion later present to hospital. Furthermore, people hospitalized may represent the more severe cases that were unable to be managed in the community. Finally, as this study was conducted in older adult men living in an Australian city the results may not be generalizable to other populations.

In 2021, to limit the negative impact of $PM_{2.5}$ on human health the WHO updated their Air Quality Guidelines[9] to recommend that long-term annual average $PM_{2.5}$ exposure should not exceed 5 μg/m^3 rather than 10 μg/m^3 because recent studies suggest that harm persists below this concentration.[5] The results of the current study support this update. Future research efforts should focus on methods of reducing $PM_{2.5}$ exposure and implementing such strategies.

Conclusions

We found little to no evidence that long-term $PM_{2.5}$ exposure was associated with significantly increased risk of HF, AF, and IHD at low concentrations.

Conflicts of interest statement

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Air pollution data that support the findings of this study are held by the Centre for Air pollution, energy and health Research (https://www.car-cre.org.au/cardatplatform) and are available from the corresponding author on reasonable request. The data derived from the Health in Men Study cannot be made publicly available due to confidentiality restrictions. Access to these data can be sought via application to the Health in Men Study investigators and will need to satisfy appropriate ethical requirements.

The funding sources had no role in the design of the study, nor the collection, management, analysis or interpretation of data, nor had any input into the preparation of this manuscript.

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