



Air Pollution

Satellite-based estimates of long-term exposure to fine particulate matter are associated with C-reactive protein in 30 034 Taiwanese adults

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Abstract

Background: Particulate matter (PM) air pollution is associated with the risk of cardiovascular morbidity and mortality. However, the biological mechanism underlying the associations remains unclear. Atherosclerosis, the underlying pathology of cardiovascular disease, is a chronic inflammatory process. We therefore investigated the association of long-term exposure to fine PM (PM_{2.5}) with C-reactive protein (CRP), a sensitive marker of systemic inflammation, in a large Taiwanese population.

Methods: Participants were from a large cohort who participated in a standard medical examination programme with measurements of high-sensitivity CRP between 2007 and 2014. We used a spatiotemporal model to estimate 2-year average PM_{2.5} exposure at each participant's address, based on satellite-derived aerosol optical depth data. General regression models were used for baseline data analysis and mixed-effects linear regression models were used for repeated data analysis to investigate the associations between PM_{2.5} exposure and CRP, adjusting for a wide range of potential confounders.

Results: In this population of 30 034 participants with 39 096 measurements, every 5 µg/m³ PM_{2.5} increment was associated with a 1.31% increase in CRP [95% confidence interval (CI): 1.00%, 1.63%] after adjusting for confounders. For those participants with repeated CRP measurements, no significant changes were observed between the first and

last measurements (0.88 mg/l vs 0.89 mg/l, $P=0.337$). The $PM_{2.5}$ concentrations remained stable over time between 2007 and 2014.

Conclusions: Long-term exposure to $PM_{2.5}$ is associated with increased level of systemic inflammation, supporting the biological link between $PM_{2.5}$ air pollution and deteriorating cardiovascular health. Air pollution reduction should be an important strategy to prevent cardiovascular disease.

Key words: Fine particulate matter, cardiovascular disease, systemic inflammation, C-reactive protein

Key Messages

- Systemic inflammation is hypothesized as a major underlying biological mechanism linking particulate matter (PM) air pollution and cardiovascular disease, but current evidence is limited and inconsistent.
- We observed positive association between long-term PM exposure and C-reactive protein (a sensitive marker of systemic inflammation and a valuable predictor of cardiovascular events) in an Asian population experiencing high-level PM air pollution.
- The $PM_{2.5}$ concentrations remained stable over the study period. For those participants with repeated CRP measurements, no significant changes were observed between the first and last measurements.
- Our findings substantially advance understanding of the mechanism linking air pollution and cardiovascular disease, supporting the global efforts towards air pollution reduction in prevention of cardiovascular disease.

Introduction

Cardiovascular disease is one of the leading causes of death worldwide, contributing to an estimated 17.5 million deaths in 2012.¹ In addition to traditional risk factors such as obesity, tobacco smoking and physical inactivity, there has been growing evidence supporting a causal link between exposure to particulate matter (PM), especially fine PM (PM with an aerodynamic diameter less than $2.5\ \mu\text{m}$, $PM_{2.5}$), and cardiovascular morbidity and mortality.² Systemic inflammation, which plays an important role in the development of atherosclerosis, has been hypothesized as the potential biological mechanism linking PM exposure with incidence of cardiovascular disease.^{2,3}

C-reactive protein (CRP) is one of the most sensitive acute-phase reactants and it has wide clinical use in evaluating the presence and intensity of systemic inflammation.^{4,5} Continuous associations have been shown between CRP and the risk of coronary heart disease, ischaemic stroke and vascular mortality,^{5,6} although findings from a recent meta-analysis did not support CRP as a causal factor for coronary heart disease.⁷ Previous panel and experimental studies show that short-term exposure to PM was associated with increased CRP levels.^{8–11} However, cardiovascular disease takes a long time to develop. Evidence on inflammatory response to prolonged PM exposure is therefore important in elucidating the underlying mechanism

linking PM exposure and cardiovascular disease. A few studies have investigated the associations between long-term exposure to PM and CRP but the results are inconsistent.^{12–18} Moreover, most of these studies were conducted in Europe and North America. There is limited information from the World Health Organization (WHO) Western Pacific and South East Asia regions, where people are experiencing much worse air pollution.¹⁹ We therefore investigated the association of long-term exposure to $PM_{2.5}$ with high-sensitivity CRP in a large population in Taiwan.

Methods

Study population

The participants were from a large prospective cohort in Taiwan. The details have been previously described.^{20,21} Briefly, more than 0.5 million Taiwanese participated in a standard medical examination programme run by a private firm (MJ Health Management Institution, Taipei, Taiwan) from 1996 to 2014. Participants received a series of medical examinations including general physical examination, anthropometric measurements and biochemical tests of blood and urine, as well as a standard self-administrated questionnaire survey. Each participant gave written consent authorizing MJ Health Management Institution to

process data generated from the medical examination programme. Personal identification was removed and the data remained anonymous when released for the purpose of research. Ethical approval for this study has been obtained from the Joint Chinese University of Hong Kong New Territories East Cluster Clinical Research Ethics Committee.

There were 264 106 participants aged 18 years or above who participated in the programme from 2007 to 2014, when measurements of high-sensitivity CRP were available. Because CRP measurement was voluntary and it is relatively expensive, there were 34 811 participants who received at least one high-sensitivity CRP measurement (up to eight measurements) with 46 252 observations during the study period. We excluded observations with incomplete information, including: 178 without anthropometric measurements, 574 without blood tests, 1605 without educational level, 3822 without lifestyle factors and 118 without PM_{2.5} exposure estimate due to missing information on address. We further excluded 859 observations with CRP levels higher than 10 mg/l, which potentially implied acute infections.²² The final sample included in the present analysis comprised 39 096 observations on 30 034 participants.

Air pollution exposure estimate

We estimated PM_{2.5} exposure at each participant's address using a satellite-based spatiotemporal model. A new algorithm was developed to retrieve ground-level PM_{2.5} concentrations, at a high spatial resolution of 1 × 1 km, from the aerosol optical depth (AOD) data. The detailed information can be accessed through the website from Hong Kong University of Science and Technology.²³ The 1-km satellite AOD data were derived from the spectral data from the two moderate resolution imaging spectroradiometer (MODIS) instruments aboard Terra and Aqua satellites from the US National Aeronautics and Space Administration (NASA).^{24,25} This algorithm has been validated against ground monitoring PM_{2.5} data from 565 stations in Mainland China, Hong Kong and Taiwan in 2013,²⁵ and was used in our previous epidemiological studies in Hong Kong.²⁶ We recently re-validated the model with the data from more than 70 monitoring stations in Taiwan between 2006 and 2014, to confirm that it can be accurately and specifically used for the present study. The correlation coefficients ranged from 0.72 to 0.83 in different years and the mean percentage errors were around 20%. (Figure 1 Panel A) The estimated annual average concentrations in Taiwan are presented in Figure 1 Panel B. The south western region was heavily polluted and the mid eastern region was least polluted.

Pollution levels were overall stable over time except for a slight reduction after 2012.

The address of each participant (either residential or company) was collected during each medical visit so that the medical report could be mailed to them. The address was geocoded into latitude and longitude. Address-specific yearly average PM_{2.5} concentrations were calculated using the new algorithm mentioned above. In the present study, we estimated annual average PM_{2.5} concentrations for the year of each medical visit and the year before the visit, and we used the mean of these two averages (2-year average) as an indicator of long-term ambient PM_{2.5} exposure.

Health outcome

The procedures of the medical examination programme in this population have been described in previous publications.^{20,21} The health outcome in the present study was the high-sensitivity CRP level. An overnight fasting blood sample was taken in the morning and CRP concentrations were measured by an automated biochemical analyser (C8000, Toshiba, Tokyo, Japan). All blood samples were analysed at the central laboratory of the MJ Health Screening Center, which has been recognized by the College of American Pathologists (CAP) since 1996 as a laboratory demonstrating continuous improvement in quality through participation in CAP Surveys, EXCEL and/or Anatomic Pathology Education Programs.

Covariates

In addition to CRP measurement, participants underwent anthropometric measurements and blood tests of lipid profile, and completed a questionnaire, at each medical visit. The details have been described in previous publications.^{20,21}

The following covariates were included in data analysis: age (years), sex (male and female), educational level [lower than high school (< 10 years), high school (10–12 years), college or university (13–16 years) or postgraduate (> 16 years)], smoking status (never, former and current), alcohol drinking (< once/week, 1–3 times/week and > 3 times/week), physical exercise (< 1 h/week, 1–2 h/week, and > 2 h/week), vegetable intake (< 1 serving/day, 1–2 servings/day and > 2 servings/day), fruit intake (< 1 serving/day, 1–2 servings/day and > 2 servings/day), occupational exposure (information was collected by asking the question 'Are there any occupational hazards in your workplace?' with a list of occupational hazards. Information was retrieved on exposure to dust or organic solvents in workplace: yes vs no), number of medical visit (one to eight), season of visit (calendar season), body mass index (BMI, calculated as weight divided by square of height),

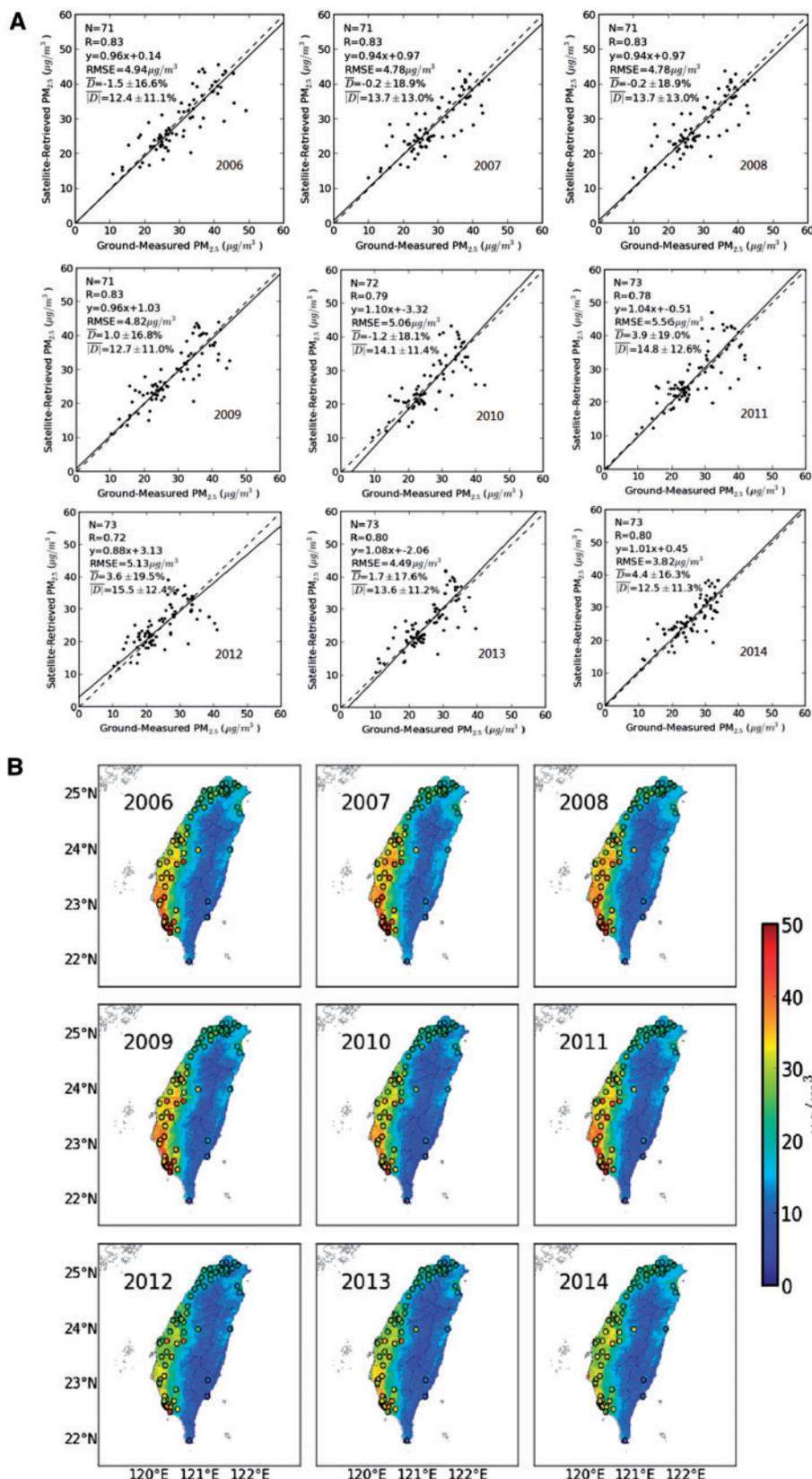


Figure 1. Panel A. Spatial correlation coefficients between the average satellite-retrieved PM_{2.5} and average ground-based PM_{2.5} from the monitoring stations in Taiwan between 2006 and 2014; N, number of monitoring stations; R, correlation coefficient; RMSE, root mean square error; \bar{D} , mean deviation. Panel B. Map of annual average concentration of satellite-based estimated PM_{2.5} in Taiwan between 2006 and 2014; circles are ground monitoring stations used for algorithm validation. Panel C. Spatial distribution of geocoded addresses of the 39 096 observations in Taiwan; dots are address locations of the observations. Panel D. Long-term ambient PM_{2.5} concentrations over all observations by the year of their visits; 1-year refers to the year of visit; 2-year refers to the year of visit and the year before the visit. Boxes cover the 25–75th percentile (IQR) with a centre line for the median concentration. Whiskers extend to the highest observation within 3 IQR of the box, with more extreme observations shown as circles.

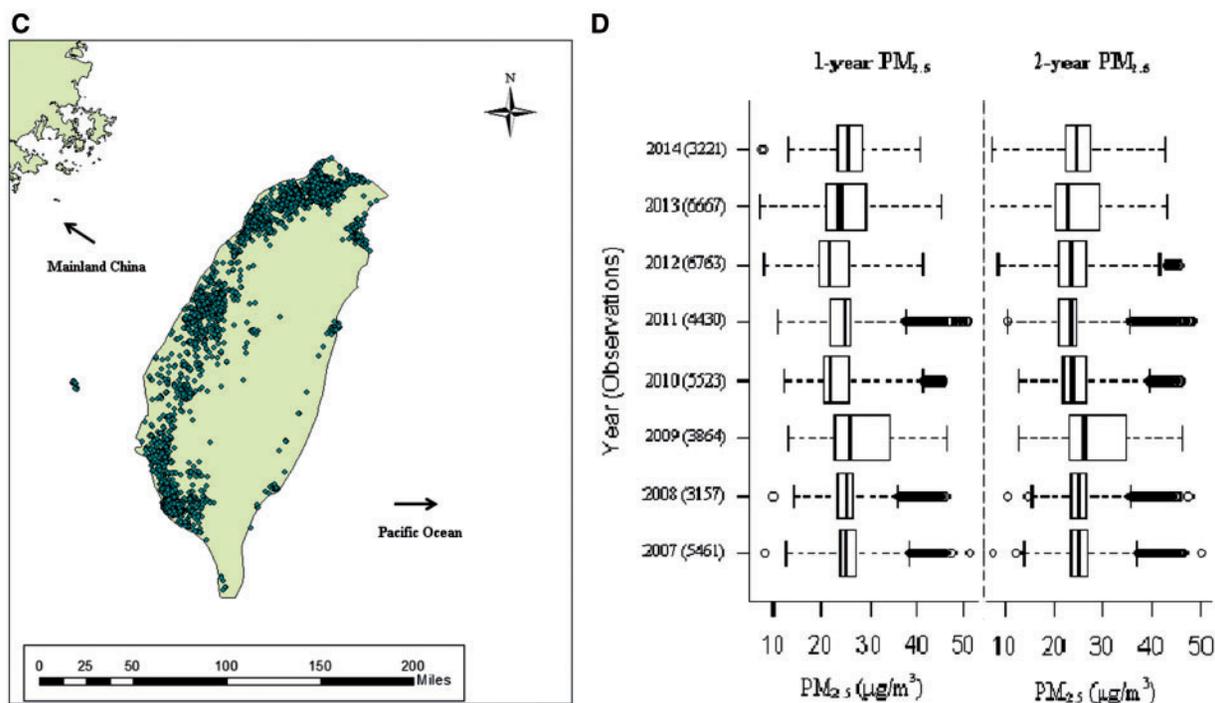


Figure 1. Continued.

hypertension (defined as systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or self-reported physician-diagnosed hypertension), diabetes (defined as fasting blood glucose ≥ 126 mg/dl, or self-reported physician-diagnosed diabetes), hyperlipidaemia (defined as total cholesterol ≥ 240 mg/dl, or triglyceride ≥ 200 mg/dl or high-density lipoprotein-cholesterol < 40 mg/dl), self-reported any cardiovascular disease or stroke (yes vs no) and self-reported any form of cancer (yes vs no).

Statistical analysis

We used the general linear regression model for baseline data analysis. Three models were used, namely: Crude Model: with no adjustment; Model 1: adjusted for age, sex, educational level, smoking, alcohol drinking, exercise, vegetable intake, fruit intake, occupational exposure and season; and Model 2: further adjusted for BMI, hypertension, diabetes, hyperlipidaemia, cardiovascular disease and cancer. CRP was log-transformed to achieve approximate normality for data analysis and then the geometric means were transformed back for presentation. Parameter estimates were reported as percentage changes in CRP for each $5 \mu g/m^3$ increment in 2-year average $PM_{2.5}$ concentrations.

We also categorized CRP level into tertiles. Participants with the highest tertile were defined as having elevated CRP. A logistic regression model was used for odds ratio

calculation to investigate the association between PM and the risk of elevated CRP.

For repeated data analysis, a mixed-effects linear regression model was used. A person-level random intercept was added to account for within-person clustering effects. Visit number (one to eight) was additionally included as a covariate in the model. The health outcome, $PM_{2.5}$ exposure and covariates entered in the model were time-varying with the exception of sex which was treated as fixed factor. We also examined potential effect modification of the following characteristics on the associations between $PM_{2.5}$ exposure and CRP by adding interactions terms in the mixed-effects models: sex (male and female), age (age < 65 years and age ≥ 65 years), school educational level [low (< 13 years) and high (≥ 13 years)], smoking status (ever and never smoker), hypertension (hypertensive and non-hypertensive), diabetes (diabetic and non-diabetic) and BMI group (normal weight: BMI < 25 kg/m², overweight: $25 \leq$ BMI < 30 kg/m² and obese: BMI ≥ 30 kg/m²). Each potential modifier was assessed in a separate model. Subgroup analyses stratified by those potential modifiers were carried out as well.

We further performed the following sensitivity analyses: (i) using the annual average $PM_{2.5}$ concentrations of the year of each visit; (ii) excluding those subjects with self-reported cardiovascular disease or cancer; (iii) excluding those subjects using a company address; and (iv) excluding those participants with only a single measurement.

For those participants who had two visits or more with a follow-up period of more than 1 year, we examined the change of PM exposure by comparing the PM_{2.5} concentrations between baseline (first visit) and the last visit. Similarly, CRP levels between baseline and the last visit were also compared. Comparisons were performed using PM_{2.5} or CRP as dependent variable and visit (first vs last) as independent variable in mixed-effects linear regression models.

Statistical analysis was performed using R 3.2.3 (R Core Team, Vienna, Austria). A two-tailed *P*-value < 0.05 for associations and a *P*-value < 0.10 for interactions were considered statistically significant.

Results

The general characteristics of the participants at baseline (the first visit in the period of 2007–14) and over all medical visits are presented in Table 1. There were more males (59.1%) than females and the mean age of participants was 41.4 years [standard deviation (SD): 11.1] at baseline. The majority of participants were never smokers and seldom alcohol drinkers. The distribution of the general characteristics was generally similar at baseline and over all visits.

The locations of the 39 096 observations are presented in Figure 1 Panel C and their average exposure concentrations by year of visit are presented in Figure 1 Panel D. In line with Figure 1 Panel B, the PM_{2.5} concentrations varied spatially among the observations within each year, but were overall stable over time. There were no apparent upward or downward trends over the study period of 2007–14. The 1-year and 2-year average PM_{2.5} concentrations were similar, but the concentrations were much higher, by a factor of around 2.6, than the WHO air quality guideline limit which is 10 µg/m³ for annual mean PM_{2.5}.

Table 2 presents the results of cross-sectional baseline analysis on the associations of CRP level with long-term exposure to PM_{2.5}. Significant concentration-response relationships were observed. Participants with higher-quartile exposure generally had higher levels of CRP. Every 5 µg/m³ increment in 2-year average PM_{2.5} concentrations was associated with a 1.34% (95% CI: 1.01%, 1.67%) increase in CRP level after full adjustment. Similar results were observed when the analyses were conducted separately for men and women.

Supplementary Table 1 (available as Supplementary data at *IJE* online) presents the associations of elevated-CRP with long-term exposure to PM_{2.5}. In line with the results of Table 2, participants with higher PM_{2.5} exposure generally had higher risk of elevated CRP.

Table 3 presents the results of the associations of CRP with long-term exposure to PM_{2.5} in repeated-measures analysis. After full adjustment, each 5 µg/m³ increment in 2-year average PM_{2.5} was associated with a 1.31% (95% CI: 1.00%, 1.63%) increase in CRP.

There was no significant effect modification by sex, age, educational level, smoking, hypertension, diabetes or BMI on the association between PM_{2.5} and CRP (all *P*-values were greater than 0.10). Positive associations between PM_{2.5} exposure and CRP levels were observed in all subgroups stratified by these characteristics except in participants with age ≥ 65 years or BMI ≥ 30 kg/m², and the 95% CIs overlapped between groups (Table 3).

Results of sensitivity analyses are presented in Supplementary Table 2, available as Supplementary data at *IJE* online. Replacing 2-year average PM_{2.5} with 1-year average PM_{2.5} did not change the results. The associations were also robust to excluding participants with self-reported cardiovascular disease or cancer, using working address or having only one visit.

Figure 2 Panel A presents the distribution of PM_{2.5} exposure and CRP level at the first and last visits. There were a total of 4449 participants with at least two visits with a follow-up duration of more than 1 year. The mean follow-up duration was 2.7 person-years (SD: 1.5). Overall, PM_{2.5} decreased from 27.2 to 25.5 µg/m³ with statistical significance (*P* < 0.01), but only 276 (6.2%) and 58 (1.3%) participants had a reduction or increase of more than 5 µg/m³ in PM_{2.5} exposure, respectively, between first and last visits. No significant changes were observed for CRP (0.88 mg/l at the first visit and 0.89 mg/l at the last visit, *P* = 0.34) after adjusting for the potential confounders. (Figure 2 Panel B).

Discussion

In this large population of Taiwanese adults, long-term exposure to ambient PM_{2.5} is associated with increased levels of CRP, a sensitive marker of systemic inflammation and a valuable predictor of future cardiovascular events. PM_{2.5} concentrations are generally stable over time. The results suggest that persistent exposure to high levels of ambient PM_{2.5} can result in a chronic state of systemic inflammation and can explain the previous findings that PM exposure is associated with cardiovascular morbidity and mortality.^{2,3}

To our knowledge, this is the largest study investigating the health effects of long-term exposure to PM_{2.5} on the inflammatory marker CRP. Three previous studies also used repeated data analysis to assess the relationship between PM_{2.5} exposure and serum CRP levels [the Multi-Ethnic Study of Atherosclerosis (MESA),¹⁵ the Study of Women's

Table 1. Characteristics of participants at baseline and over all visits

Characteristics	Baseline N = 30034	All visits N = 39096
Age (years)	41.4 (11.1)	41.7 (10.6)
Males	17761 (59.1%)	24138 (61.7%)
Educational level		
lower than high school (< 10 years)	2115 (7.0%)	2314 (5.9%)
high school (10–12 years)	4157 (13.8%)	4849 (12.4%)
college or university (13–16 years)	17451 (58.1%)	22626 (57.9%)
postgraduate (> 16 years)	6311 (21.0%)	9307 (23.8%)
Cigarette smoking		
never	22055 (73.4%)	28867 (73.8%)
former	2212 (7.4%)	2977 (7.6%)
current	5767 (19.2%)	7252 (18.5%)
Alcohol drinking		
< once/week	25605 (85.3%)	33266 (85.1%)
1–3 times/week	3148 (10.5%)	4158 (10.6%)
> 3 times/week	1281 (4.3%)	1672 (4.3%)
Physical exercise		
< 1 h/week	10107 (33.7%)	12165 (31.1%)
1–2 h/week	14058 (46.8%)	19340 (49.5%)
> 2 h/week	5869 (19.5%)	7591 (19.4%)
Vegetable intake ^a		
< 1 serving/day	3423 (11.4%)	4202 (10.7%)
1–2 servings/day	17626 (58.7%)	22870 (58.5%)
> 2 servings/day	8985 (29.9%)	12024 (30.8%)
Fruit intake		
< 1 serving/day	9449 (31.5%)	11757 (30.1%)
1–2 servings/day	16700 (55.6%)	22126 (56.6%)
> 2 servings/day	3885 (12.9%)	5213 (13.3%)
Occupational exposure		
dust	1048 (3.5%)	1401 (3.6%)
organic solvent	1416 (4.7%)	1869 (4.8%)
Body mass index (kg/m ²)	23.7 (3.7)	23.7 (3.6)
CRP (mg/l) ^a	0.9 (2.8)	0.9 (2.8)
Hypertension	4813 (16.0%)	6229 (15.9%)
Diabetes	1504 (5.0%)	1892 (4.8%)
Hyperlipidaemia	7409 (24.7%)	9555 (24.4%)
Address		
residential address	20580 (68.5%)	25593 (65.5%)
company address	9454 (31.5%)	13503 (34.5%)
PM _{2.5} (µg/m ³)		
1-year average	25.9 (6.8)	25.9 (6.7)
2-year average	26.1 (6.7)	26.0 (6.6)

Data are presented as mean (SD) for continuous variables and number (percentage) for categorical variables, unless stated otherwise.

^aGeometric mean (SD).

Health Across the Nation (SWAN) in the USA¹⁸ and the Heinz Nixdorf Recall (HNR) study¹⁶ in Germany]. Our results are in line with the SWAN study which also reported a positive association between CRP level and average

PM_{2.5} concentration of the previous year (21% per 10 µg/m³ PM_{2.5}, 95% CI: 6.6%, 37%).¹⁸ Similar results were reported in the HNR study. An increase of 2.4 µg/m³ in long-term (1-year) PM_{2.5} was associated with an increase of 5.4% (95% CI: 0.6%, 10.5%) in CRP.¹⁶ However, the MESA study did not find significant associations between PM_{2.5} exposure and CRP.¹⁵ Two cross-sectional studies in the USA and Europe showed that long-term exposure to PM_{2.5} was not associated with CRP levels.^{14,17} Another two studies investigated the health impact of PM₁₀ on CRP. Shima *et al.* reported a significant association in children,¹² but no associations were observed in Forbes *et al.*'s study.¹³ A couple of studies used other biomarkers of systemic inflammation, such as white blood cells, neutrophils and interleukin-6, and positive associations were reported with exposure to PM air pollution.^{27,28} The inconsistency of current evidence might be due to a number of reasons such as differences in populations, study regions or components of PM_{2.5}, as well as research methodology. Our study targeted an Asian ethnic population and participants were relatively younger and healthier. Furthermore, the PM_{2.5} levels were much higher than those in North America and Europe.^{14–18} The accuracy of PM exposure estimate is also an important issue. Some previous studies estimated PM exposure using residential proximity to routine ground-level air pollution monitoring stations. The exposure was typically at the community (district, county or city) rather than individual level, with the same exposure level assigned to all of a community. This limitation (ecological fallacy) may mask the variation, or cause misclassification, thus leading to the inconsistent results.²⁹

Atherosclerosis is a major underlying pathology of cardiovascular disease.⁴ Results from both animal³⁰ and epidemiological studies^{31–33} have shown that long-term PM_{2.5} exposure was associated with accelerated progression of atherosclerosis. Because atherosclerosis is also regarded as a process of inflammation,⁴ the positive association observed between CRP and exposure to PM_{2.5} in our study supports the hypothesis of a mechanism linking PM_{2.5} and cardiovascular disease. Furthermore, PM_{2.5} concentrations were generally stable over the study period. The mean PM_{2.5} concentration decreased 1.7 µg/m³ for an average period of 2.7 years in the 4449 participants, and only 7.4% of them had an exposure change of more than 5 µg/m³. We speculate that the stable exposure resulted in little change in CRP over time. Our results suggest that persistent exposure to high levels of PM_{2.5} air pollution can induce a prolonged state of systemic inflammation, which subsequently accelerates atherosclerosis and eventually results in cardiovascular morbidity and premature mortality.

In addition to PM air pollution, many other risk factors can induce chronic systemic inflammation. Cigarette

Table 2. Associations of CRP with long-term exposure to PM_{2.5} in baseline analysis among Taiwanese adults

	Crude model			Model 1 ^a			Model 2 ^a		
	Mean (SE) ^b	% difference (95% CI)	P	Mean (SE) ^b	% difference (95% CI)	P	Mean (SE) ^b	% difference (95% CI)	P
Men (N = 17761)									
1st quartile	0.96 (1.01)	Ref	Ref	0.92 (1.03)	Ref	Ref	0.98 (1.05)	Ref	Ref
2nd quartile	0.96 (1.01)	0.34 (-1.36, 2.05)	0.69	0.95 (1.03)	1.18 (-0.01, 2.89)	0.18	1.01 (1.05)	1.49 (-0.01, 3.05)	0.06
3rd quartile	0.98 (1.01)	0.93 (-0.77, 2.62)	0.28	0.97 (1.03)	1.94 (0.23, 3.65)	0.03	1.03 (1.05)	2.19 (0.63, 3.76)	0.006
4th quartile	1.07 (1.01)	4.78 (3.09, 6.48)	< 0.001	1.03 (1.03)	4.71 (3.01, 6.41)	< 0.001	1.08 (1.05)	4.27 (2.72, 5.82)	< 0.001
trend test ^c	-	-	< 0.001	-	-	< 0.001	-	-	< 0.001
every 5 µg/m ³ increment ^d	-	1.42 (0.96, 1.87)	< 0.001	-	1.35 (0.89, 1.81)	< 0.001	-	1.21 (0.79, 1.63)	< 0.001
Women (N = 12273)									
1st quartile	0.76 (1.02)	Ref	Ref	0.70 (1.06)	Ref	Ref	0.85 (1.07)	Ref	Ref
2nd quartile	0.68 (1.02)	-4.79 (-0.01, -2.42)	< 0.001	0.67 (1.06)	-1.52 (-0.01, 0.78)	0.19	0.84 (1.07)	-0.82 (-0.01, 1.23)	0.43
3rd quartile	0.70 (1.02)	-3.54 (-5.91, -1.16)	0.004	0.70 (1.06)	0.37 (-1.95, 2.70)	0.75	0.88 (1.07)	1.44 (-0.63, 3.51)	0.17
4th quartile	0.82 (1.02)	3.30 (0.92, 5.68)	0.006	0.79 (1.06)	5.19 (2.88, 7.5)	< 0.001	0.95 (1.07)	4.89 (2.84, 6.95)	< 0.001
trend test ^c	-	-	< 0.001	-	-	< 0.001	-	-	< 0.001
Every 5 µg/m ³ increment ^d	-	1.27 (0.66, 1.89)	< 0.001	-	1.64 (1.04, 2.24)	< 0.001	-	1.62 (1.09, 2.15)	< 0.001
All (N = 30034)									
1st quartile	0.87 (1.01)	Ref	Ref	0.80 (1.03)	Ref	Ref	0.90 (1.04)	Ref	Ref
2nd quartile	0.83 (1.01)	-1.58 (-3.00, -0.17)	0.03	0.80 (1.03)	-0.25 (-1.63, 1.14)	0.73	0.91 (1.04)	0.31 (-0.94, 1.55)	0.63
3rd quartile	0.86 (1.01)	-0.35 (-3.00, 1.06)	0.63	0.82 (1.03)	1.19 (-0.21, 2.59)	0.10	0.94 (1.04)	1.86 (0.60, 3.12)	0.004
4th quartile	0.95 (1.01)	4.27 (2.86, 5.69)	< 0.001	0.89 (1.03)	4.55 (3.16, 5.94)	< 0.001	1.00 (1.04)	4.31 (3.06, 5.56)	< 0.001
trend test ^c	-	-	0.003	-	-	< 0.001	-	-	< 0.001
every 5 µg/m ³ increment ^d	-	1.33 (0.96, 1.71)	< 0.001	-	1.40 (1.03, 1.77)	< 0.001	-	1.34 (1.01, 1.67)	< 0.001

^aModel 1: adjusted for age, sex (not in sex-specific analysis), educational level, smoking, alcohol drinking, exercise, vegetable intake, fruit intake, occupational exposure to dust and organic solvent and season; Model 2: further adjusted for BMI, hypertension, diabetes, hyperlipidaemia, self-reported cardiovascular disease and self-reported cancer.

^bGeometric mean [standard error(SE)].

^cTrend test was performed with PM_{2.5} quartiles treated as numerical variables.

^dPercentage changes in CRP for every 5 µg/m³ increment in 2-year average PM_{2.5} concentrations.

Table 3. Associations of CRP with long-term exposure to PM_{2.5} in repeated-measures analysis in Taiwanese adults

	Crude model		Model 1 ^a		Model 2 ^a	
	% difference (95% CI)	P	% difference (95% CI)	P	% difference (95% CI)	P
All (N = 39096)	1.21 (0.85, 1.57)	< 0.001	1.34 (0.99, 1.69)	< 0.001	1.31 (1.00, 1.63)	< 0.001
Sex						
men (N = 24138)	1.32 (0.89, 1.76)	< 0.001	1.28 (0.84, 1.72)	< 0.001	1.19 (0.79, 1.59)	< 0.001
women (N = 14958)	1.17 (0.58, 1.76)	< 0.001	1.58 (1.01, 2.16)	< 0.001	1.57 (1.06, 2.08)	< 0.001
Age group						
< 65 years (N = 37846)	1.30 (0.94, 1.66)	< 0.001	1.33 (0.97, 1.69)	< 0.001	1.32 (1.00, 1.64)	< 0.001
≥ 65 years (N = 1250)	1.11 (−0.79, 3.01)	0.25	1.21 (−0.71, 3.12)	0.21	1.14 (−0.67, 2.96)	0.22
School educational level						
< 13 years (N = 7163)	0.39 (−0.36, 1.15)	0.31	0.94 (0.18, 1.69)	0.02	1.02 (0.34, 1.70)	0.003
≥ 13 years (N = 31933)	1.40 (1.00, 1.8)	< 0.001	1.55 (1.16, 1.95)	< 0.001	1.45 (1.09, 1.80)	< 0.001
Smoking						
never smoker (N = 28867)	1.18 (0.76, 1.60)	< 0.001	1.37 (0.96, 1.79)	< 0.001	1.38 (1.01, 1.75)	< 0.001
ever smoker (N = 10229)	1.32 (0.66, 1.98)	< 0.001	1.21 (0.56, 1.87)	< 0.001	1.10 (0.50, 1.70)	< 0.001
Hypertension						
non-hypertensive (N = 32867)	1.27 (0.88, 1.66)	< 0.001	1.37 (0.98, 1.76)	< 0.001	1.31 (0.96, 1.66)	< 0.001
hypertensive (N = 6229)	1.20 (0.42, 1.98)	< 0.001	1.06 (0.28, 1.84)	0.008	1.32 (0.61, 2.03)	< 0.001
Diabetes						
non-diabetic (N = 37204)	1.23 (0.86, 1.59)	< 0.001	1.34 (0.98, 1.70)	< 0.001	1.31 (0.98, 1.63)	< 0.001
diabetic (N = 1892)	1.63 (0.21, 3.05)	0.02	1.50 (0.09, 2.90)	0.04	1.56 (0.26, 2.87)	0.02
BMI group						
< 25 kg/m ² (N = 26409)	1.48 (1.06, 1.90)	< 0.001	1.60 (1.19, 2.02)	< 0.001	1.49 (1.08, 1.91)	< 0.001
25–30 kg/m ² (N = 10684)	0.75 (0.20, 1.30)	0.008	0.83 (0.27, 1.38)	0.003	0.75 (0.20, 1.30)	0.007
≥ 30 kg/m ² (N = 2003)	1.05 (−0.10, 2.20)	0.07	0.79 (−0.35, 1.93)	0.17	0.67 (−0.46, 1.81)	0.25

Results are from the mix-effects linear regression models and estimates are presented as percentage changes in CRP for every 5 µg/m³ increment in 2-year average PM_{2.5} concentrations.

^aModel 1: adjusted for age (not in age-specific analysis), sex (not in sex-stratified analysis), educational level (not in educational level-specific analysis), smoking (not in smoking-stratified analysis), alcohol drinking, exercise, vegetable intake, fruit intake, occupational exposure to dust and organic solvent, number of medical visits (one through eight) and season; Model 2: further adjusted for BMI (not in BMI-stratified analysis), hypertension (not in hypertension-stratified analysis), diabetes (not in diabetes-stratified analysis), hyperlipidaemia, self-reported cardiovascular disease and self-reported cancer.

smoking is a well-documented factor which can induce chronic inflammation, and our previous study has observed increased levels of CRP in smokers.³⁴ Other traditional risk factors may also induce chronic inflammation, including obesity, hypertension, diabetes and dyslipidaemia, which was also demonstrated in our previous study.³⁵ In the present study, the significant associations remained after we took into account the effects of these potential confounders/modifiers.

Our study has some important strengths. It is the largest study so far to investigate long-term PM_{2.5} exposure and CRP. The participants were relative healthier and younger and were experiencing relatively higher exposure. The detailed information on a wide range of potential confounders and modifiers enables us to take into account the effects of these factors. Another strength is that we used a high-resolution and accurate satellite-based technology in our PM_{2.5} exposure estimate, which allowed us to overcome the spatial coverage and interpolation problems that occur when using only data from monitoring stations.

Furthermore, by using the satellite data, we could trace the change of PM_{2.5} exposure over time and take into account the impact of change on CRP variation.

One limitation is that we included exposure either at a residential or at a company address. There is no published literature we could find that relates residential and work locations. However, anecdotal evidence suggests that Taiwanese do not live very far from their places of work. Thus, using residential or company addresses for exposure estimate should not result in serious misclassification. Our sensitivity analysis also demonstrates similar results when we excluded those participants giving a company address. Another limitation is that information on indoor PM_{2.5} was not available. However, we have taken into account smoking, one of the most important sources of household air pollution in a developed economy.

In conclusion, our study shows that long-term exposure to PM_{2.5} is associated with increased levels of CRP. Evidence from this study strongly supports that PM-induced inflammation is a major biological pathway

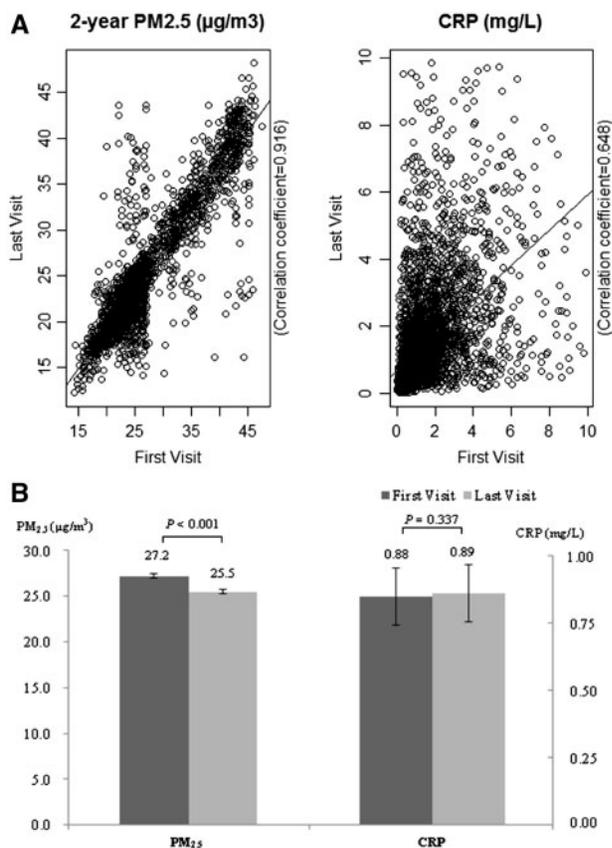


Figure 2. Panel A. Distribution of $PM_{2.5}$ and CRP concentrations at first and last visits in the 4449 Taiwanese adults. Panel B. Comparison of $PM_{2.5}$ and CRP concentrations between first and last visits in the 4449 Taiwanese adults; CRP means in Panel B were adjusted for age, sex, educational level, smoking, alcohol drinking, exercise, vegetable intake, fruit intake, occupational exposure to dust and organic solvent, season, BMI, hypertension, diabetes, hyperlipidaemia, self-reported cardiovascular disease and self-reported cancer.

linking PM air pollution and cardiovascular events. We advocate strategies of global air pollution reduction to prevent cardiovascular disease.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: The authors declare that they have no conflict of interest related to this manuscript.

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