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The Different Impact of PM2.5 on Atherogenesis in Overseas vs. Native Chinese in the CATHAY Study

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Abstract: Air pollution (PM2.5) has been associated with cardiovascular disease (CVD) globally and with early atherosclerosis surrogate markers in modernized China. A sizeable number of Chinese have migrated overseas, with an increase in their vulnerability to CVD. To evaluate the impact of PM2.5 air pollution on atherogenesis in native vs. overseas Chinese, we recruited 756 asymptomatic native Chinese and 507 age- and gender-matched overseas Chinese from Sydney and San Francisco. Their cardiovascular profiles were evaluated. PM2.5 was derived from remote sensing technology; atherosclerosis surrogate markers, flow-mediated dilation (FMD) and carotid intima-media thickness (IMT) were measured by ultrasound. The native Chinese had a higher proportion of smokers as well as higher blood pressure, glucose, metabolic syndrome and PM2.5 exposure ($p < 0.001$), but lower lipids and folate than the overseas Chinese ($p < 0.0001$). Carotid IMT was lower in the native Chinese ($p < 0.0001$), but the other vascular parameters were similar. A multivariate regression revealed that FMD in the native Chinese was related to the male gender, age and location; in the overseas Chinese, it was related to age, but not to PM2.5. Carotid IMT in the native Chinese was related to PM2.5, independent of atherosclerotic risk factors and location ($R^2 = 0.384$, $F = 34.5$, $p < 0.0001$) whereas in the overseas Chinese, IMT was related to the male gender and age, but not to PM2.5 or overseas location ($R^2 = 0.282$, $F = 19.7$, $p < 0.0001$). PM2.5 had a greater impact on atherogenesis in the native Chinese, independent of traditional risk factors, with implications for preventive strategies.

Keywords: PM2.5 air pollution; atherogenesis; native Chinese; overseas Chinese

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1. Introduction

Cardiovascular disease (CVD) and strokes are the leading causes of morbidity and mortality worldwide due to atherosclerosis as the main underling pathological process [1,2]. Each year, over 420 million cases of CVD and 17.9 million deaths from CVD have been reported [3]. Apart from traditional modifiable and non-modifiable atherosclerosis risk factors [4,5], the detrimental impact of air pollution, especially particulate matters less than 2.5 µm in diameter (PM2.5), has been realized [6–8]. Of the 7 million premature deaths linked to outdoor and household PM2.5 pollution, 34% were due to ischemic heart disease, 21% to pneumonia and 20% to strokes [9].

Over the past century, many Chinese have migrated overseas, including to North America and Australia, with 1–2 generations born overseas. Recent epidemiological studies have suggested that these overseas migrants (overseas Chinese) are more vulnerable to the

development of atherosclerotic disease compared with those staying behind in mainland China (native Chinese) [10,11]. The modernization of overseas living, with fast economic developments and associated lifestyle changes, has been implicated. In this regard, the recent modernization process for native Chinese—with similar economic developments, but probably worse air pollution problems—has been acknowledged [12]. We have previously reported on the different relationships between traditional cardiovascular risk factors and the early atherogenic process in native vs. Sydney Chinese [10,11,13,14]. We have also recently documented the impact of air pollution on atherosclerosis markers in northern vs. southern mainland Chinese adults [15]. The aim of the current report was to evaluate the impact of PM2.5 air pollution on atherogenesis in native Chinese compared with overseas Chinese from Sydney and San Francisco.

2. Subjects and Methods

We studied 1263 Han Chinese from southern China (Hong Kong, Macau and Pan Yu; n = 371), northern China (Yu County in Shanxi and the Three Gorges territories of the Yangtze River; n = 385) and age- and gender-matched ethnic Chinese from Sydney (n = 141) and the San Francisco Bay area (n = 366) from 1996–2007 as part of our multinational collaborative Chinese Atherosclerotic Study in the Aged and Young (CATHAY Study) project (Table 1 and Figure 1). The project protocol has previously been outlined and the related findings reported previously [13–18]. The overseas Chinese were either born overseas or had migrated and stayed overseas for at least 10 years.

Table 1. Mean yearly PM2.5 air pollution exposure.

Location	Year of Study	Number of Subjects	PM2.5 (μg/m^3)
Sydney	1997–1999	141	5.8 ± 0.1
San Francisco (Bay Area)	1999–2001	366	14.8 ± 2.8
Southern China (Hong Kong, Macau, Pan Yu)	1991–1997	371	41.5 ± 5.4
Northern China (Three Gorges Territories, Yu County)	2000–2007	385	73.2 ± 0.17

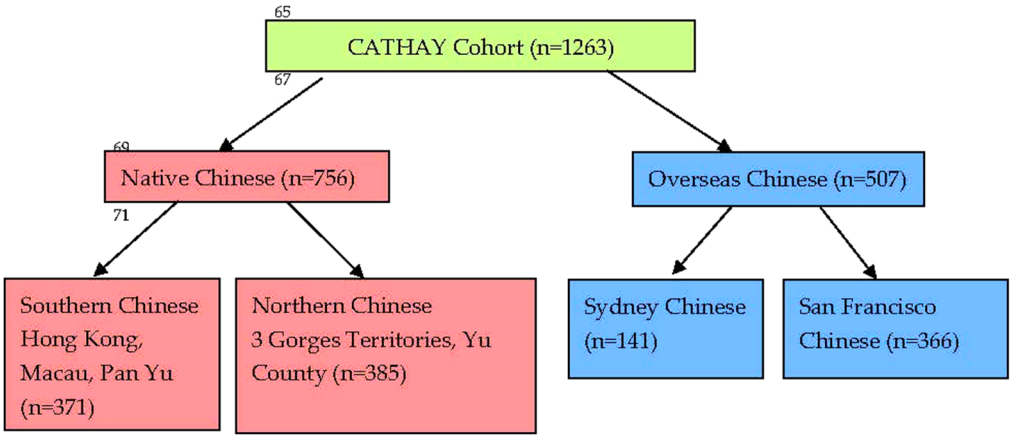

Figure 1. Schematic diagram of enrolment in the CATHAY Study. Overall, 1263 Chinese (507 overseas Chinese and 756 native Chinese) with complete and accessible data were recruited.

All participants were apparently healthy and asymptomatic; had no known major renal, hepatic or vascular diseases; and were not taking any regular medications or vitamin supplements. Those discovered after a physical examination and blood tests to have renal hepatic, cardiovascular or thyroid derangements were excluded. After fasting for 14 h and providing written informed consent, their cardiovascular profiles were evaluated, including smoking status, body mass index (BMI), waist–hip ratio (WHR) and systolic

and diastolic blood pressures (SBP and DBP). On recruitment, blood was taken once for the lipid profiles (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG)), fasting glucose, folate, total homocysteine (HC) and methylenetetrahydrofolate reductase (MTHFR) C/T genotypes. Fasting glucose was measured by haemstix and HC by an enzymatic immune assay (Abbott X analyses, Abbott Peak, IL, USA). The MTHFR C/T genotypes were evaluated by the PCR technique at the Li Hysan Research Laboratory of the Chinese University of Hong Kong.

Blood was assayed in batches at the Prince of Wales Hospital in Hong Kong, Centro Hospitalar Conde de Sao Januario in Macau and the Second Hospital of Chongqing Medical University, all currently accredited by USA laboratory centers. Metabolic syndrome (MS) was diagnosed according to the International Diabetes Federation (IDF) criteria [19].

2.1. Particulate Matter (PM2.5) Concentration Evaluation

The average (mean ± SD) yearly long-term satellite-derived PM2.5 concentration over southern and northern China as well as Sydney and the San Francisco Bay area in the period 1997–2007 was evaluated by satellite remote sensing technology [20–22]. For each subject, the mean concentration of PM2.5 over the study year was registered. The evaluation of such long-term PM2.5 concentrations against the ground observations demonstrated a root-mean-squared error of 8.9 $\mu g/m^3$, a correlation coefficient of >0.9 ($R^2 > 0.8$) and a mean absolute percentage error within ±20%.

2.2. Vascular Studies

The endothelial function (vascular reactivity) of the brachial artery (flow-mediated dilation (FMD)) was studied once upon recruitment using high-resolution B-mode ultrasonography, as described previously [23–25]. In brief, the diameter of the brachial artery was measured from B-mode images using a linear array transducer (L10-5) with a median frequency of 7.5 MHg and a standard Advanced Technology Laboratories (ATL300 USA) or Sonosite (model Micormaxx, Bothell, WA, USA) system. A forearm tourniquet cuff was applied to induce reactive hyperemia upon deflation. The scans were acquired at rest and during reactive hyperemia (to induce endothelium-dependent dilation (FMD)) and after 200 µg sublingual glyceryltrinitrate (GTN, an endothelium-independent dilation). GTN and FMD were expressed as a percentage dilation of the vessel diameter from the baseline. Hyperemia, as an indicator of stress to the endothelium, was calculated as the maximal percentage increase in the blood flow after cuff deflation compared with the baseline.

Carotid intima-media thickness (IMT) was measured using a standardized scanning protocol for both carotid arteries, as described by Salonen and Salonen and Bots and Touboul et al. [26–28]. Images of the far wall of the distal of 10 mm of the common carotid artery were used. All scans were evaluated offline by a verified automatic edge-detecting and measurement software package with an intra-observer variability for a mean IMT of 0.03 ± 0.01 mm and a coefficient of variation of 1% (R = 0.99) and good inter-observer reproducibility (R = 0.95) [10].

3. Statistical Analyses

The project data were processed to obtain the mean values, standard deviations and 95% confidence intervals (CI), when appropriate. The normal distribution was assessed by the standard testing of the normality of distribution; the intergroup differences were tested with an independent sample Student's *t*-test and a one-way ANCOVA model. The primary study endpoints were brachial FMD and carotid IMT. The other outcome variables were compared after a Bonferroni adjustment for multiple comparisons. On the assumption of the mean brachial FMD being 7.9 ± 2.1% and the mean carotid IMT being 6.2 ± 0.12 mm in the cohort, we estimated that the enrolment of 700 native Chinese and 500 overseas Chinese with complete datasets would result in an adequate power of 80% to detect a 4% difference in brachial FMD and a power of 85% to detect a 6% difference in carotid IMT between the native Chinese and overseas Chinese at the $2p < 0.05$ significance level [29]. Multivariate

regression analyses were carried out to assess the determinants of the major risk factors for FMD and IMT in the native and overseas Chinese cohorts, respectively, including age, gender, smoking status, PM2.5, BMI, metabolic syndrome, LDL-C, homocysteine, MTHFR genotypes and location (southern or northern China for the native Chinese; Sydney or San Francisco for the overseas Chinese). The beta effect was evaluated by mixed effects. The variables with significant standardized beta coefficients (beta-value with $p < 0.05$) as a measure of the contribution to the model were identified and insignificant variables ($2p > 0.05$) were subsequently removed from the regression model. The interaction effect was examined by including the interaction terms (product of PM2.5 and age, PM2.5 and location or PM2.5 and male gender) into the regression model. A group difference with an error probability of less than 5% ($2p < 0.05$) was considered to be statistically significant. The statistical analyses were performed with SPSS version 25 (IBM, Armonk, NY, USA).

This study complied with the 1995 and 2003 Declaration of Helsinki for human studies. Our institutional research ethics committee at the Chinese University of Hong Kong approved the research study and written informed consent form (CREC 2018.157).

4. Results

A total of 1263 subjects were recruited, with mean ages ranging from 44.9 ± 10.5 to 47.1 ± 11.9 years. The mean PM2.5 exposure ranged from 5.8 ± 0.1 μg/m^3 in Sydney to 73.2 ± 0.7 μg/m^3 in northern China (Table 1); approximately half the subjects from each location were male.

4.1. Demographic and Clinical Characteristics

Compared with the southern Chinese, the northern Chinese were characterized by a higher smoking status, PM2.5 exposure, SBP, DBP, TG, MTHFR TT genotype, MS and homocysteine ($p < 0.0001$), but a lower LDL-C, HDL-C and folate ($p < 0.0001$) (Table 2). Compared with the Sydney Chinese, the Chinese from the San Francisco Bay area had a higher PM2.5 exposure, LDL-C and folate ($p < 0.0001$) as well as a higher MS ($p < 0.001$), SBP and DBP ($p < 0.005$), but a lower smoking status ($p < 0.0001$), male gender, MTHFR and HC ($p < 0.001$).

Table 2. Demographic and clinical characteristics of 1263 Chinese.

	Southern China	Northern China	Sydney	San Francisco
Total Subjects	371	385	141	366
Male (%)	53	55	55	46 §§
Age (Years)	45.6 ± 13.1	45.1 ± 10.1	44.9 ± 10.5	47.1 ± 11.9
Smoking (%)	11	39 *	20	9 §
PM2.5 (μg/m^3)	41.5 ± 5.4	73.2 ± 0.7 *	5.8± 0.1	14.8 ± 2.8 §
BMI	23.2 ± 3.6	24.4 ± 3.4	23.0 ± 3.0	23.7 ± 4.0
SBP (mmHg)	117.5 ± 14.8	124.5 ± 15.0 *	115.7 ± 15.5	120.4 ± 17.1 §§§
DBP (mmHg)	75.3 ± 9.3	82.0 ± 10.0 *	76.7 ± 9.5	79.8 ± 10.5 §§§
WHR	0.84 ± 0.06	0.84 ± 0.07	0.84 ± 0.06	0.84 ± 0.07
Glucose (mmol/L)	5.55 ± 1.13	5.54 ± 0.94	5.01 ± 0.57	5.18 ± 0.85
HDL-C (mmol/L)	1.33 ± 0.36	1.11 ± 0.30 *	1.42 ± 0.36	1.34 ± 0.38
LDL-C (mmol/L)	3.52 ± 0.95	2.34 ± 0.74 *	3.21 ± 0.83	3.54 ± 0.87 §
TG (mmol/L)	1.21 ± 0.79	1.60 ± 0.88 *	1.45 ± 1.03	1.47 ± 1.05

Table 2. *Cont.*

	Southern China	Northern China	Sydney	San Francisco
MS (%)	16.3	29.9 *	10.6	17.2 §§
Folate (nmol/L)	29.5 ± 15.2	13.2 ± 5.5 *	21.0 ± 6.1	29.9 ± 13.6 §
MTHFR (TT%)	3.8	28.5 *	13.5	5.0 §§
Homocysteine (μmol/L)	9.6 ± 4.3	24.5 ± 20.3 *	8.3 ± 2.3	7.2 ± 1.8 §§

*: Compared with southern China, $p < 0.0001$; §: compared with Sydney, $p < 0.0001$; §§: compared with Sydney, $p < 0.001$; §§§: compared with Sydney, $p < 0.005$. BMI: body mass index; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MS: metabolic syndrome; MTHFR: methylenetetrahydrofolate reductase; PM2.5: particulate matter < 2.5 um in diameter; SBP: systolic blood pressure; TG: triglycerides; WHR: waist–hip ratio.

The native Chinese cohort had a higher proportion of smokers (29% vs. 12%), higher PM2.5 exposure (37.7 ± 6.3 vs. 12.3 ± 4.4 μg/m^3), blood fasting glucose (5.6 ± 1.0 vs. 5.1 ± 0.8 mmol/L), MTHFR TT genotype (17% vs. 13.5%) and blood homocysteine (17.2 ± 16.5 vs. 7.6 ± 2.1 μmol/L, $p < 0.0015$), but significantly lower HDL-C (1.22 ± 0.36 vs. 1.37 ± 0.37 mmol/L), LDL-C (2.92 ± 1.04 vs. 3.44 ± 0.87 mmol/L) and folate (21.2 ± 13.9 vs. 28.6 ± 13.2 nmol/L) compared with the overseas Chinese ($p < 0.0015$) (Table 3).

Table 3. Demographic and clinical characteristics of 1263 asymptomatic Chinese.

Risk Factors	Native Chinese	Overseas Chinese	*p*-Value	Post-Bonferroni Adjustment
Total Subjects	756	507		
Male (%)	54	49	0.078	(>0.9)
Age (Years)	45.3 ± 11.7	46.5 ± 11.6	0.087	(>0.9)
Smoking (%)	29	12	<0.0001	(<0.0015)
PM2.5 (μg/m^3)	57.7 ± 6.3	12.3 ± 4.4	<0.0001	(<0.0015)
BMI	23.8 ± 3.6	23.5 ± 3.8	−0.149	(>0.9)
SBP (mmHg)	121.2 ± 15.3	119.1 ± 16.8	0.025	−0.375
DBP (mmHg)	78.7 ± 10.2	79.0 ± 10.3	0.681	(>0.9)
WHR	0.84 ± 0.07	0.84 ± 0.07	0.84	(>0.9)
Glucose (mmol/L)	5.6 ± 1.0	5.1 ± 0.8	<0.0001	(<0.0015)
HDL-C (mmol/L)	1.22 ± 0.35	1.37 ± 0.37	<0.0001	(<0.0015)
LDL-C (mmol/L)	2.92 ± 1.04	3.44 ± 0.87	<0.0001	(<0.0015)
TG (mmol/L)	1.41 ± 0.86	1.47 ± 1.04	0.271	(>0.9)
MS (%)	23.1	15.4	<0.0001	(<0.0015)
Folate (mmol/L)	21.2 ± 13.9	28.6 ± 13.2	<0.0001	(<0.0015)
MTHFR (TT%)	17.1	13.5	<0.0001	(<0.0015)
Homocysteine (μmol/L)	17.2 ± 16.5	7.6 ± 2.1	<0.0001	(<0.0015)

BMI: body mass index; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MS: metabolic syndrome; MTHFR: methylenetetrahydrofolate reductase; PM2.5: particulate matter < 2.5 um in diameter; SBP: systolic blood pressure; TG: triglycerides; WHR: waist–hip ratio.

4.2. Vascular Parameters from Different Locations

Carotid IMT and brachial FMD were normally distributed. Brachial FMD in the southern native Chinese was higher (8.5 ± 2.6, 95% CI 8.2–8.8%); carotid IMT (0.58 ± 0.13, 95% CI 0.56–0.59 mm) and hyperemia were lower (649 ± 273, 95% CI 619–680%) com-

pared with FMD (7.2 ± 1.9, 95% CI 6.9–7.0, $p < 0.001$), carotid IMT (0.68 ± 0.16, 95% CI 0.62–0.65 mm, $p < 0.0001$) and hyperemia (782 ± 201, 95% CI 753–812%, $p < 0.0004$) in the northern native Chinese. In the overseas cohort, the Sydney Chinese had better brachial FMD (8.8 ± 2.6, 95% CI 8.1–9.5 vs. 8.1 ± 2.2%, 95% CI 7.9–8.4%, $p = 0.044$), lower carotid IMT (0.59 ± 0.15, 95% CI 0.57–0.62 mm vs. 0.68 ± 0.15, 95% CI 0.66–0.69 mm, $p < 0.0001$) and higher GTN (20.1 ± 4.2, 95% CI 19.0–21.6% vs. 18.0 ± 2.9, 95% CI 17.6–18.3%, $p < 0.0004$) than the San Francisco Chinese (Table 4). The overall native Chinese cohort had lower carotid IMT (0.61 ± 0.12, 95% CI 0.60–0.62 mm) than the overseas Chinese (0.65 ± 0.16, 95% CI 0.64–0.67 mm, $p < 0.0001$), but their brachial FMD and other vascular parameters were similar (Table 5).

Table 4. Vascular parameters from different locations.

	Native Chinese (n = 756)			Overseas Chinese (n = 507)		
Parameters	**Southern China**	**Northern China**	***p*-Value**	**San Francisco**	**Sydney**	***p*-Value**
GTN (%)	18.2 ± 4.1	18.5 ± 3.2	>0.9 §	18.0 ± 2.9	20.1 ± 4.2	<0.0004 §
(95% CI)	(17.8–18.7)	(18.0 –18.9)		(17.6–18.3)	(19.0–21.6)	
Hyperemia (%)	649 ± 273	782 ± 201	<0.0004 §	716 ± 264	696 ± 243	>0.9
(95% CI)	(619–680)	(753–812)		(682–750)	(63–762)	
FMD (%)	8.5 ± 2.6	7.2 ± 1.9	<0.0001	8.1 ± 2.2	8.8 ± 2.6	0.044
(95% CI)	(8.2–8.8)	(6.9–7.4)		(7.9–8.4)	(8.1–9.5)	
Carotid IMT (mm)	0.58 ± 0.13	0.64 ± 0.12	<0.0001	0.68 ± 0.15	0.59 ± 0.15	<0.0001
(95% CI)	(0.56–0.59)	(0.62–0.65)		(0.66–0.69)	(0.57–0.62)	

GTN: glyceryltrinitrate-induced dilation; FMD: brachial flow-mediated dilation; IMT: intima-media thickness. §: Post-Bonferroni adjustment.

Table 5. Vascular parameters of 756 native vs. 507 overseas Chinese.

Parameters	**Native Chinese (n = 756)**	**Overseas Chinese (n = 507)**	***p*-Value**
GTN (%)	18.3 ± 3.8	18.4 ± 3.3	>0.9 §
(95% CI)	(18.0–18.6)	(18.0–18.8)	
Hyperemia (%)	698 ± 257	712 ± 260	>0.9 §
(95% CI)	(675–721)	(682–743)	
FMD (%)	8.0 ± 2.5	8.3 ± 2.3	0.136
(95% CI)	(7.8–8.2)	(8.0–8.5)	
Carotid IMT (mm)	0.61 ± 0.12	0.65 ± 0.16	<0.0001
(95% CI)	(0.60–0.62)	(0.64–0.67)	

GTN: glyceryltrinitrate-induced dilation; FMD: brachial flow-mediated dilation; IMT: intima-media thickness. §: Post-Bonferroni adjustment.

4.3. Determinants of the Risk Factors for Brachial FMD and Carotid IMT

From the multivariate regression analyses, brachial FMD in the native Chinese was inversely related to age (beta = −0.217, $p < 0.0001$), male gender (beta = −0.139, $p = 0.022$) and northern and southern locations (beta = 0.281, $p = 0.011$), but not to PM2.5 or other risk factors (model $R^2 = 0.180$, F = 8.37, $p < 0.0001$). In the overseas Chinese, brachial FMD was inversely related to age (beta = −0.189, $p = 0.003$), but not to PM2.5 or other risk factors (model $R^2 = 0.101$, F = 4.12, $p < 0.0001$) (Table 6). In the native Chinese, carotid IMT was related to PM2.5 (beta = 0.389, $p < 0.0001$), independent of the male gender (beta = 0.123, $p = 0.040$), age (beta = 0.412, $p < 0.0001$), smoking status (beta = 0.084, $p = 0.049$), BMI (beta = 0.097, $p = 0.015$), MS (beta = 0.107, $p = 0.011$), LDL-C (beta = 0.114, $p = 0.009$), homocysteine (beta = 0.125, $p = 0.004$) or southern and northern locations (beta = −0.241, $p < 0.0001$) (model $R^2 = 0.384$, F = 34.5, $p < 0.0001$). Direct interaction effects of different

locations (beta = 0.240, $p < 0.0001$) and age (beta = 0.406, $p = 0.034$) with PM2.5 on carotid IMT were observed for the native Chinese. In the overseas Chinese, however, carotid IMT was related to the male gender (beta = 0.133, $p = 0.004$), age (beta = 0.380, $p < 0.0001$) and LDL-C (beta = 0.113, $p = 0.006$), but not to PM2.5 or location (model $R^2 = 0.282$, F = 19.7, $p < 0.0001$) (Table 7). No significant direct interaction effects of gender, age or LDL-C with PM2.5 on carotid IMT were identified for the overseas Chinese ($p > 0.5$).

Table 6. Determinants of risk factors for brachial FMD in 1263 Chinese.

Factors	Native Chinese *		Overseas Chinese **	
	Beta-Value	***p*-Value**	**Beta-Value**	***p*-Value**
Gender	−0.139	0.022	−0.089	0.187
Age (Years)	−0.217	< 0.0001	−0.189	0.003
Smoking Status	−0.105	0.091	−0.105	0.072
BMI	0.013	0.814	−0.009	0.882
MS	−0.038	0.650	−0.121	0.049
LDL-C (mmol/L)	−0.108	0.108	0.008	0.896
Homocysteine (μmol/L)	−0.028	0.678	−0.054	0.486
MTHFR (TT%)	−0.023	0.699	0.039	0.499
PM2.5 ($\mu g/m^3$)	−0.058	0.630	0.186	0.230
Location	−0.281	0.011	−0.268	0.060

* Model $R^2 = 0.180$; F = 8.37; $p < 0.0001$. ** Model $R^2 = 0.101$; F = 4.12; $p < 0.0001$. BMI: body mass index; LDL-C: Low-density lipoprotein cholesterol; Location: native Chinese (Hong Kong, Macau, Pan Yu, Yu County, Three Gorges) and overseas Chinese (Sydney, San Francisco); MS: metabolic syndrome; MTHFR: methylenetetrahydrofolate reductase; PM2.5: particulate matter < 2.5 um in diameter.

Table 7. Determinants of risk factors for carotid IMT in 1263 Chinese.

Factors	Native Chinese *		Overseas Chinese **	
	Beta-Value	***p*-Value**	**Beta-Value**	***p*-Value**
Gender	0.123	0.040	0.133	0.004
Age (Years)	0.412	<0.0001	0.380	<0.0001
Smoking Status	0.084	0.049	−0.037	0.376
BMI	0.097	0.015	0.051	0.226
MS	0.107	0.011	0.070	0.099
LDL-C (mmol/L)	0.114	0.009	0.113	0.006
Homocysteine (μmol/L)	0.125	0.004	0.047	0.350
MTHFR (TT%)	−0.024	0.552	0.008	0.832
PM2.5 ($\mu g/m^3$)	0.389	<0.0001	0.050	0.659
Location	−0.241	<0.0001	0.159	0.137

* Model $R^2 = 0.180$; F = 8.37; $p < 0.0001$. ** Model $R^2 = 0.101$; F = 4.12; $p < 0.0001$. BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; Location: native Chinese (Hong Kong, Macau, Pan Yu, Yu County, Three Gorges) and overseas Chinese (Sydney, San Francisco); MS: metabolic syndrome; MTHFR: methylenetetrahydrofolate reductase; PM2.5: particulate matter < 2.5 um in diameter.

In the simple regression model of the whole group, brachial FMD was inversely related to PM2.5 (beta = −0.368, $p < 0.0001$) and to native/overseas location (beta = −0.210, $p < 0.0001$); carotid IMT was significantly related to PM2.5 (beta = 0.369, $p < 0.0001$) and native/overseas location (beta = 0.419, $p < 0.0001$) (Table 8).

Table 8. Determinants of risk factors for brachial FMD and carotid IMT in 1263 Chinese.

Factors	Brachial FMD *		Carotid IMT **	
	Beta-Value	***p*-Value**	**Beta-Value**	***p*-Value**
Gender	−0.163	<0.0001	0.180	<0.0001
Age (Years)	−0.264	<0.0001	0.461	<0.0001
Smoking Status	−0.099	0.013	−0.026	0.37
PM2.5 (μg/m^3)	−0.368	<0.0001	0.359	<0.0001
Location	−0.210	<0.0001	0.419	<0.0001

* Model R^2 = 0.154; F = 26.5; $p < 0.0001$. ** Model R^2 = 0.279; F = 87.3; $p < 0.0001$. FMD: flow-mediated dilation; IMT: intima-media thickness; Location: native vs. overseas.

5. Discussion

Advances in high-resolution B-mode ultrasonography allow the evaluation of subclinical atherogenic processes, including endothelial dysfunction and intima-media thickening to plaque deposits, with prognostic implications for CVD outcomes. Nevertheless, of the two early processes, FMD measured once is more dynamic and vulnerable to daily fluctuations of the more labile impacts of PM2.5 and other risk factors whereas IMT measurements may reflect the more stable and overall adverse effects of these risk factors on atherogenic processes [2,17,23,28,30,31]. This could account for the insignificant independent association of PM2.5 air pollution with brachial FMD in both the native and overseas Chinese from the multivariate analyses, despite an obvious significant difference in their FMD from the univariate analyses. We recently reported that despite higher PM2.5 pollution in northern China, PM2.5 pollution was more significantly associated with atherogenic surrogate markers in southern compared with northern Chinese [15]. The present study evaluated southern and northern Chinese and compared these groups with overseas Chinese from Sydney and the San Francisco Bay area.

Our research confirmed the detrimental impact of PM2.5 air pollution on atherosclerosis surrogate markers in modernized China, particularly in the more polluted northern native Chinese, as well as in the overseas Chinese, although to a lesser extent. The reasons for the differences are not clear. One could speculate that in the presence of western lifestyle factors that promote atherogenesis in overseas Chinese, the effect of lower PM2.5 pollution might be less important than in native Chinese as the western lifestyle factors could "overwhelm" the possibly detrimental effects of PM2.5 that are apparent in native Chinese. The absolute difference in carotid IMT between the overseas and native Chinese (7%) was relatively small. However, to contextualize this difference, a 0.164 mm increase in carotid IMT has been associated with a 41% increase in strokes and a 43% increase in acute myocardial infarctions over a follow-up period of 2.7 years [26]. The 7% difference in carotid IMT in the present study was similar to the type of difference seen between diabetic and non-diabetic Chinese adults [14].

The WHO revised the optimal PM2.5 guideline to 5 μg/m^3 in September 2021, further endorsing the detrimental effects of PM2.5 on human health. The mean PM2.5 concentrations in the overseas Chinese were slightly higher, but those in the native Chinese were much higher than this WHO standard. Greater efforts are urgently needed to contain the problem.

In general, the atherogenic processes in the overseas Chinese exposed to lower PM2.5 pollution were more related to traditional risk factors whereas in the native Chinese, they were related to both traditional risk factors and environmental PM2.5 concentrations. Therefore, from our present study, we suggest slightly different preventive strategies for atherogenic processes. In overseas Chinese, PM2.5 exposure should be reduced for a variety of health reasons, including lung protection, even though we have not been able to show an independent significant effect on the atherogenic markers. Other preventive strategies should be targeted toward the optimal control of atherosclerotic risk factors,

including active and passive cigarette smoking, hypertension (blood pressure targeted below 130/80 mmHg) and the optimal control of diabetes mellitus, metabolic syndrome, central obesity and hyperlipidemia as well as the promotion of daily physical activities. For native Chinese, apart from these preventive approaches, more effective strategies and measures should be targeted to lower PM2.5 exposure and combat the detrimental influence of PM2.5 air pollution. These factors should incorporate the adoption of global and nationwide policies on air pollution [12,32] as well as personalized strategies of wearing facial masks, using air filtering or other purifying devices at home, schools or the workplace and the administration of certain health foods or nutrients, statins or leukotriene-modifier medicines [32–38].

6. Study Limitations

We acknowledge certain limitations in the present study. Firstly, we did not assess other biological parameters for PM2.5-induced atherogenesis such as high-sensitivity C-reactive protein, fibrinogen and cytokines, which may be more relevant to reflect inflammation and metabolic syndrome-induced atherogenesis. Secondly, we did not observe any detrimental effects of smoking on the vascular parameters in both the native and overseas Chinese groups. We have previously reported regarding this issue that smoking had less impact on carotid IMT or brachial FMD in rural and urbanized Chinese compared with white people in Australia [10,11]. This may suggest a less important impact of smoking compared with PM2.5 pollution in this study population. Thirdly, the overall yearly average of PM2.5 in each location was used and we did not address individual PM2.5 exposure. To measure this, a portable and handy PM2.5 monitor would need to be allocated to each individual subject, which would be logistically and technically demanding for a sample size of 1263 subjects, if not impossible. Fourthly, the location of the native Chinese was an important determinant of carotid IMT apart from PM2.5, implicating possible confounding effects of differences in lifestyle, dietary patterns and/or physical activities in different locations, which we did not assess in all subjects. However, we have previously reported that changes in lifestyle and dietary patterns were associated with a significant worsening of vascular biomarkers in a group of ex-farmers in the Three Gorges territories [39]. Lastly, the impact of ancestry or birth location on PM2.5 estimates and the impact of occult thyroid function, Lp(a) information, family history of cardiovascular disease and menopause were not tested.

7. Conclusions

PM2.5 air pollution has a greater impact on atherogenic processes in native Chinese than in overseas Chinese, independent of the traditional risk factors, with implications for different preventive strategies in the Chinese population.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The research data are available from the corresponding author to the editor and Atmosphere readers upon reasonable request.

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