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The Impact of Air Pollution (PM2.5) on Atherogenesis in Modernizing Southern versus Northern China

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Abstract: To evaluate the impact of PM2.5 air pollution on atherogenic processes in modernizing Southern versus Northern China, we studied 1323 asymptomatic Chinese in Southern and Northern China in 1996–2007. PM2.5 exposure and metabolic syndrome (MS) were noted. Brachial flow-mediated dilation (endothelial function FMD) and carotid intima-media thickness (IMT) were measured by ultrasound. Although age and gender were similar, PM2.5 was higher in Northern China than in Southern China. The Northern Chinese were characterized by lower lipids, folate and vitamin B12, but higher age, blood pressures, MS and homocysteine (HC) (p = 0.0015). Brachial FMD was significantly lower and carotid IMT was significantly greater (0.68 ± 0.13) in Northern Chinese, compared with FMD and IMT (0.57 ± 0.13, $p < 0.0001$) in Southern Chinese. On multivariate regression, for the overall cohort, carotid IMT was significantly related to PM2.5, independent of location and traditional risk factors (Model $R^2 = 0.352$, F = 27.1, $p < 0.0001$), while FMD was inversely related to gender, age, and northern location, but not to PM2.5. In Southern Chinese, brachial FMD was inversely correlated to PM2.5, independent of age, whereas carotid IMT was significantly related to PM2.5, independent of age and gender. In Northern Chinese, brachial FMD was inversely related to gender only, but not to PM2.5, while carotid IMT was related to traditional risk factors. Despite a higher PM2.5 pollution in Northern China, PM2.5 pollution was more significantly associated with atherogenic surrogates in Southern compared to Northern Chinese. This has potential implications for atherosclerosis prevention.

Keywords: atherogenesis; flow-mediated dilation; carotid intima-media thickness; air-pollution (PM2.5); modernizing China

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1. Introduction

Atherosclerotic diseases (stroke and heart attack CVS) are currently the most important global health hazard, including for mainland China, which is now in a rapid phase of modernization [1,2]. Traditional atherosclerosis risk factors, including smoking, hypertension, diabetes mellitus, hyperlipidemia, obesity and physical inactivity, have been implicated [3]. Recently the detrimental association of air pollution (AP) with CVS in modernized society has been realized. In particular, small particulate matter less than 2.5 µm in diameter (PM2.5) has been associated with cardiovascular morbidity and mortality [4–6]. Of the 7 million premature deaths each year linked to air pollution (PM2.5), 34% were related to ischemic heart disease, 26% to respiratory disease and 20% were due to stroke [7].

The pathobiology of PM2.5-related atherosclerotic disease may involve direct effects of PM2.5 on cardiovascular system and/ or indirect effects of PM2.5 mediated by oxidative stress and vascular inflammation [8,9]. In other words, PM2.5 can act as a trigger in susceptible persons, or it can contribute to long-term atherogenic processes. On this issue, we and others have previously documented the negative impact of long-term PM2.5 exposure on atherosclerosis surrogates (brachial endothelial dysfunction FMD and carotid intima-media thickening IMT), which are closely linked to cardiovascular and stroke outcome [10–12].

In the past three decades, China has been undertaking a process of rapid economic development and modernization [13]. This started from the Southern seashore region and the greater Pearl Delta Bay area, and later moved to the Northern parts of the country, with different PM2.5 pollution exposure. The present study aimed to evaluate the impact of PM2.5 pollution on atherogenic process in Southern compared with Northern China.

2. Subjects and Methods

A total of 1323 asymptomatic Chinese adults (mean age 47.1 $\pm$ 11.7 years and 47.5% male) in Southern China (Hong Kong, Macau, Pan Yu, n = 395) and Northern China (Yu County in Shanxi and Three Gorges Territories of Yangtze River, n = 928) were studied in 1996–2007, as part of the international collaborative Chinese Atherosclerosis in the Aged and Young Project (CATHAY Study). The study protocol and some related findings have been reported previously [14–18].

All recruited subjects were apparently healthy. They were not known to have hypertension, diabetes mellitus or metabolic syndrome, had no major vascular, hepatic or renal disease, and were not taking any regular medications, including vitamin supplementation. Nearly all subjects (>95%) were local born residents and the other migrated to the county for over 10 years. After fasting for 14 h and signing written informed consent, their cardiovascular risk profiles, including smoking, body mass index (BMI), waist circumference, waist hip ratio (WHR), systolic and diastolic blood pressure (SBP, DBP) were measured. On recruitment, blood was taken once for fasting lipid profile (total, high and low lipoprotein cholesterol, TC, HDL-C, LDL-C and triglycerides TG), creatinine, vitamin B12, folate, and fasting total homocysteine (HC). Fasting glucose was measured by haemstix and HC was evaluated on stored frozen sample by enzymatic immune assay (Abbott IMX analyses, Abbott Peak, IL, USA). Blood was assayed in batches at the The Hospital Central Corde de Januarie, Macau, and The Prince of Wales Hospital, Hong Kong, currently accredited by the USA laboratory centres. MTHFR genotypes were evaluated by PCR technique at the Li Hysan research laboratory of the Chinese University of Hong Kong. Metabolic Syndrome (MS) was diagnosed according to International Diabetes Federation (IDF) criteria [19,20].

Our research study and informed consent form were reviewed and approved by our institutional research ethics committee of The Chinese University of Hong Kong (CREC 2000-108). This study complied with the 1995 and 2003 Helsinki Declaration for human studies.

2.1. PM2.5 Air Pollution Exposure

The yearly mean PM2.5 concentration over China was assessed by using the satellite remote sensing technology. Firstly, spectral data from the two moderate resolution imaging spectroradiometer (MODIS) instruments aboard the Terra and Aqua satellites were used to build aerosol optical depth (AOD) data at a resolution of $0.01^\circ \times 0.01^\circ$, over China [21]. Secondly, an observational data-driven algorithm, which took the ground-observed visibility and relative humidity data as inputs, was developed to derive the yearly mean ground-level PM2.5 concentration from the AOD [22]. Evaluation of the long-term satellite-derived PM2.5 concentration against the ground observations demonstrated a correlation coefficient of >0.9 and a mean absolute percentage error within $\pm$20% [23]. The mean concentration of PM2.5 over a single year was registered, corresponding to the study year of each subject.

2.2. Arterial Ultrasound Studies

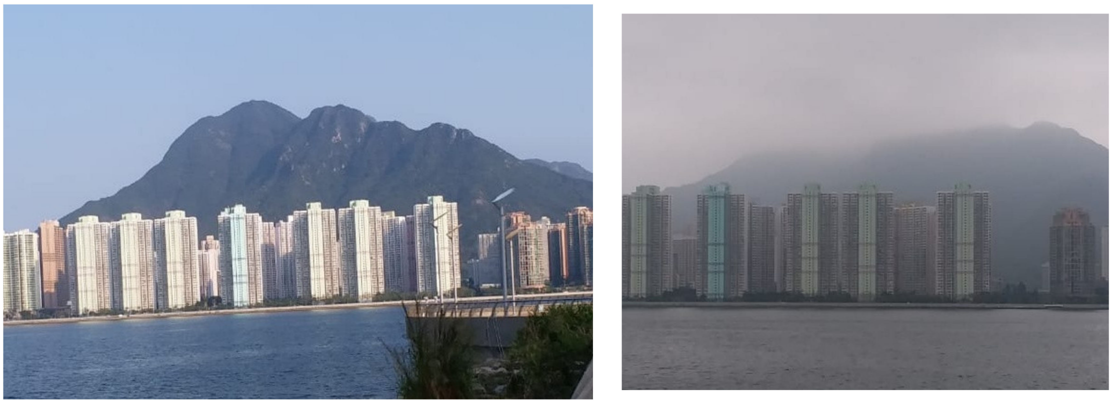
Atherosclerotic surrogate markers, flow-mediated dilation (FMD) of brachial artery, and carotid intima-media thickness (IMT), were studied once on recruitment using high resolution ultrasound as reported previously [24,25]. Briefly, forearm tourniquet cuff placement was applied to induce reactive hyperemia on deflation, and percentage of dilation in vessel diameter (from baseline) was computed, as indicator of endothelium-dependent dilation, in comparison with dilation after sublingual glyceryltrinitrate (endothelium-independent dilation GTN). Similarly carotid IMT was measured by using a standard scanning protocol for both carotid arteries as described by Salonen and Salonen, Bots and Touboul et al. [26–28]. Images of the far wall of the distal 10 mm of the common carotid artery were used. All scans were evaluated off-line by a verified automatic edge-detecting software device. The intra-observer variability for mean IMT was 0.03 ± 0.01 mm (coefficient of variation 1%, R = 0.99).

2.3. Statistical Analyses

The group mean values, standard deviation and 95% confidence intervals (CI) when appropriate were computed. Standard testing of normality of distribution was used for the assessment of normal distribution. Possible intergroup differences were identified with independent samples Students' test and a one-way ANCOVA model. The primary study endpoints were carotid IMT and brachial FMD, whereas other outcome variables were compared after Bonferroni adjustment for multiple comparisons. On the assumption of mean carotid IMT being 0.61±0.14 mm and brachial FMD being 8% ± 1% in the subjects, we estimated that enrolment of 350 subjects in Southern China and 600 subjects in Northern China would result in adequate power (80%) to detect a 18% difference in carotid IMT and an 8% difference in brachial FMD, between the two location groups at $2p < 0.05$ significance level [29]. Linear multivariate regressions were performed to assess the major determinants of IMT and FMD, including age, gender, smoking status, BMI, metabolic syndrome, LDL-C, PM2.5, southern and northern locations. The variables with significant standardized beta coefficients (beta value with $2p < 0.05$) as an indicator of the contribution to the model, were identified, and insignificant variables ($2p > 0.05$) were removed subsequently. Group differences with an error probability of 5% ($2p < 0.05$) were considered statistically significant. Analyses were performed with SPSS version 25.

3. Results

The demographic and clinical characteristics of the southern/ northern groups were tabulated (Table 1). While their gender, mean age, BMI and fasting glucose were similar, smoking status, SBP, DBP, metabolic syndrome and homocysteine were significantly lower, but their LDL-C, vitamin B12 and folate were significantly higher in Southern Chinese compared with the Northern Chinese ($p < 0.0015$). PM2.5 exposure in Southern China (44.0 ± 6.8 μg/m^3) (Figure 1A,B) was significantly lower than in Northern China (71.1 ± 15.8 μg/m^3), $p < 0.0015$. (Figure 2A,B).



(**A**) (**B**)

Figure 1. (**A**) Far view of residential estates and Mount Ma On along the Shing Moon River of Shatin, Hong Kong on clear day with PM2.5 concentration of 14 μg/m^3, and (**B**) on foggy polluted day with PM2.5 concentration of 45 μg/m^3 (Woo et al. [18]).

(**A**) (**B**)

Figure 2. (**A**) Sky view of Chongqing Garden on clear day with PM2.5 concentration of 45 μg/m^3, and (**B**) Chongqing residence estate near riverside on a foggy day with PM2.5 concentration of 79 μg/m^3 (Courtesy of Prof. YH Yin).

Table 1. Demographic Characteristics of Southern–Northern China.

	Southern China (n = 395)	**Northern China (n = 928)**	***p*-Value (Bonferroni Adjusted)**
Male Gender (%)	48	47	0.719 (>0.99)
Age (yr)	46.8 ± 12.8	47.4 ± 9.5	0.340 (>0.99)
Smoking Status (%)	15	35	<0.0001 (0.0015)
BMI	23.0 ± 4.0	23.4 ± 3.4	<0.203 (>0.99)
SBP (mmHg)	119.0 ± 15.7	123.7 ± 17.6	<0.0001 (0.0015)
DBP (mmHg)	75.9 ± 9.3	80.2 ± 11.0	<0.0001 (0.0015)
PM2.5 (μg/m^3)	44.0 ± 6.8	71.1 ± 15.8	<0.0001 (0.0015)
Creatinine (μmol/L)	81.7 ± 16.1	63.2 ± 16.7	<0.0001 (0.0015)
Glucose (mmol/L)	5.6 ± 1.2	5.4 ± 6.0	0.004 (0.06)
LDL-C	3.4 ± 1.0	2.56 ± 0.82	<0.0001 (0.0015)
Metabolic Syndrome (%)	15.0	24.5	<0.0001 (0.0015)
B12 (pmol/L)	411.7 ± 249.4	156.5 ± 90.6	<0.0001 (0.0015)
Folate (nmol/L)	31.1 ± 15.6	13.1 ± 5.6	<0.0001 (0.0015)
Homocysteine (umol/L)	9.6 ± 4.5	25.0 ± 21.0	<0.0001

B12: Vitamin B12. BMI: Body Mass Index. DBP: Diastolic Blood Pressure. LDL-C: Low Density Lipoprotein Cholesterol. PM2.5: Particulate Matter <2.5 um in Diameter.

3.1. Vascular Parameters

Brachial FMD and carotid IMT were normally distributed. Brachial FMD was significantly lower (7.5 ± 18, 95% CI 7.3–7.7%, $p < 0.001$), but carotid IMT was significantly greater (0.68 ± 0.13, 95% CI 0.67–0.69 mm, $p < 0.0001$) in Northern Chinese, compared with their Southern counterparts (8.1 ± 3.0, 95% CI 7.8–8.5% and 0.57 ± 0.13, 95% CI 0.56–0.58 mm, respectively) (Table 2). The GTN responses of the two groups were similar.

Table 2. Vascular Parameters in Northern–Southern China Locations.

	Location		
	Southern	**Northern**	***p*-Value**
Hyperemia (%)	655 ± 289	715 ± 217	0.006
(95% CI)	(623–686)	(687–743)	
GTN (%)	18.1 ± 4.8	18.2 ± 3.0	0.912
(95% CI)	(17.6–18.7)	(17.8–18.6)	
FMD (%)	8.1 ± 3.0	7.5 ± 1.8 †	0.001
(95% CI)	(7.8–8.5)	(7.3–7.7)	
Carotid IMT (mm)	0.57 ± 0.13	0.68 ± 0.13 ††	0.0001
(95% CI)	(0.56–0.58)	(0.67–0.69)	

Compared with Southern China † $p < 0.0001$; †† $p = 0.01$. FMD: Flow-mediated Dilation. GTN: Glyceryltrinitrate Dilation. IMT: Intima-media Thickness.

3.2. Determinants of Risk Factors for Impaired Brachial FMD

On multivariate regression analyses, in Southern Chinese, brachial FMD was inversely related to PM2.5 (beta = −0.274, $p = 0.001$), age (beta= −0.238, $p < 0.005$), but not to gender, smoking status, BMI, MS, homocysteine, LDL-C or MTHFR. (Model $R^2 = 0.202$, F = 4.026, $p < 0.0001$) (Table 3). In Northern Chinese, brachial FMD was related to gender (beta = −0.329, $p = 0.009$), but not to other traditional risk factors (Model $R^2 = 0.211$, F = 3.802, $p < 0.0001$). In the overall 1323 Chinese cohort, lower brachial FMD was related to older age, male gender and northern location, but not to PM2.5 (Model $R^2 = 0.190$, F = 7.802, $p < 0.0001$).

Table 3. Determinants of Risk Factors for Brachial FMD *.

	Southern Chinese *		Northern Chinese **		Overall Cohort ***	
Risk Factors	**Beta Value**	***p*-Value**	**Beta Value**	***p*-Value**	**Beta-Value**	***p*-Value**
Age (yr)	−0.238	0.005	−0.163	0.062	−0.210	<0.0001
Gender	−0.174	0.050	−0.329	0.009	−0.163	0.013
Smoking status	−0.154	0.077	0.029	0.802	−0.118	0.075
BMI	−0.036	0.674	−0.040	0.415	0.005	0.938
MS	−0.067	0.436	−0.032	0.741	−0.051	0.403
Homocysteine	0.076	0.374	−0.196	0.066	−0.025	0.725
LDL-C	−0.058	0.473	−0.057	0.502	−0.090	0.206
MTHFR	−0.097	0.201	0.158	0.114	−0.014	0.822
PM2.5	−0.274	0.001	0.011	0.892	−0.022	0.862
Location	-	-	-	-	−0.325	0.005

* Model $R^2 = 0.202$; F-value = 4.026; $p < 0.0001$. ** Model $R^2 = 0.211$; F-value = 3.802; $p < 0.0001$. *** Model $R^2 = 0.190$; F-value = 7.802; $p < 0.0001$. BMI: Body Mass Index. FMD: Flow-mediated Dilation. LDL-C: Low Density Lipoprotein Cholesterol. MTHFR: Methylenetetrahydrofolate Reductase Gene Polymorphisms. PM2.5: Particulate Matters < 2.5 um in Diameter.

On multivariate regression analyses, carotid IMT in Southern Chinese was significantly related to PM2.5 (beta = 0.334, $p < 0.0001$), independent of age (beta = 0.393, $p < 0.0001$) and gender (beta = 0.146, $p = 0.043$) (Model $R^2 = 0.451$, F = 13.3, $p < 0.0001$) (Table 4). In Northern Chinese, carotid IMT was related to age (beta = 0.385, $p < 0.0001$), smoking status (beta = 0.157, $p = 0.01$), MS (beta = 0.110, $p = 0.039$), homocysteine (beta = 0.137, $p = 0.014$) and LDL-C (beta = 0.145, $p = 0.0003$), but not to PM2.5 (beta = 0.033, $p = 0.471$). For the overall cohort, carotid IMT was related to PM2.5 (beta = 0.368, $p < 0.0001$), independent of other atherosclerotic risk factors including age, male gender, BMI, MS, HC, LDL-C and northern location (beta = 0.206, p = 0.002) (Model R^2 = 0.362, F = 27.1, p < 0.0001). No PM2.5 and age (beta = 0.305, p = 0.125), or PM2.5 and location (beta = 0.093, p = 0.056) interactions were identified.

Table 4. Determinants of Risk Factors for Carotid IMT.

	Southern Chinese *		Northern Chinese **		Overall Cohort ***	
Risk Factors	**Beta Value**	***p*-Value**	**Beta Value**	***p*-Value**	**Beta-Value**	***p*-Value**
Age (yr)	0.393	<0.0001	0.385	<0.0001	0.396	<0.0001
Gender	0.146	0.043	0.058	0.357	0.127	0.006
Smoking status	0.061	0.388	0.157	0.010	0.091	0.053
BMI	0.074	0.299	0.088	0.103	0.121	0.005
MS	0.119	0.095	0.110	0.039	0.099	0.019
Homocysteine	0.048	0.501	0.137	0.014	0.121	0.010
LDL-C	0.084	0.204	0.145	0.003	0.136	0.004
MTHFR	0.046	0.463	−0.065	0.223	−0.026	0.554
PM2.5	0.334	<0.0001	0.033	0.471	0.368	<0.0001
Location	-	-	-	-	−0.206	0.002

* Model R^2 = 0.451; F-value = 13.3; p < 0.0001. ** Model R^2 = 0.335; F-value = 7.67; p < 0.0001. *** Model R^2 = 0.362; F-value = 27.1; p < 0.0001. BMI: Body Mass Index. IMT: Intima-media thickness. LDL-C: Low Density Lipoprotein Cholesterol. MS: Metabolic Syndrome. MTHFR: Methylenetetrahydrofolate Reductase Gene Polymorphisms. PM2.5: Particulate Matters < 2.5 um in Diameter.

4. Discussion

The present report further confirms the detrimental impact of PM2.5 air pollution on atherogenic processes in modernizing China, independent of traditional atherosclerotic risk factors [12,18,30]. Specifically, Northern Chinese were more prone to higher carotid IMT and worse arterial endothelial dysfunction, compared with Southern Chinese. This may be attributed to more smoking, higher SBP, DBP, homocysteine, PM2.5 exposure and metabolic syndrome rates, and lower (unfavorable) vitamin B12 and folate levels. Metabolic syndrome includes the impact of several atherosclerotic risk factors i.e., blood pressure, waist circumference, HDL and LDL-cholesterol and fasting glucose. We and others have documented its detrimental impact on atherogenesis, independent of PM2.5 [18,31].

Multivariate regression of the overall cohort suggested that PM2.5 exposure and location were important determinants of carotid IMT, independent of homocysteine and other traditional vascular risk factors. Higher homocysteine presumably could be related to unique Northern dietary pattern of low folate and vitamin B12 intakes, the formal documentation of which is awaited with interest. On this issue, we have previously confirmed the beneficial effects of vitamin B12 and folate supplementations on atherogenic process (FMD and IMT) in 207 Northern Chinese adult subjects with subnormal nutritional status [32].

Greater carotid IMT is an important prognostic atherosclerosis surrogate related to later risk of stroke and cardiovascular diseases [33]. We have previously shown that increased carotid IMT is a marker of subclinical atherosclerosis in westernized as compared with rural Southern Chinese [15]. To contextualize the magnitude of the IMT difference (19.3%, 0.11 mm), a 0.16 mm increase in carotid IMT has been associated with 41% increase in stroke and 43% increase in acute myocardial infarction over a follow up period of 2–7 years [33]. The 19.3% difference in carotid IMT in the present study was far greater than the kind of difference between diabetic and non-diabetic Chinese adults [17].

4.1. Limitations

We acknowledge some limitations in our present study. Firstly, we have not explored inflammatory markers, such as fibrinogen, C-reactive protein or cytokine family, in the Northern compared with Southern Chinese. This will be valuable for confirming the hypothesis of generalized vascular inflammation in AP-induced atherogenic process. Secondly, the concentration and LDL-C happened (by chance) to be lower, but hyperemia (by ultrasound) to be higher in Northern Chinese. These, however, have not contributed to the worse FMD and IMT results, since these two factors would have been associated with better rather than worse FMD and IMT levels in the Northern Chinese. Thirdly, we have identified FMD, an early atherosclerotic surrogate, is lower in Northern Chinese on univariate analyses, but its relationship with PM2.5 concentration is borderline only on multivariate analyses. FMD in more labile and dynamic compared with carotid IMT measurement, subjected to daily fluctuation of PM2.5 concentration. This was measured once only during the study period. Perhaps more FMD measurements for individual subject over the study period may illuminate the real impact of PM2.5 on FMD. Fourthly, realtime long term PM2.5 measurement is more informative and better than yearly mean PM2.5 estimation for studying its relationship with more labile FMD measurement. This, however, has logistic and economic implications which may not be readily resolved.

4.2. General Remarks

We propose carotid IMT and brachial FMD as two surrogate targets for measuring the success of possible prevention of PM2.5-related atherogenesis in Chinese. While the nationwide adoption of PM2.5-reduction policies will be welcomed in both Northern and Southern Chinese, our present study would suggest the possible importance of micronutrient (folate and vitamin B12) deficiencies in some areas of Northern China, apart from control of vascular risk factor [31]. In addition, strategies on a more personal approach may be advisable particularly in southern China, including face-mask and filtering devices for indoor air pollution [34–37], as well as exploration of potential medical therapies to reduce the impact of atherosclerosis.

5. Conclusions

PM2.5 air pollution in China, in particular in Southern Chinese, is related to atherogenic surrogates, independent of traditional risk factors, with potential implications in both dietary and air pollution reduction strategies for atherosclerosis prevention.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board.

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

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

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References

1. Lloyd-Jones, D.; Adams, R.; Carnethon, M.; de Simone, G.; Ferguson, T.B.; Flegal, K.; Ford, E.; Furie, K.; Go, A.; Greenlund, K.; et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* **2009**, *119*, 480–486. [PubMed]
2. Roth, G.A.; Johnson, C.; Abajobir, A.; Abd-Allah, F.; Abera, S.F.; Abyu, G.; Ahmed, M.; Aksut, B.; Alam, T.; Alam, K.; et al. Global regional and national burden of cardiovascular diseases for 10 causes, 1990-2015. *J. Am. Coll. Cardiol.* **2017**, *70*, 1–25. [CrossRef] [PubMed]
3. Danaei, G.; Ding, E.L.; Mozaffarian, D.; Taylor, B.; Rehm, J.; Murray, C.J.L.; Ezzati, M. The preventable causes of death in the United States: Comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med.* **2009**, *6*, e1000058. [CrossRef] [PubMed]
4. Rajagopalan, S.; Al-Kini, S.G.; Brook, R.D. Air pollution and cardiovascular disease. *J. Am. Coll. Cardiol.* **2018**, *72*, 2054–2070. [CrossRef] [PubMed]
5. Liang, F.; Liu, F.; Huang, K.; Yang, X.; Li, J.; Xiao, Q.; Chen, J.; Liu, X.; Cao, J.; Shen, C.; et al. Longterm exposure to fine particulate matter and cardiovascular disease in China. *J. Am. Coll. Cardiol.* **2020**, *75*, 707–717. [CrossRef]
6. Brook, R.D.; Rajagopalan, S.; Pope, C.A., 3rd; Brook, J.R.; Bhatnagar, A.; Diez-Roux, A.V.; Holguin, F.; Hong, Y.; Luepker, R.V.; Mittleman, M.A.; et al. American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* **2010**, *121*, 2331–2378.
7. Jasarevic, T.; Thomas, G.; Osseiran, N. 7 Million Premature Deaths Annually Lined to Air Pollution. WHO Media Centre 2014. Available online: https://www.who.int/mediacentre/news/releases/2014/air-pollution/en/ (accessed on 25 March 2014).
8. Arden Pope, C., 3rd; Burnett, R.T.; Thurston, G.D.; Thun, M.J.; Calle, E.E.; Krewski, D.; Godleski, J.J. Cardiovascular mortality and long-term exposure to particular air pollution – Epidemiological evidence of general pathophysiological pathways of disease. *Circulation* **2004**, *109*, 71–77. [CrossRef]
9. Pepine, C.J. The effects of angiotensin-converting enzyme inhibition on endothelial dysfunction: Potential role in myocardial ischemia. *Am. J. Cardiol.* **1998**, *82*, 23S–27S. [CrossRef]
10. Roux, A.V.D.; Auchincloss, A.H.; Franklin, T.G.; Raghunathan, T.; Barr, R.G.; Kaufman, J.; Astor, B.; Keeler, J. Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. *Am. J. Epidemiol.* **2008**, *167*, 667–675. [CrossRef]
11. Bauer, M.; Moebus, S.; Möhlenkamp, S.; Dragano, N.; Nonnemacher, M.; Fuchsluger, M.; Kessler, C.; Jakobs, H.; Memmesheimer, M.; Erbel, R.; et al. HNR Study Investigative Group. Urban particulate matter air pollution is associated with subclinical atherosclerosis: Results from the HNR (Heinz Nixdorf Recall) study. *J. Am. Coll. Cardiol.* **2010**, *56*, 1803–1808. [CrossRef]
12. Woo, K.S.; Chook, P.; Hu, Y.J.; Lao, X.Q.; Lin, C.Q.; Lee, P.; Kwok, C.; Wei, A.N.; Guo, D.S.; Yin, Y.H.; et al. The Impact of Particulate Matter Air Pollution (PM2.5) on Atherosclerosis in Modernizing China: The report from CATHAY Study. *Int. J. Epid.* **2020**, *50*, 1–11. [CrossRef]
13. Yang, J.; Siri, J.G.; Remais, J.V.; Cheng, Q.; Zhang, H.; Chan, K.K.Y.; Sun, Z.; Zhao, Y.; Cong, N.; Li, X.; et al. The Tsinghua-lancet commission on healthy cities in China: Unlocking the power of cities for a healthy China. *Lancet* **2018**, *391*, 2140–2184. [CrossRef]
14. Woo, K.S.; Robinson, J.T.; Chook, P.; Adams, M.R.; Yip, G.; Mai, Z.J.; Lam, C.W.; Sorensen, K.E.; Deanfield, J.E.; Celermajer, S.D. Differences in the effect of cigarette smoking on endothelial function in Chinese and white adults. *Ann. Int. Med.* **1997**, *127*, 372–375. [CrossRef]
15. Woo, K.S.; Chook, P.; Raitakari, O.T.; McQuillan, B.; Feng, J.Z.; Celermajer, D.S. Westernization of Chinese adults and increased subclinical atherosclerosis. *Arter. Thromb. Vasc. Biol.* **1999**, *19*, 2487–2493. [CrossRef]
16. Thomas, G.N.; Chook, P.; Qiao, M.; Huang, X.S.; Leong, H.C.; Celermajer, D.S.; Woo, K.S. Deleterious impact of "high normal" glucose levels and other metabolic syndrome components on arterial endothelial function and intima-media thickness in apparently healthy Chinese subject: The CATHAY study. *Arterioscler. Thromb. Vasc. Biol.* **2004**, *24*, 739–743. [CrossRef]
17. Woo, K.S.; Chook, P.; Yu, C.W.; Sung, R.Y.T.; Qiao, M.; Leung, S.S.F.; Lam, C.W.K.; Metreweli, C.; Celermajer, D.S. Effects of diet and exercise on obesityrelated vascular dysfunction in children. *Circulation* **2004**, *109*, 1981–1986. [CrossRef] [PubMed]
18. Woo, K.S.; Timothy, K.C.Y.; Chook, P.; Hu, Y.J.; Yin, Y.H.; Lin, C.Q.; Lau, K.H.A.; Lee, P.W.A.; Celermajer, D.S. Independent Effects of Metabolic Syndrome and Air Pollution (PM2.5) on Atherosclerosis in Modernizing China. *Austin J. Public Health Epidemiol.* **2021**, *8*, 1097.

19. Zimmet, P.; Alberti, K.; George, M.M.; Rios, M.S. A new International Diabetes Federation (IDF) worldwide definition of the metabolic syndrome: The rationale and the results. *Rev. Esp. Cardiol.* **2005**, *58*, 1371–1376. [CrossRef]
20. Woo, K.S.; Hu, Y.J.; Chook, P.; Wei, A.N.; Chan, R.; Yin, Y.H.; Celermajer, D.S. A Tale of Three Gorges in the Yangtze River: Comparing the Prevalence of Metabolic Syndrome According to ATP III, WHO, and IDF Criteria and the Association with Vascular Health in Modernizing China. *Metab. Syndr. Relat. Disord.* **2019**, *17*, 137–142. [CrossRef]
21. Li, C.; Lau, A.K.H.; Mao, J.; Chu, D.A. Retrieval, validation, and application of the 1-km aerosol optical depth from MODIS measurements over Hong Kong. *IEEE Trans. Geosci. Remote Sens.* **2005**, *43*, 2650–2658.
22. Lin, C.Q.; Li, Y.; Yuan, Z.B.; Lau, A.K.H.; Li, C.C.; Fung, J.C.H. Using satellite remote sensing data to estimate the high-resolution distribution of ground-level PM2.5. *Remote Sens. Environ.* **2015**, *156*, 117–128. [CrossRef]
23. Lin, C.Q.; Liu, G.; Lau, A.K.H.; Li, Y.; Li, C.C.; Fung, J.C.H.; Lao, X.Q. High-resolution satellite remote sensing of provincial PM2.5 trends in China from 2001 to 2015. *Atmos. Environ.* **2018**, *180*, 110–116. [CrossRef]
24. Celermajer, D.S.; Sorensen, K.; Gooch, V.; Spiegelhalter, D.J.; Miller, O.I.; Sullivan, I.D.; Lloyd, J.K.; Deanfield, J.E. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* **1992**, *340*, 1111–1115. [CrossRef]
25. Woo, K.S.; Chook, P.; Yu, C.W.; Sung, R.Y.T.; Qiao, M.; Leung, S.S.F.; Lam, C.W.K.; Metreweli, C.; Celermajer, D.S. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int. J. Obes.* **2004**, *28*, 852–857. [CrossRef]
26. Salonen, J.T.; Salonen, R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler. Thromb. Vasc. Biol.* **1991**, *11*, 1245–1249. [CrossRef] [PubMed]
27. Bots, M.L.; Hoes, A.W.; Koudstaal, P.J.; Hofman, A.; Grobbee, D.E. Common carotid intima-media thickness and risk of stroke and myocardial infarction: The Rotterdam Study. *Circulation* **1997**, *96*, 1432–1437. [CrossRef]
28. Touboul, P.J.; Hennerici, M.G.; Meairs, S.; Adams, H.; Amarenco, P.; Desvarieux, M.; Ebrahim, S.; Fatar, M.; Hernandez Hernandez, R.; Kownator, S.; et al. Advisory Board of the 3rd Watching the Risk Symposium 2004, 13th European Stroke Conference. Mannheim intima-media thickness consensus. *Cereb. Dis.* **2004**, *18*, 346–349. [CrossRef] [PubMed]
29. Schulz, K.F.; Grimes, D.A. Sample size calculations in randomised trials: Mandatory and mystical. *Lancet* **2005**, *365*, 1348–1353. [CrossRef]
30. Li, H.; Cai, J.; Chen, R.; Zhao, Z.; Ying, Z.; Wang, L.; Chen, J.; Hao, K.; Kinney, P.L.; Chen, H.; et al. Particulate matter exposure and stress hormone levels: A randomized, double-blind, crossover trial of air purification. *Circulation* **2017**, *136*, 618–627. [CrossRef] [PubMed]
31. Maloberti, A.; Bombelli, M.; Vallerio, P.; Milani, M.; Cartella, I.; Tavecchia, G.; Tognola, C.; Grasso, E.; Sun, J.; de Chiara, B.; et al. Metabolic syndrome is related to vascular structural alterations but not to functional ones both in hypertensives and healthy subjects. *Nutr. Metab. Cardiovas. Dis.* **2021**, *31*, 1044–1052. [CrossRef]
32. Woo, K.S.; Kwok, T.C.Y.; Celermajer, D.S. Vegan diet, subnormal vitamin B-12 status and cardiovascular health. *Nutrients* **2014**, *6*, 3259–3273. [CrossRef] [PubMed]
33. O'Leary, D.H.; Polak, J.F.; Kronmal, R.A.; Manolio, T.A.; Burke, G.L.; Wolfson, S.K., Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N. Engl. J. Med.* **1999**, *340*, 14–22. [CrossRef]
34. Baumgartner, J.; Smith, K.R.; Chockalingam, A. Reducing CVD through improvements in household energy - Implications for policy-relevant research. *Global. Heart* **2012**, *7*, 243–247. [CrossRef] [PubMed]
35. Langrish, J.; Mills, N.; Chan, J.; Leseman, D.; Aitken, R.; Fokkens, P.; Cassee, F.; Li, J.; Donaldson, K.; Newby, D.; et al. Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Part. Fibre Toxicol.* **2009**, *6*, 8. [CrossRef]
36. Allen, R.W.; Carlsten, C.; Karlen, B.; Leckie, S.; van Eeden, S.; Vedal, S.; Wong, I.; Brauer, M. An air filter intervention study of endothelial function among healthy adults in a woodsmoke-impacted community. *Am. J. Respir. Crit. Care Med.* **2011**, *183*, 1222–1230. [CrossRef] [PubMed]
37. Rajagopalan, S.; Brook, R.D. Indoor-outdoor air pollution continuum and CVD burden–An opportunity for improving global health. *Glob. Heart* **2012**, *7*, 207–213. [CrossRef]