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Endothelial Function and Short-term Exposure to Particulate Matter: A Systematic Review and Meta-analysis

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Abstract

Association of particulate matter with endothelial function Current evidence has confirmed the definite correlation between air pollution and cardiovascular disease. One of the mechanisms was the adverse effect on endothelial function. However, there is heterogeneity between the air pollution and endothelial function in different studies. We performed a meta-analysis to determine the direction and strength of the association. PubMed, EMBASE, Cochrane library and Web of Science were searched for a combination of keywords related to major air pollutants and to the indexes of endothelial function, including reactive hyperemia, flow-mediated dilation and nitroglycerin-mediated dilatation. Thirteen of reviewed articles with sufficient details met inclusion criteria. Descriptive and quantitative information was extracted from the included studies. A pooled estimate in a random effects model was computed, and change in endothelial function (95% CIs) were calculated for each increment of 10 μg/m^3 in $PM_{2.5}$, and 1 μg/m^3 scaled for black carbon. A 0.27% decrease in flow-mediated dilation was marginally associated with per 1 μg/m^3 increase in $PM_{2.5}$ in overall risk estimate analysis, with the greatest effect occurred in $PM_{2.5}$ exposure for 1-day lag. Subgroup analyses have shown that the effect was modified by the factors as follows: American, subjects aged less than 55 years old, the proportion of female less than 50%, and the panel design. A 0.07 mm decrease in brachial artery diameter and 2.46% decrease in nitroglycerin-mediated dilation for per 1 μg/m^3 increment in BC were observed in the pooled analysis from two studies(P=0.005 and P=0.043, respectively). No significant association was found between black carbon and flow-mediated dilation. Short-term exposure to $PM_{2.5}$ and black carbon was associated with endothelial function, which provided the evidence for the increased risk of cardiovascular disease due to air pollution.

Keywords: Endothelial dysfunction; Flow-mediated dilation; Cardiovascular disease; Particulate matter; Meta-analysis.

Introduction

A growing body of evidence has confirmed the association between air pollutants and increased risk of cardiovascular morbidity and mortality [1], either short-term or long-term exposure. What's more, exposure to air pollution has been emerging as an important risk factor for the development and progression of cardiovascular disease (CVD), which has been set forth in the guidelines and scientific statement [2,3]. Many credible pathological mechanisms of PM-mediated cardiovascular effects have been elucidated, including systemic autonomic nervous system imbalance, systemic proinflammatory responses, thrombosis and coagulation, oxidative stress, vascular or endothelial dysfunction [4]. Atherosclerosis is the major cause of CVD. In the earliest time, 2 clinical trials with 798 participants conducted in the Los Angeles, arrived at the conclusion that 10 μg/m^3 higher in $PM_{2.5}$ was associated with non-significant 4.2% elevation in common carotid intima-media thickness (CIMT), a marker of subclinical atherosclerosis [5]. Afterwards, related studies have been increasing with heterogeneity between different studies concerning the strength of the association. In 2015, Provost et al. performed a meta-analysis and drew a conclusion that an increase of 5 μg/m^3 $PM_{2.5}$ was associated with a 1.66% thicker CIMT in the combined cross-sectional studies and a 1.04 μm per year greater CIMT progression in the combined longitudinal studies [6].

Endothelial dysfunction, as a possible and important mechanism, is an initial step in atherosclerosis and caused principally by loss of endothelium-derived nitric oxide [7]. The noninvasive tools to evaluate the endothelial function are brachial artery ultrasound and peripheral arterial tonometry (PAT). The former is a commonly used and widely accepted measure of peripheral macrovascular endothelial function, reported as baseline arterial diameter (BAD), nitroglycerin-mediated dilation (NMD), flow-mediated dilation (FMD). The latter is commonly used to assess microvascular endothelial function via changes in finger pulse wave amplitude in response to reactive hyperemia. Indeed, both macrovascular endothelial dysfunction, as measured by flow-mediated dilation, and microvascular endothelial dysfunction have been found to be independent predictors of future cardiovascular events in large cohort studies in healthy individuals over and above traditional risk factor assessment [8].

Several studies have reported an association between endothelial function and particulate air pollution [9-12]. However, there is heterogeneity in the strength and direction of the reported association. Therefore, we performed a meta-analysis to evaluate the short-term exposure to particulate air pollution and endothelial function, such as BAD, NMD, FMD, and reactive hyperemia index (RHI).

Methods

Search strategy and selection criteria

PubMed, EMBASE, Cochrane library and Web of Science were searched to identify relevant articles that were published through Aug 1, 2015, according to the search strategy as follows: ("air pollution" OR "air pollutant*" OR "particle" OR "particulate matter" OR aerosol OR "$PM_{2.5}$" OR "PM_{10}" OR "Black carbon" OR "carbon black" OR sulfate OR nitrate) AND ("reactive hyperemia" OR "endothelial function" OR "endothelial dysfunction" OR "Peripheral arterial tonometry" OR "flow-mediated dilation" OR "endothelium-dependent dilatation" OR

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"RHI" OR "reactive hyperemia index" OR "vascular function" OR "Nitroglycerin-mediated vasodilation" OR "Nitroglycerin-mediated dilatation" OR "flow-mediated dilatation" OR "flow-mediated vasodilation") (Table 1), with restriction of human and not review. We also considered references found in the literature search.

Study selection

The cross-sectional and longitudinal cohort studies were included to evaluate the association between particulate air pollution (PM_{10}, $PM_{2.5}$, Black carbon, sulfate and nitrate) and endothelial function as assessed by BAD, NMD, FMD and RHI. Only English language was including in our search. We excluded non-human studies, studies reporting gaseous pollutants exposure, studies reporting estimates other than absolute and percent change in outcome per change in the level of particulate air pollutants, and studies with incomplete data. There were 2073 non-duplicate abstracts searched from the four databases, which were evaluated by all the authors independently using the search algorithm. Articles relevant to our meta-analysis (n=33) were reviewed by two separate authors to identify the final studies based on our inclusion and exclusion criteria. If any disagreement, a third author determined and resolved the final results.

Data extraction

There were 6 cross-sectional studies and 7 longitudinal studies on the association between the particulate air pollutants and endothelial function. If a group published two or more papers based on the same study participants, only articles with more details were included in our analysis. Information extracted included citation data, authors' names, publication year, data source, country, sample size, age distribution, sex distribution, study design, baseline exposure level, outcome measure, effect estimate, and standard error of effect estimate. For studies that reported multiple effect estimates, we extracted the estimate from the main model or model that reflected the greatest degree of control for potential confounders. For each included studies, we extracted mean change in the indexes of endothelial function.

Statistics analysis

All estimates were standardized to per 10 μg/m^3 increase in $PM_{2.5}$, per 1 μg/m^3 for black carbon (BC), and per 1000/cm^3 for particle number concentration (PNC). In all included studies, linear mixed or general linear models were used to analyze the association between air pollution and the indicators of endothelial function. Therefore, we pooled absolute and percent change (with upper and lower 95% CI) for an increment per unit in air pollutants based on the assumption of the linear association between the both factors. Effect estimates were derived from the point estimate of each separate study weighted by the inverse of the variance ($1/SE^2$). The combined estimate was computed using the random effect model. Delayed and cumulative effects of air pollutants on endothelial function were evaluated with multiple lag patterns, (e.g., lag 0 meant the present day exposure of BP measurement, lag 1 meant the day before and so on; 5-day moving average (MA) referring to the average of the same day and the previous four days), in many studies. If there were several estimates for multiple lag patterns reported in the same article, we chose the lag pattern with the largest estimate size, which was most frequently used in all the selected studies to assess overall risk estimates. In addition, we pooled the various estimates according to lag pattern separately and only pooled estimates where more than two estimates were available. Heterogeneity between studies was detected by the forest plot, and I-squared (I^2) statistic. Consistent with prior thresholds we considered an I^2 statistic ≥ 50% to represent substantial heterogeneity and ≥ 75% to represent considerable heterogeneity. Meta-regression was used to assess potential sources of heterogeneity, such as year of publication, country, study design, sample size, and baseline level of exposure. Subgroup analyses were conducted to explore the impact of possible confounding factors. All statistical tests were two-sided and p values <0.05 were considered to be statistically significant. Analyses were conducted with STATA Version 12(Stata Corp., College Station, Texas, USA).

Results

Study selection

There were 2073 articles screened by title and abstract, 2224 of which were excluded, and the remaining 33 articles were reviewed by full text according to the inclusion criteria of the meta-analysis (Figure 1). Thirteen studies were considered for data extraction, a total of 11226 subjects (51% female) from 6 studies in a cross-sectional design [11-16] and 7 in a longitudinal design [9,17-22]. The number of subjects for both groups was 7934 and 3293, respectively. The mean age for the subjects in the included studies except one study [11] was more than 45 years old. The mean level of $PM_{2.5}$ exposure among studies ranged from 6.8 to 28 μg/m^3, ranged from 0.36 to 4.7 μg/m^3 for BC concentration. Most of the studies focused on the short-term effect of air pollutants on endothelial function. The long-term effect was depicted only in the two studies [9,15] (Tables 2 and 3).

Association between $PM_{2.5}$ and endothelial function

We found nine studies reporting on the association between $PM_{2.5}$ and FMD, which reflected the macrovascular function as described above. The meta-analysis based on the largest estimates chosed from different lag patterns pooled as overall risk estimates showed that a 0.27% decrease in FMD was associated with per 10 μg/m^3 increase in $PM_{2.5}$ exposure with marginal significance (P=0.05) (Figure 2).

In addition, subgroup analysis for different lag pattern between $PM_{2.5}$ and FMD has been performed, which indicated that the greatest effect was found for per 10 μg/m^3 increase in 1-day lag $PM_{2.5}$ exposure with 0.092% decline in FMD (P=0.014) (Figure 3). However, no significant association was found for other lag pattern and 5-day average exposure (all P>0.05). There were moderate heterogeneity between studies (I^2=49.2%, P=0.046). Therefore, we performed further subgroup analysis on this issue, according to whether ambient or personal exposure, study design, the percentage of female, whether age>55 years or not and non-American or American (Figure 4 and Table 4), which demonstrated that larger effect in pooled analysis was found for American with a 0.551% decrease in FMD for per 10 μg/m^3

Search criteria for Medline*	
#1	"reactive hyperemia" OR "endothelial function" OR "endothelial dysfunction" OR "Peripheral arterial tonometry" OR "flow-mediated dilation" OR "endothelium-dependent dilatation" OR "RHI" OR "reactive hyperemia index" OR "vascular function" OR "Nitroglycerin-mediated vasodilation" OR "Nitroglycerin-mediated dilatation" OR "flow-mediated dilatation" OR "flow-mediated vasodilation"
#2	"air pollution" OR "air pollutant*" OR "particle" OR "particulate matter" OR aerosol OR "$PM_{2.5}$" OR "PM_{10}" OR "Black carbon" OR "carbon black" OR sulfate OR nitrate
#3	(#1) AND #2 NOT review Filters: Humans

Table 1: Detailed search strategy. *Similar search criteria executed for EMBASE using specific Mesh terms.

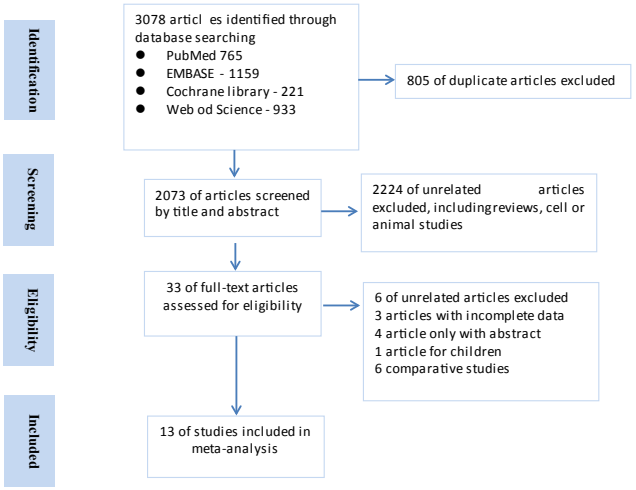

Figure 1: Flow chart of study selection for meta-analysis.

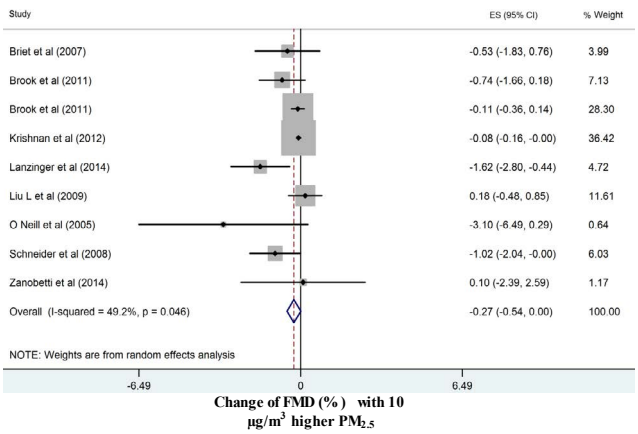

Figure 2: Change of FMD (95% CI) with 10 μg/m³ higher short-term exposure to PM $_{2.5}$ in the meta-analysis.

increase in $PM_{2.5}$ exposure (P=0.002), -0.457% for subjects aged less than 55 years old (P=0.048), -0.837% for the group with the proportion of female less than 50% (P=0.032), -0.357% for the group in the panel design (P=0.022). Meanwhile, meta regression in univariate analysis was conducted to find out the sources of heterogeneity and showed that the listed factors, including publication year, location, data source, population, age, sex and study design were not contributing to the heterogeneity (all P>0.05). However, multivariate meta-regression analysis was not performed, because the poor rationality resulted from few studies.

There were 5 studies evaluating the association between $PM_{2.5}$ and BAD, as well as NMD, and 2 studies for $PM_{2.5}$ and RHI. The pooled estimates in the meta-analysis demonstrated no significant association in the random-effect model (P=0.40, P=0.33, and P=0.48, respectively) (Figure 5).

Association between other pollutants and endothelial function

BC, an important pathogenic component of $PM_{2.5}$, has proved to be associated with cardiovascular morbidity and mortality [23]. A 0.07 mm decrease in BAD and 2.461% decrease in NMD for per 1 μg/m³ increment in BC were observed in the pooled analysis from two studies(P=0.005 and P=0.043, respectively) [14,21,22]. Meanwhile, 5.9% decline in RHI was associated with 1 μg/m³ increment in BC according to the pooled results of the studies conducted by Ljungman et al. [13] and Zhao et al. [16], respectively (P=0.028) (Figure 6). However, we didn't find the association between BC and FMD (P=0.928).

Limited studies on the association between PM_{10}, sulfate and endothelial function, and the indicators of endothelial function were different for these studies, which made the difficulty for the overall risk estimate in the meta-analysis [13,14,22].

Discussion

The finding of the meta-analysis based on the 13 current human studies comprising 11226 study participants has indicated that FMD is marginally and negatively associated with short-term exposure to $PM_{2.5}$, with the largest effect for 1-day lag $PM_{2.5}$ exposure. We also observed the association between BC and BAD, NMD, RHI, but not FMD. The effect of BC was calculated from only two or three studies. The association of other pollutants, including PM_{10}, sulfate and nitrate,

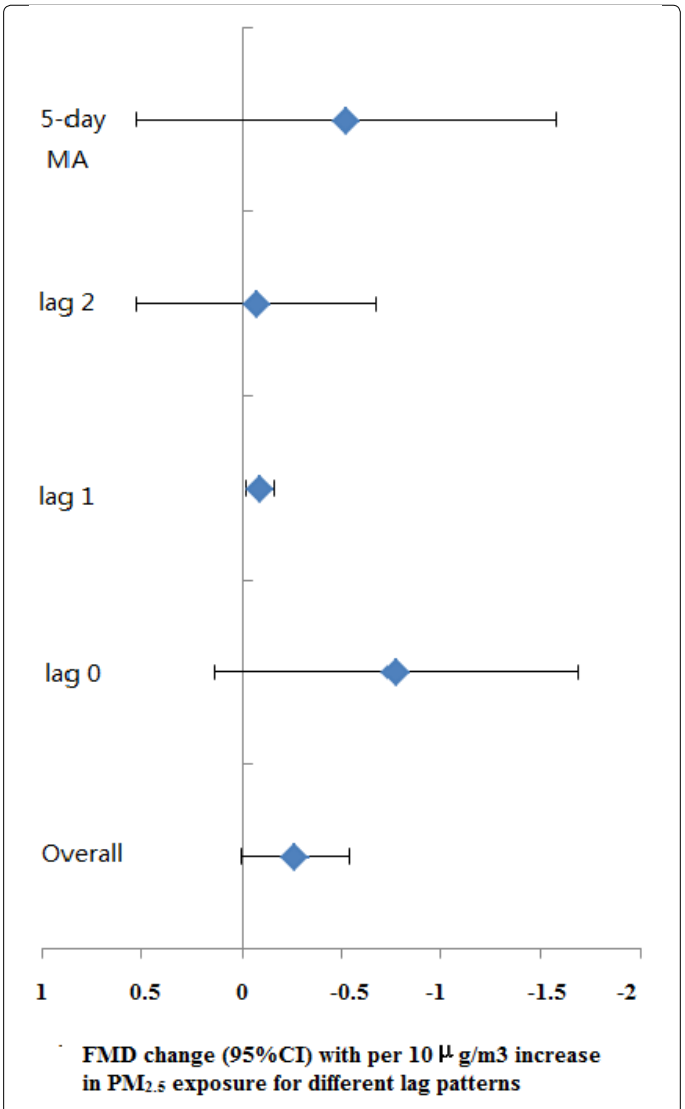

Figure 3: Change of FMD (95% CI) with 10 μg/m³ higher PM $_{2.5}$ for different lag patterns in the meta-analysis.

Authors	Year	Location	Study period	Study design	Data source	Population	Number of participants	Age	% female
Briet et al. [11]	2007	Paris	2000-2006	Cross-sectional	study to evaluate the arterial effects of partial genetic deficiency in tissue kallikrein activity on endothelial function	healthy, nonsmoking male subjects	40	22	0
Brook et al. [18]	2011	Michigan	2005-2007	longitudinal	Non reported	non-smoking subjects	65	45	77
Brook et al. [19]	2011	Detroit	2005-2007	longitudinal	Non reported	non-smoking subjects	51	45	75
Karottki et al. [12]	2014	Copenhagen	2011-2012	cross-sectional	Non reported	non-smoking volunteers	78	55	42
Krishnan et al. [9]	2012	Six cities in US	2000-2002	longitudinal	MESA cohort	Subjects free of clinical cardiovascular disease	3040	61	49
Lanzinger et al. [20]	2014	North Carolina	2004-2005	longitudinal	Non reported	Subjects with T2DM	22	61	36
Liu L et al. [21]	2009	Ottawa	2007	longitudinal	Non reported	nonsmoking seniors	28	78	61
Ljungman et al. [13]	2014	Massachusetts	2003-2008	Cross-sectional	the Framingham Heart Study.	the participants from the study	2369	56	51
O'Neill et al. [14]	2005	Boston	1998-2002	Cross-sectional	4 clinical trials conducted at the Joslin Diabetes Center and Beth Israel Deaconess Medical Center in Boston	participants either had DM (type I or type II) or were at risk for diabetes	270	55	41
Schneider et al. [17]	2008	North Carolina	2004-2005	longitudinal	Non reported	subjects with T2DM	22	61	36
Wilker et al. [15]	2014	Boston	2001	cross-sectional	Framingham Offspring Study and Third Generation Studies	participants from Framingham study	5112	49	53
Zanobetti et al. [22]	2014	Boston	2006-2009	longitudinal	Non reported	Subjects with T2DM	64	64	50
Zhao et al. [16]	2014	Beijing	2012	cross-sectional	Non reported	Subjects with MtS	65	61	57

Table 2: Demographic characteristics of the 13 studies. DM: Diabetes mellitus; T2DM: Type 2 diabetes mellitus; Mts: Metabolic syndrome; MESA: Multi-ethnic of atherosclerosis.

Authors	Year	Exposure	Concentration	Method of exposure measurement	Exposure way	Outcome
Briet et al. [11]	2007	$PM_{2.5}$	28	Fixed station gives hourly level of air pollutants	Short-term	FMD
		PM_{10}	43			
Karottki et al. [12]	2014	Indoor PNC	12400	Monitored with Philips NanoTracer1000	Short-term	RHI
		Outdoor PNC	3900	Monitored at an urban background station		
		Indoor $PM_{2.5}$	11.8	gravimetrically on Fluoropore Membrane PTFE filter		
		Outdoor $PM_{2.5}$	14.4	Monitored at an urban background station		
		Outdoor PM_{10}	21.4			
Ljungman et al. [13]	2014	$PM_{2.5}$	9.6	Using a tapered-element oscillating microbalance	Short-term	RHI
		BC	0.7	Using an Aethalometer		
		PNC	20560	With a condensation particle counter		
		$SO4^{2-}$	3.2	Measured by x-ray fluorescence analysis of the $PM_{2.5}$ filter samples		
O'Neill et al. [14]	2005	$PM_{2.5}$	11.5	Measured at a site established by the Harvard School of Public Health, located near the site where patients were examined	Short-term	NMD, FMD
		$SO4^{2-}$	3.3			
		BC	1			
		PNC	36155			
Wilker et al. [15]	2014	$PM_{2.5}$	10.9	Daily $PM_{2.5}$ concentration was predicted by aerosol optical density(AOD), ground $PM_{2.5}$ measurements from 78 monitoring stations, land use regression and meteorological	Long-term	FMD
Zhao et al. [16]	2014	BC	4.7	Measured by personal Aethalometer	Short-term	RHI

Table 3: Characteristics of the cross-sectional studies included in the meta-analysis. PNC: Particle number concentration, with the unit of per cm^3; BC: Black carbon, with the unit of $\mu g/m^3$; The unit of $PM_{2.5}$, PM_{10} and SO_4^{2-} is $\mu g/m^3$; NMD: Nitroglycerin-mediated dilation; FMD: Flow-mediated dilation; RHI: Reactive hyperemia index.

Authors	Year	Exposure	Concentration	Method of exposure measurement	Exposure way	Outcome
Brook et al. [18]	2011	Outdoor $PM_{2.5}$	15.4	Monitored at a nearby state of Michigan air quality monitoring site	Short-term	BAD, NMD,FMD
Brook et al. [19]	2011	Personal $PM_{2.5}$	22.5	Using a modified personal DataRam mephelometer	Short-term	BAD, NMD,FMD
Krishnan et al. [9]	2012	$PM_{2.5}$	10.6-24.7	Estimated at each participant's residence using a spatio-temporal model	Long-term	FMD, BAD
		$PM_{2.5}$	1-74	Based on daily central-site monitoring in each of the 6 cities	Short-term	FMD, BAD
Lanzinger et al. [20]	2014	$PM_{2.5}$	13.6	Obtained from a monitoring site	Short-term	BAD, FMD
Liu L et al. [21]	2009	personal $PM_{2.5}$	6.30	An active personal monitor,which was a modified (pDR) that consisted of, in series, an personal data random access memory air sampling pump	Short-term	BAD, FMD
		Indoor BC	0.36	by Aethalometers		
		Outdoor BC	0.71	by Aethalometers		
		Indoor $PM_{2.5}$	6.80	Measured using a DustTrak at each of the three nursing homes		
		Outdoor $PM_{2.5}$	15.30	Measured using a DustTrak,located close to the homes		
Schneider et al. [17]	2008	$PM_{2.5}$	13.60	Obtained at central monitoring sites	Short-term	NMD, FMD
Zanobetti et al. [22]	2014	Ambient $PM_{2.5}$	8.37	measured hourly at a central monitoring site	Short-term	BAD, FMD, NMD
		Indoor $PM_{2.5}$	7.11	Measured by fine particle samplers		
		Home/trip-integrated $PM_{2.5}$ (5-day)	9.18	Collect fine particles on Teflon filters to determine $PM_{2.5}$ and BC mass concentration		
		ambient BC	0.61	measured hourly at a central monitoring site		
		HOME/trip-integrated BC	0.77	Collect fine particles on Teflon filters to determine $PM_{2.5}$ and BC mass concentration		
		PNC	13270	measured hourly at a central monitoring site		
		SO_4^{2-}	2.13			BAD

Table 4: Characteristics of the longitudinal studies included in the meta-analysis. PNC: Particle number concentration, with the unit of per cm^3; BC: Black carbon, with the unit of $\mu g/m^3$; The unit of $PM_{2.5}$, PM_{10} and SO_4^{2-} is $\mu g/m^3$; BAD: Baseline arterial diameter; NMD: Nitroglycerin-mediated dilation; FMD: Flow-mediated dilation.

with endothelial function was not explored due to the limited studies and different indicators of endothelial function.

FMD and NMD were calculated by the extent of reactive hyperemia after the occlusion of brachial artery, which represented the endothelial function and comprised the combined effects of endothelial-dependent processes and endothelial-independent process. The former influenced the production and quenching of vasodilatory nitrogen oxide (NO), while the latter influenced vascular smooth muscle responsiveness to NO [24,25]. NMD, a measure of the change in BAD before and after administration of nitroglycerin (an exogenous source of NO), reflects autonomic vascular smooth muscle responsiveness occurring independently of endothelial NO production. A decrease in FMD but not NMD suggests an effect on endothelial function specifically, whereas a decrease in both outcomes suggests that part or all of the change is due to endothelial-independent effects. Combined with our results, the association of $PM_{2.5}$ with FMD represented the dysfunction of the endothelial-dependent process, depending on the vascular condition of the subjects. However, the effect of BC on NMD found in the meta-analysis has been demonstrated the dysfunction of vascular smooth muscle responsiveness to NO. The generalization of the results should take caution due to the limited studies on BC and NMD.

The results from our pooled analysis absolutely provided the certain evidence of mechanisms of PM-mediated adverse effect on cardiovascular morbidity and mortality- endothelial dysfunction. It is a systemic process, not only reflecting atherosclerotic risk [26], but also serving as a prognostic marker for future cardiovascular events [27]. As described in the meta-analysis, BAD, FMD, and peripheral arterial tonometry (PAT) (expressed as RHI) have been shown to correlate well with invasive measures. What's more, there were 3 meta-analyses

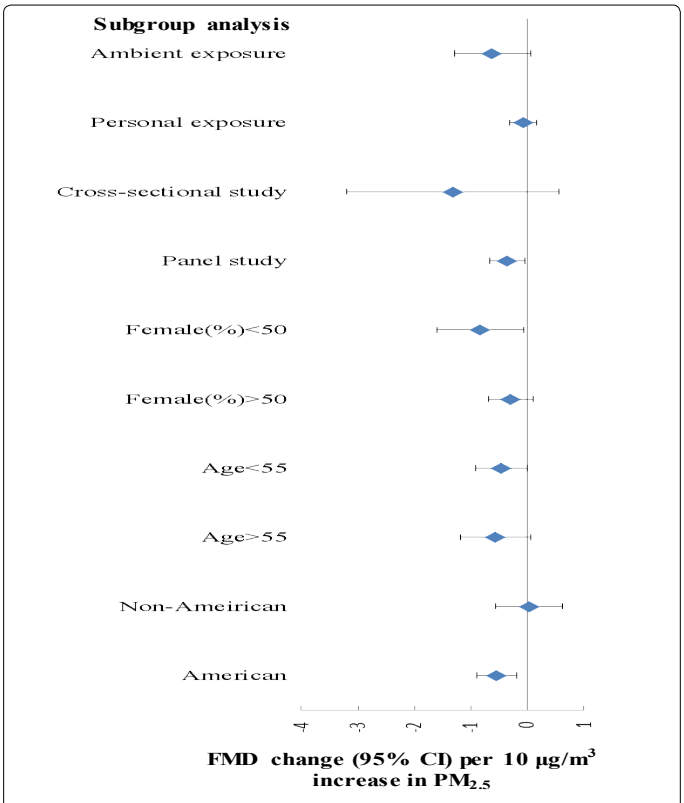

Figure 4: Change of FMD (95% CI) with 10 $\mu g/m^3$ higher $PM_{2.5}$ in the sub-group analysis.

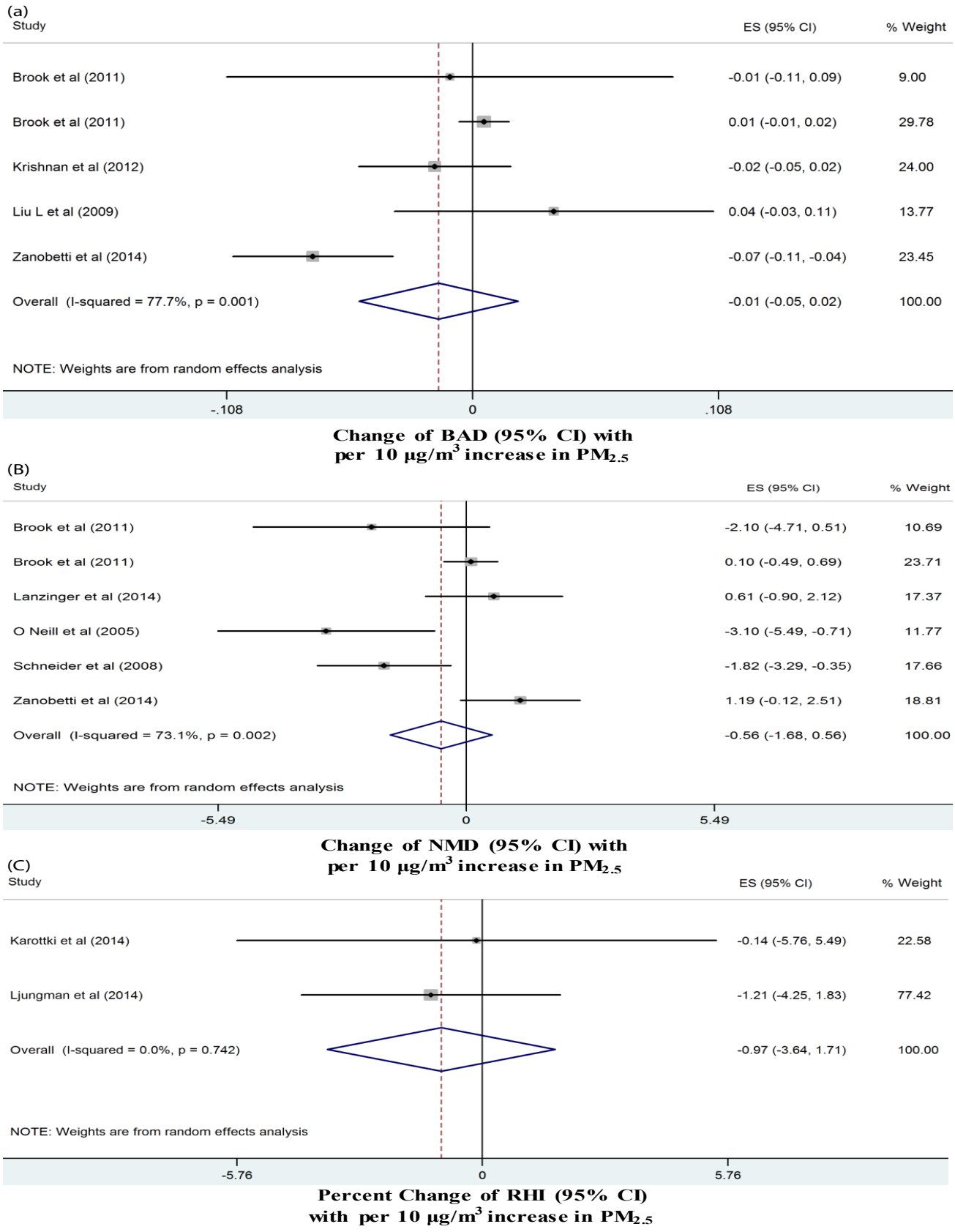

Figure 5: Change of BAD(a), NMD(b) and RHI(c) (95%CI) with 10 µg/m^3 higher short-term exposure to $PM_{2.5}$ in the meta-analysis.

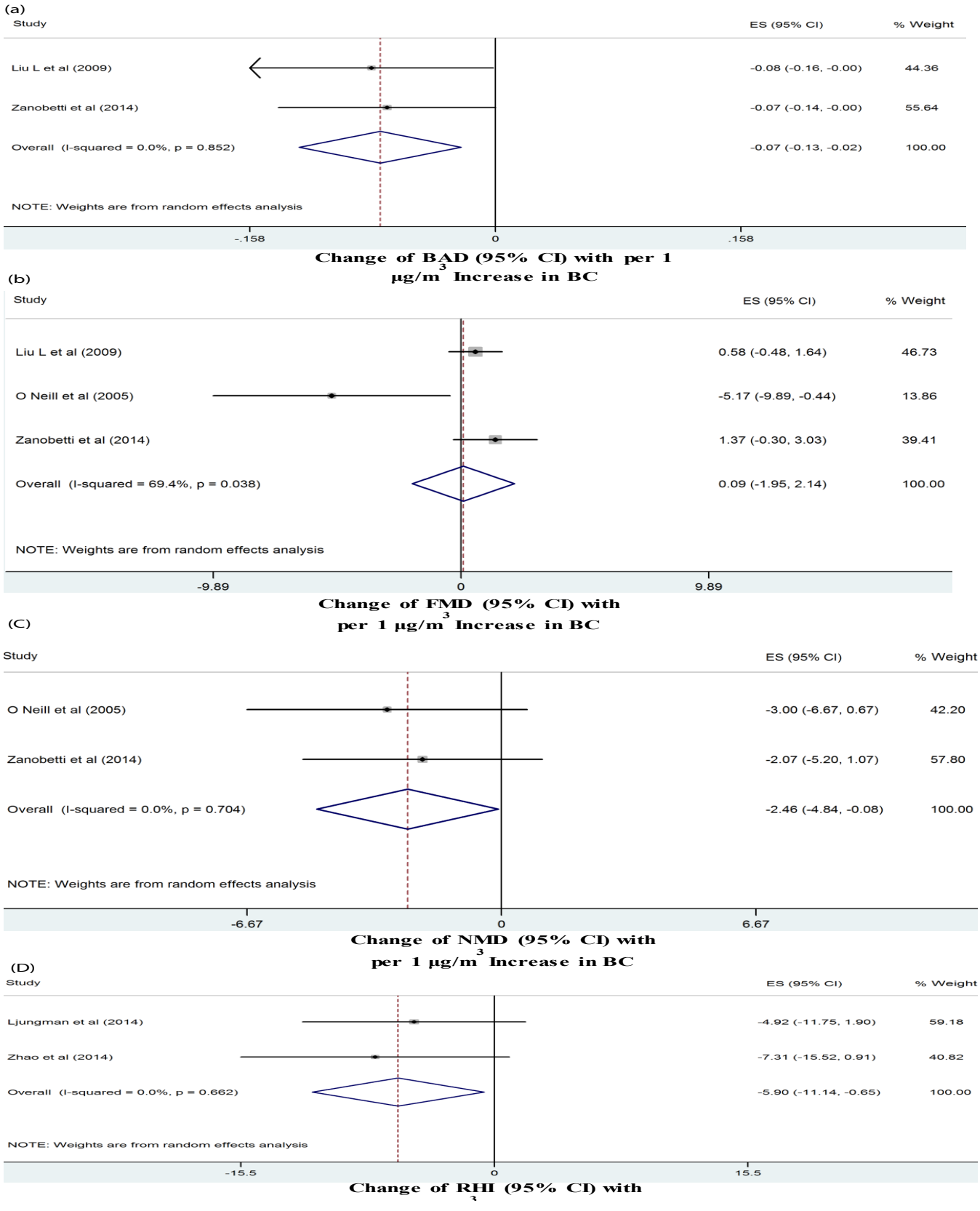

Figure 6: Change of BAD(a), FMD(b), NMD(c) and RHI(d) (95% CI) with 1 µg/m^3 higher short-term exposure to BC in the meta-analysis.

reporting the prognostic value of non-invasive endothelial function and the risk of adverse outcomes, which demonstrated that the pooled RR of overall CVD risk, cardiovascular events and all-cause mortality or only cardiovascular events per 1% increase in brachial FMD was 0.92 (0.88-0.95), 0.90 (0.88-0.92) and 0.87 (0.83-0.91), and the pooled RR per 0.1 increase in RHI for cardiovascular events was 0.85 (0.78-0.93) [8,28,29].

The potential implication of the effect of particulate air pollution on endothelial function has deduced based on our result. The results were also verified by controlled exposure studies in a comparative way [30,31] and current air filtration-based intervention studies. Conclusion was drawn based on a randomized, double-blind, crossover study design published in 2008 by Brauner et al. that indoor air filtration significantly improved microvascular function by 8.1% [32]. However, there are several studies with the results of no association between filtration and endothelial function [33]. Just as the studies included in the meta-analysis with heterogeneity in results, there were several reasons to explain the potential factors, such as population sensitivity, models, the relative low baseline pollution concentrations, methods if vascular function measurement, the exposure error or indoor sources, and the composition of the particles.

There was moderate heterogeneity between studies included the meta-analysis, and the meta-regression found no factors listed explaining the source of heterogeneity according to univariate meta-regression analysis. The subgroup analysis has shown that there were several potential effect modified factors, such as study design, age, gender, and American.

Although, the mechanisms of the effect of air pollution on endothelial function have been explored gradually, including the destruction of endothelium, the imbalance of vasoconstriction and vasodilation factor, such as increased endothelin-1 (ET-1), decreased nitric oxide bioavailability, inflammation with thrombosis/coagulation, as well as PM-mediated reactive oxygen species (ROS) [21,28].

There are several strengths and limitations in our meta-analysis. This is the first study to pool effect based on the current studies which have inconsistent results and the study areas are focused on the three different countries (United State, Canada, China), comprised developed and developing countries. The potential limitations as follows deserve consideration. First, the number of included studies was relatively small, particularly for BAD, NMD and RHI, which limited our ability to derive strong conclusion from these analysis and to explore the source of heterogeneity. Second, the measurement error in assessment of exposure was different in different studies, which may result in the biased estimates.

Conclusion

In conclusion, short-term exposure to $PM_{2.5}$ was marginally and negatively associated with FMD, which reflected the imbalance of endothelial-dependent dilation. BC was associated with NMD and BMD based on a very small number of studies. The interpretation of the results based on the meta-analysis need to be careful.

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