Supplement "Exposure to particulate matter and detrimental effects in arteries of animals"

Peter Møller[1]*, Daniel Vest Christophersen[1], Nicklas Raun Jacobsen[2], Astrid Skovmand[1], Ana Cecília Damião Gouveia[1], Maria Helena Guerra Andersen[1], Ali Kermanizadeh[1], Ditte Marie Jensen[1], Pernille Høgh Danielsen[1], Martin Roursgaard[1], Kim Jantzen[1], Steffen Loft[1]

[1]Department of Public Health, Section of Environmental Health, University of Copenhagen, Øster Farimagsgade 5A, DK-1014 Copenhagen K, Denmark, [2]The National Research Centre for the Working Environment, Lersø Parkalle 105, 2100 Copenhagen, Denmark

Searches: The publications were identified by PubMed and EMBASE using combinations of exposure terms ("Nanoparticle" OR "Nanoparticles" OR "Nanomaterial" OR "Nanomaterials" OR "Diesel exhaust" OR "Diesel engine exhaust" OR "Concentrated ambient air particles" OR "Ultrafine" OR "Urban air pollution" OR "Particulate matter"), effect terms ("Atherosclerosis" OR "Atherosclerotic" OR "Atherogenesis" OR "Vascular function" OR "Vascular dysfunction" OR "Endothelium-dependent" OR "Endothelium-independent" OR "Endothelial dysfunction" OR "Cardiovascular effect" OR "Cardiovascular effects" OR Acetylcholine OR "Phenylephrine" OR "Sodium nitroprusside" OR "Vasorelaxation" OR "Vasoconstriction" OR "Vasodilation" OR "Vasodilatation" OR "Vasoconstriction" OR "Vasocontraction"), vessel type ("Artery" OR "Arteriole" OR "Aorta" OR "Aortic" OR "Coronary" OR "Mesenteric" OR "Cerebral" OR "Spinotrapezius" OR "Pulmonary" OR "Brachiocephalic" OR "Cremaster" OR "Carotid") and non-human species ("Dog" OR "Dogs" OR "Guinea pig" OR "Guinea pigs" OR "Hamster" OR "Hamsters" OR "Mice" OR "Mouse" OR "Rabbit" OR "Rabbits" OR "Rat" OR "Rats").

The primary search produced 376 and 482 hits in PubMed and EMBASE, respectively. A number of the publications have assessed vascular effects in terms of blood pressure, heart rate variability, electrocardiogram traces, blood flow, plasma levels of markers for vascular disease, or gene expression or protein levels in vessel walls. These publications have not been included in the quantitative analysis of effect size, although certain publications have been included as supporting information in the text. Seventy-one publications were included in the quantitative analysis, whereas 22 publications have been excluded for various reasons as explained in the "Notes about excluded papers" section. Moreover, two publications were identified from the publications in the primary search and included in the quantitative analysis (Bai *et al*., Atherosclerosis 216: 299-306, 2011 [PMID: 21435644]; Lippmann *et al.*, Res. Rep. Health Eff. Inst. 5-13, 2013 [PMID: 24377209]). Five studies were not identified with the applied combination of keywords, whereas they were found by using broad searches with few keywords (Kampfrath *et al.* 2011; Kim *et al.* 2011; Liu *et al.* 2014; Vidanapathirana *et al.* 2014; Ying *et al.* 2014). The full dataset consists of results from 78 publications (excluding Wan *et al.* 2014).

Notes about excluded papers: Two publications described effects on vasoconstriction in the abstract; however, they have not been included in the review because the vasomotor response was assessed by histopathology (Batalha *et al*., Environ Health Perspect. 110: 1191-1197, 2002 [PMID: 12460797]; Rivero *et al.*, Toxicol. Sci. 85: 898-905, 2005 [PMID: 15746007]). A study on residual oil fly ash was excluded because rats were exposed to leaches rather than the particulate matter (Proctor *et al.*, Toxicol. Sci. 90: 385-391, 2006 [PMID: 16407093]). One study investigated vasomotor dysfunction following exposure to welding fumes (Zeidler-Erdely *et al.*, Inhal. Toxicol. 26:697-707, 2014 [PMID: 25140454]). An investigation of vasomotor dysfunction following exposure to particulate matter from an Appalachian mountaintop mining site was excluded because it is a special type of environmental exposure (Knuckles *et al.*, Microcirculation 20: 158-169, 2013

[PMID: 22963349]). Certain studies on *ex vivo* exposure to nanomaterials have not been included in the review because there is no *in vivo* exposure study to support the findings, silver nanoparticles (Rosas-Hernandez *et al*., Toxicol. Lett. 191: 305-311, 2009 [PMID: 19800954]), manganese ferrite-based nanoparticles (Nunes *et al*., Int. J. Nanomed. 9: 3299-3312 [PMID: 25031535]), and silica (Akbar *et al.*, Biotechnol. Appl. Biochem. 58: 353-362, 2011 [PMID: 21995538); Farooq *et al.*, Nanomedicine 9: 413-425, 2014 [PMID: 23432341]). Similarly, certain studies on *ex vivo* exposure of vessel segments to combustion-derived particulate matter have been excluded from the review, including motorcycle exhaust particles (Cheng and Kang, J. Toxicol. Environ. Health Part A 56: 75-87, 1999 [PMID: 10344225]; Tzeng *et al.*, Toxicol. Sci. 75: 66-73, 2003 [PMID: 12805640]), diesel exhaust particles (Campen *et al.*, Toxicol. Sci. 88: 95-102, 2005 [PMID: 16093524]; Ikeda *et al.*, Jpn. J. Pharmacol. 68: 183-189, 1995 [PMID: 7563975]; Miller *et al.*, Environ. Health Perspect. 117: 611-616, 2009 [PMID: 19440501], Mutu *et al*., Life Sci 59: 1563-1570, 1996 [PMID: 8890937]), EHC-93 (Bagate *et al*., Inhal. Toxicol. 16: 431-436, 2004 [PMID: 15204758]; Bagate *et al.*, Toxicol. In Vitro 20: 52-62, 2006 [PMID: 16055302], and total suspended particles from Duisburg, Germany (Knaapen *et al.*, Human Exp. Toxicol. 20: 259-265, 2001 [PMID: 11476159]).

Publication by Nurkiewicz *et al.* have not been included in the analyses because it is based on fine or coarse size particles (Environ Health Perspect. 112: 1299-1306, 2004 [PMID: 15345343] and Environ Health Perspect. 114: 412-419, 2006 [PMID: 16507465]).

Cascio *et al.* 2007 (Inhal. Toxicol. 19 (Supplement): 67-76 [PMID: 17886053]) is a review that reported data from Cozzi *et al.*, 2006. Publications from Bai *et al*. (Toxicol. Appl. Pharmacol. 255: 184-192, 2011 [PMID: 21722660] and Inhal. Toxicol. 24: 518-527, 2012 [PMID: 22746401]) have been regarded as showing results from the same study as Kido *et al.*, Inhal. Toxicol. 23: 593-601, 2001 [PMID: 21848409]).

We have excluded one publication by Wan *et al.* 2014 (Cell Stress Chaperons 19: 715-724 [PMID: 24534034]). This publication formally fulfills all inclusion criteria, but we have considered it to be a replicate of the publication from Chen *et al.* 2013b. The paper by Wan *et al.*, 2014 (submitted 22th November 2013) is surprisingly similar to the paper by Chen *et al.* 2013b (available online 14th September 2013). The two publications have identical information about the location of the exposure facility. Wan *et al.* reports to have conducted the study three years later than Chen *et al.* (15th January to 15th March 2013). There were identical exposure contrast (63 ± 68 $\mu g/m^3$ and 19 ± 12 $\mu g/m^3$ in non-filtered and filtered air, respectively). In addition, the biological endpoints, including plaque progression assessed in H&E stained cross-sections of the aorta, showed virtually identical responses. The aortic plaque area was 1.2% and 2.6% in filtered air and air pollution exposed animals, respectively in Wan *et al.*, 2014. We have contacted both research groups by e-mail. Wan *et al.* has not responded, whereas Chen *et al.* responded immediately and provided additional information about the study. In addition, it should be emphasized that Wan *et al.* has affiliation to a university in a different city that is more than 2,000 km from the exposure location (School of Traditional Chinese Medicine, Southern Medical University, Guangzhou, Guangdong). The study requires special equipment for exposure and animal facility, which is not described by Wan *et al.*

Abbreviations used in tables and main text

ACH: acetylcholine, AHA: American Heart Association, ANOVA: analysis of variance, ApoE: apolipoprotein E, BALF: bronchoalveolar lavage fluid, BCA: brachiocephalic artery, BH4: tetrahydrobiopterin, CAPs: concentrated ambient air particles, CD68: cluster of differentiation 68, CCL2: chemokine (C-C motif) ligand 2 (same as MCP-1), CMAD: count median aerodynamic diameter, COX: cyclooxygenase, CRP: C-reactive protein, CXCL2: chemokine (C-X-C motif) ligand 2 (same as MIP-2), DCFH: dichloro-dihydro-fluorescein, DE: diesel exhaust, EC: elemental

carbon. EHC-93: Environmental Health Center 93, ET-1: endothelin 1, GM-CSF: Granulocyte macrophage colony-stimulating factor, GSD: geometric standard deviation, GSH: reduced glutathione, GSSG: oxidized glutathione, H&E: hematoxylin and eosin, HDL: high density lipoprotein, HO-1: heme oxygenase 1 (same as HMOX-1), ICAM-1: intercellular adhesion molecule 1, IL: interleukin, INFγ: interferon-γ, eNOS: endothelial nitric oxide synthase (same as NOS3), iNOS: inducible nitric oxide synthase (same as NOS2), I.p.: intraperitoneal. I.t.: intratracheal, I.v.: intravenous, LDL: low density lipoprotein, LDLr: LDL receptor, L-NAME: N^{ω}-Nitro-L-arginine, L-NMMA: N^{G}-monomethyl-L-arginine, LOX-1: lectin-like oxidized LDL receptor, MCP-1: monocyte chemoattractant protein-1 (same as CCL2), MIP-1α: macrophage inflammatory protein 1α (same as CCL3), MIP-1β: macrophage inflammatory protein 1β (same as CCL4), MIP-2: macrophage inflammatory protein 2 (same as CXCL2), MMAD: mass median aerodynamic diameter, MMP-9: Matrix metallopeptidase 9, NM: nanomaterial, OC: organic carbon, oxLDL: oxidized LDL, PAH: polycyclic aromatic hydrocarbon, PAI-1: plasminogen activator inhibitor 1, PE: phenylephrine, PMNs: polymorphonuclear neutrophils, PVP: polyvinylpyrrolidine, SAA: Serum Amyloid A, SD: standard deviation, SEM: scanning electron microscope, SOD: superoxide dismutase, SHR: spontaneous hypertensive rats, SNP: sodium nitroprusside, SRM: standard reference material, SSA: specific surface area, TEM: transmission electron microscope, TIMP-9: tissue inhibitor of metalloproteinase 9, TNF: tumor necrosis factor, VCAM-1: vascular cell adhesion molecule 1, VEGF: Vascular endothelial growth factor, VMF: vasomotor function, vWF: von Willebrand factor, WHHL: Watanabe heritable hyperlipidemic, 3-NT: 3-nitrotyrosine.

Supplementary table 1. Vasomotor dysfunction in animals following exposure to particulate matter in urban air or diesel exhaust

Type	Exposure	Vascular effect	Other effects	Reference
EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[1]	10 mg/kg by i.t. instillation in 13-15 weeks old male spontaneous hypertensive rats and sacrifice at 4 or 24 h after the exposure	Increased ACH and SNP relaxation in aorta rings at 4 h and no effect of PE-induced vasoconstriction. Unaltered vasomotor response at 24 h post-exposure	Increased pulmonary inflammation (percentage of PMNs in BALF)	Bagate *et al.* 2004b
SRM2975 No information on particle characteristics in suspension	0.25 or 0.50 mg/kg by i.v. injection in C57 mice and sacrifice at 1 h post-exposure	Unaltered vasomotor response to ACH, SNP and PE in thoracic aorta rings. *Ex vivo* exposure (1 h) attenuated the ACH vasorelaxation response (50 and 100 µg/ml), whereas there was no effect on vasomotor responses by SNP and PE	Increased plasma levels of TNF at 0.50 mg/kg. Unaltered IL-1β and IL-6 levels	Bai and van Eeden 2013
DE (single cylinder 5500 W Yanmar diesel generator, 90% load, certified diesel fuel). CMAD: 80 nm MMAD: 100 nm[2]	300 µg/m^3 by whole-body inhalation for 5 h in male Sprague-Dawley rats	Increased ET-1 induced vasoconstriction in pressurized coronary arteries	Unaltered levels of ET-1 and cytokines in plasma (including IL-6 and TNF)	Cherng *et al.* 2009
DE (single cylinder, 5500 W Yanmar diesel generator, 90% load, certified diesel fuel) CMAD: 80 nm MMAD: 100 nm[2]	300 µg/m^3 by whole-body inhalation for 5 h in male Sprague-Dawley rats	Reduced ACH-induced vasorelaxation in pressurized coronary arteries, which was blunted by supplementation with sepiapterin and inhibition of NOS activity (L-NAME). No effect by inhibition of COX on vasomotor responses	Increased superoxide anion radical production in coronary arteries (DHE assay)	Cherng *et al.* 2011
UFPs from Chapel Hill, NC (collected in 7-day periods in October, 2002)[3]	100 µg/mouse by i.t. instillation in 6-12 weeks old ICR mice. Sacrifice at 24 h after the instillation	Reduced ACH-induced vasorelaxation in aorta rings. Unaltered PE-induced vasoconstriction	Increased pulmonary inflammation (histology)	Cozzi *et al.* 2006
SRM1648 (0.4 µm in diameter, inorganic carbon (63%), organic carbon (4-7% and elements)	5 mg by i.t. instillation in 12-14 weeks old male Wistar rats and sacrifice at 6, 12, 24 or 72 h post-exposure	Reduced ACH-induced vasorelaxation in intra-pulmonary artery rings at 12 h post-exposure. No effect at 6, 24 or 72 h	Not assessed	Courtois *et al.* 2008
$PM_{2.5}$ from Jinchang (harboring a nickel refinery) and Zhangye,	50 µg/mouse by oropharyngeal aspiration (twice weekly) for 3 weeks in 12 weeks old male	Reduced ACH-induced vasorelaxation in 2nd order mesenteric arteries, which was restored by *ex vivo* addition of L-NAME,	Increased pulmonary inflammation (total cells) and cell damage (protein in BALF) of both samples.	Cuevas *et al.* 2015

China (collected simultaneously from March 6th, 2009 to March 26th, 2010). Elements measured on $PM_{2.5}$ filters	FVB/N mice[4]. Sacrifice 24 h after the last exposure	apocynin or VAS2870 to vessel rings. Unaltered SNP and PE response	Increased serum IL-10 and VEGF (unaltered IL-13, IL-6, TNF, CSF, MCP-1. Increased TNF, IL-6, SOD, NADPH oxidase 4 in mesenteric arteries and unaltered MMP-9 and eNOS (RT-PCR)	
CAPs (Sao Paulo, Brazil). Contains information on elemental composition	593 µg/m^3 by inhalation (3.3 h/day, 7 days) for 14 days in 3 months old male Wistar rats. Sacrifice at 24 h after the last exposure	Reduced ACH-induced vasorelaxation in pulmonary artery rings and unaltered response to SNP	Increased TNF in arteries (unaltered IL-1β and IL-6) and oxidative stress (hydroethidine fluorescence). Unaltered levels of TNF, IL-1 β and IL-6 in plasma	Davel *et al.* 2012
DE (idling condition). MMAD: 76 nm (GSD: 2.0 nm). Measurement of volatile organic compounds	174 µg/m^3 by inhalation (6 h/day, 5 days/week) for 4 weeks in male Fisher 344 rats (age not specified) and sacrificed the day after the last exposure. Rats were pre-exposed to ozone (0.4 ppm for 12 h) to induce mild pulmonary inflammation	Unaltered PE-induced vasoconstriction and vasorelaxation responses (ACH, SNP and verapamil) in aorta rings	Unaltered pulmonary inflammation (BALF cell counts, TNF and IL-6) and oxidative stress (GSH/GSSG and HO-1). Unaltered effects in plasma (vWF and PAI-1)	Gerlofs-Nijland *et al.* 2010
CAPs (Utrecht, The Netherlands). MMAD: 104 nm (GSD: 31 nm). Measurement of volatile organic compounds	485 µg/m^3 by inhalation (6 h/day, 5 days/week) for 4 weeks in male Fisher 344 rats (age not specified) and sacrificed the day after the last exposure. Rats were pre-exposed to ozone (0.4 ppm for 12 h) to induce mild pulmonary inflammation	Unaltered PE-induced vasoconstriction and vasorelaxation responses (ACH, SNP and isoprenaline) in aorta rings	Unaltered pulmonary inflammation (BALF cell counts, TNF and IL-6) and oxidative stress (GSH/GSSG and HO-1). Unaltered effects in plasma (vWF and PAI-1)	Gerlofs-Nijland *et al.* 2010
SRM2975 No information on particle characteristics in suspension	0.5 or 5 mg/kg by i.p. injection in 11-13 week old female C57BL/6 or *ApoE*$^{-/-}$ mice and sacrifice 1 h post-exposure	Decreased ACH-induced vasorelaxation in aorta rings at 0.5 mg/kg in *ApoE*$^{-/-}$ mice. No effect on SNP or PE response in wild-type or *ApoE*$^{-/-}$ mice	Not assessed	Hansen *et al.* 2007
CAPs (Columbus, OH). No information on particle characterization	94.1 µg/m^3 by inhalation for 20 weeks (6 h/d, 5 d/week) in 6 weeks old male BALB/c and C57BL/6 mice on normal diet	Reduced ACH-induced vasorelaxation and increased PE-induced vasoconstriction in aorta from BALB/c mice. Increased PE-induced vasoconstriction and unaltered ACH-induced vasorelaxation in aorta rings of C57BL/6 mice[5]	Increased lung levels of TNF, MCP-1 and IL12p70 (unaltered IL-6 and INFγ levels, decreased IL-10 levels). Increased serum levels of TNF and MCP-1 (unaltered IL12p70, INFγ, IN-6	Kampfrath *et al.* 2011

			and IL-12 levels)	
DE (no information about particle characteristics)	200 or 400 µg/m^3 for either 3 days (6 h/day) or 7 weeks (6 h/day, 5 days/week) in 30 weeks old male *ApoE*$^{-/-}$ mice on normal diet	Unaltered ACH-induced vasorelaxation in aorta rings (data were not shown). Decreased PE-induced vasorelaxation[6]	Increased heat shock protein 70 expression in lung tissue and plasma	Kido *et al.* 2011a
EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[1]	10 or 200 µg by i.t. instillation in 10-12 weeks old male C57BL/6 mice and sacrifice at 4 or 24 h post-exposure	Reduced ACH-induced vasorelaxation in abdominal aorta rings at 4 h after exposure to the highest dose (no effect at 24 h). Unaltered vasoconstriction response to PE. The highest dose (200 µg) did not affect vasomotor function in IL-6 knockout mice (4 h)[7]	Pulmonary inflammation at both 4 and 24 h post-exposure (increased IL-6 in BALF). Increased IL-6 levels in serum	Kido *et al.* 2011b
DE (single cylinder, 5500 W Yanmar diesel generator). CMAD: 80 nm[8] MMAD: 110 nm[8]	350 µg/m^3 by whole-body inhalation for 4 h in 8-10 weeks old male C57BL/6 mice	Unaltered myogenic tone, ET-1 induced vasoconstriction and NONOate induced vasorelaxation in mesenteric arteries	Not reported	Knuckles *et al.* 2008
SRM2975 Hydrodynamic diameter in phosphate buffer saline with Tween 80: 189 nm (SD: 16 nm)	0.8 mg/rat by i.t. instillation (3 times per week for 4 weeks) in 14-16 weeks old male Wistar or spontaneous hypertensive rats. Sacrifice 4 h after the last exposure	Reduced vasorelaxation response to ACH (but not SNP) in aorta rings from SHR rats. No effect in wild-type rats. *Ex vivo* treatment of aorta rings from wild-type rats attenuated both ACH and SNP induced vasorelaxation (100 µg/ml, 30 min incubation)[9]	Increased mRNA of p22phox in aorta of SRM2975 exposed SHR rats	Labranche *et al.* 2012
CAPs (Columbus, OH). Information on elemental composition	117 µg/m^3 by inhalation (6 h/day, 5 days/week) for 6 months in 18 weeks old male C57BL/6 mice on normal high-fat diet	Reduced vasorelaxation response to ACH or insulin in aorta rings	Unaltered plasma levels of INFγ, IL-6, IL-12 p70, MCP-1, and TNFα	Liu *et al.* 2014
SRM2975 Hydrodynamic diameter: 257 nm (SD: 46 nm)	35 µg/mouse by oropharyngeal aspiration twice a week for 4 weeks in 8-9 weeks old male *ApoE*$^{-/-}$ mice on a Western-type diet. Sacrificed 3-4 days after the last exposure	Unaltered vasorelaxation response to ACH or SNP in PE (or noradrenalin) preconstricted aorta rings from the distal portion of the thoracic aorta	Pulmonary inflammation (BALF cells) Unaltered plasma levels of cholesterol, triglycerides, CRP, and fibrinogen	Miller *et al.* 2013
EHC-93 CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[1]	1 mg/kg by i.t. instillation (3 times per week for 3 weeks) in 12 weeks old male New Zealand White rabbits on normal diet. Sacrifice at 4 h after the last exposure	Increased PE-induced vasoconstriction in carotid arteries. Reduced vasorelaxation response to ACH. Unaltered response to SNP. Effects were attenuated by treatment with Lovastatin	Increased plasma ET-1. Unaltered cholesterol, triglycerides, HDL and LDL	Miyata *et al.* 2013

CAPs (Tuxedo, NY, USA). CMAD: 80 nm (GSD: 1.9 nm), MMAD: 223 nm (GSD: 1.6 nm)	105 µg/m^3 by inhalation (5 h/day, 4 days/week) for 5 months in 12 weeks old male *ApoE*$^{-/-}$ mice on normal chow. Sacrifice at 18 h after the last exposure	Increased PE-induced vasoconstriction in aorta rings. Unaltered vasoconstriction response to serotonin. Unaltered ACH and SNP induced vasorelaxation	Unaltered pulmonary inflammation (PMNs in BALF). Unaltered serum IL-6, IL-10, VCAM-1, ICAM-1 and E-selectin levels in serum	Quan *et al.* 2010
DE (5500 W single-cylinder diesel engine generator, 91% engine load, fuel from a local gas station). CMAD: 78 nm (GSD: 1.7 nm), MMAD: 148 nm (GSD: 1.5 nm)	436 µg/m^3 by inhalation (5 h/day, 4 days/week) for 5 months in 12 weeks old male *ApoE*$^{-/-}$ mice on normal chow. Sacrifice at 18 h after the last exposure	Increased PE-induced vasoconstriction in aorta rings. Unaltered vasoconstriction response to serotonin. Unaltered ACH and SNP induced vasorelaxation. Similar response of DE gasses and whole DE on vasomotor function responses	Unaltered pulmonary inflammation (PMNs in BALF). Unaltered serum IL-6, IL-10 and E-selectin levels in serum. Increased VCAM-1 and decreased ICAM-1 in serum. Similar effect on pulmonary/systemic inflammation by DE gasses and whole DE	Quan *et al.* 2010
SRM2975 (particle characteristics in exposure vehicle not reported)	500 µg/rat by i.t. instillation in male Wistar rats and sacrifice at 2 or 24 h after exposure	Reduced SNP-induced vasodilatation in femoral arteries after intra-arterial injection in hind-limb vascular bed (6 and 24 h). No effect after ACH injection. *Ex vivo* (wire myograph) experiments showed increased PE-induced vasoconstriction (6 h) in aorta and unaltered response in femoral and mesenteric arteries. Unaltered ACH response in aorta, femoral and mesenteric arteries (2 [data not shown], 6, 24 h). Increased SNP sensitivity in mesenteric arteries (6 h) and no effect at other times or vessels[10]	Pulmonary inflammation (total cells in BALF, IL-6 and protein). Increased systemic inflammation in plasma (IL-6 and TNF) at 24 h post-exposure. Unaltered CRP levels in plasma	Robertson *et al.* 2012
CAPs (Tuxedo, NY, USA)	85 µg/m^3 by inhalation (6 h/day, 5 days/week) for 6 months in 6 weeks old male *ApoE*$^{-/-}$ mice on normal chow or high-fat diet. Sacrificed at day 15-16 after the last exposure	Increased vasoconstriction response in aorta rings by exposure to PE or serotonin, and reduced ACH-induced vasorelaxation in mice on high-fat diet. Unaltered vasomotor response in mice on regular chow	Inflammation response (CD68-positive cells, 3-nitrotyrosine and iNOS) and oxidative stress (DCFH staining) in aorta. Unaltered levels of cholesterol and triglycerides in serum[11]	Sun *et al.* 2005
CAPs (Tuxedo, NY)	79.1 µg/m^3 by inhalation (6 h/day, 5 days/week) for 10 weeks in Sprague-Dawley rats that were treated by infusion of angiotensin II during the last week of	Reduced ACH-induced vasorelaxation in aortic rings and increased PE-induced vasoconstriction. PE-precontracted aorta released tension by ex vivo treatment with a Pho-kinase inhibitor (Y-27632)	Increased expression of NADPH oxidase subunits in aorta tissue	Sun *et al.* 2008b

	exposure			
CAPs (Tuxedo, NY)	72.7 µg/m^3 by inhalation (6 h/day, 5 days/week) for 128 days in 8 weeks old male C57BL/6 mice on high-fat diet	Reduced ACH and insulin induced vasodilation in aorta rings	Increased LDL, glucose, fasting insulin, insulin resistance, TNF and IL-6 and reduced HDL in plasma. Unaltered cholesterol and triglycerides in plasma. Adipose tissue inflammation	Sun *et al.* 2009
EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[1]	2.6 mg/kg (every second day for 5 days) or 2 mg/kg (2 times per week for 4 weeks) in 12 weeks old female New Zealand White rabbits on normal diet. Sacrifice after the final instillation (assumed to be immediately after the instillation)	Reduced ACH-induced vasorelaxation in carotenoid arteries. Unaltered responses to SNP and PE	Pulmonary inflammation (predominantly macrophages) and increased plasma levels of IL-6 and unaltered endothelin levels (4-week experiment only)	Tamagawa *et al.* 2008
Mixed vehicle exhaust (gasoline and diesel) from a single cylinder 5500 W Yanmar engine and a General Motors 4.3 L V6 gasoline engine. CMAD: 60 nm, MMAD: 1 µm, EC/OC and PAH levels measured	100 or 300 µg/m^3 (6 h/day) for 50 consecutive days in 9-10 weeks old male *ApoE*$^{-/-}$ mice on high-fat diet. Sacrifice the day after the last exposure	Increased PE-induced vasoconstriction in aorta rings. Unaltered ACH-induced vasorelaxation[12]	Increased gelatinase (MMP-2/9) activity in aorta. Unaltered expression levels of *ET-1*, *Hmox-1*, *Timp-2*, *Mmp-2* and *Mmp-9* in aorta	Vedal *et al.* 2013
SRM2975 Hydrodynamic diameter in saline: 280 nm (SD: 9 nm)[D]	0.5 mg/kg by i.t. instillation twice during 24 h and sacrifice at 2 h post-exposure (total dose = 1 mg/kg) in 11-13 weeks old female *ApoE*$^{-/-}$ mice on a normal diet	Unaltered ACH-induced vasorelaxation in prostaglandin $F_{2\alpha}$ pre-contracted aorta rings. No effect of L-sepiapterin supplementation to aorta rings	Unaltered expression of *Ccl2, Vcam-1*, *Icam-1* and *Hmox-1* in lungs	Vesterdal *et al.* 2014
SRM1649b Hydrodynamic diameter in cell medium: 224 nm (SD: 44 nm)[13]	0.5 mg/kg by i.t. instillation twice during 24 h and sacrifice at 2 h post-exposure (total dose = 1 mg/kg) in 11-13 weeks old female *ApoE*$^{-/-}$ mice on a normal diet	Unaltered ACH-induced vasorelaxation in prostaglandin $F_{2\alpha}$ pre-contracted aorta rings. No effect of L-sepiapterin supplementation to aorta rings	Unaltered expression of *Ccl2, Vcam-1*, *Icam-1* and *Hmox-1* in lungs	Vesterdal *et al.* 2014
DE (single cylinder Yanmar diesel engine). No information on particle characteristics	300 µg/m^3 for 6 h in male C57BL/6 mice on normal diet	Unaltered response to PE-induced vasoconstriction and vasorelaxation responses to ACH and SNP in aorta rings[14]	Increased pulmonary inflammation (percentage of neutrophils in BALF). Unaltered GSH levels in plasma	Weldy *et al.* 2013

CAPs (Columbus, OH). Information on elemental composition	111 µg/m^3 (6 h/day, 5 days/week) for 10 weeks in 3 weeks old male C57BL/6 or NADPH oxidase p47^{phox} knockout mice on either normal or high-fat diet	Increased vasoconstriction response to PE and reduced ACH-induced vasorelaxation in aorta rings after CAPs exposure in wild-type mice fed a normal or high-fat diet. Unaltered responses in knockout mice. Decreased insulin-induced vasorelaxation in aorta[15]	Increased TNF in plasma (unaltered INFγ, MCP-1 and RANTES) in wild type on either diet. Increased glucose and insulin resistance wild-type mice on normal diet	Xu *et al.* 2010
CAPs (New York, NY)	138.4 µg/m^3 (6 h/day, 5 days/week) for 4 months in male *ApoE*$^{-/-}$ mice fed a high-fat diet	No difference in ACH-induced vasorelaxation in aorta rings. Abolished A23187 induced vasorelaxation. Reduced SNP vasorelaxation. Reduced PE-induced vasoconstriction	Increased inflammation in aortic tissue (iNOS expression, 3-NT) and oxidative stress (superoxide radical generation)	Ying *et al.* 2009a
CAPs (Columbus, OH). Information on elemental composition[16]	74.3 µg/m^3 (6 h/day, 5 days/week) for 12 weeks in 8 weeks old male C57BL/6 mice that were infused with angiotensin II 14 days before sacrifice	Increased PE-induced vasoconstriction in aorta rings, which was blunted by inhibition of RhoA/Rho-kinase in ex vivo condition	Not reported	Ying *et al.* 2009b
CAPs (Columbus, OH). Information on elemental composition	107 µg/m^3 by inhalation for 6 months (6 h/d, 5 d/week) in 9 weeks old male C57BL/6 mice on regular diet	Increased vasoconstriction response (PE or U-46619) and unaltered ACH-induced in mesenteric artery rings	Not reported	Ying *et al.* 2014
CAPs (Columbus, OH). Information on elemental composition	128 µg/m^3 (6 h/day, 5 days/week) for 15 weeks, or 5 weeks further recovery, in 6 weeks male spontaneous hypertensive rats	Increased vasoconstriction response to PE or U-46619 in aorta rings. Reduced ACH-induced vasorelaxation. Five weeks recovery normalized the vasomotor function	Increased gene expression of *Tnf*, *Cox-2* and *Il-6* in lung tissue (unaltered *IL-1β*). There was still elevated levels of *Tnf* and *Il-6* after a five weeks recovery period	Ying *et al.* 2015

[1]CMAD and MMAD have been reported in Vincent *et al.* 1997. [2]Information on particle size in aerosol has been reported in a separate publication (McDonald *et al.* Aerosol Sci Technol 38: 62-78, 2004). [3]There is no description of the location or sources of UFPs or particle characteristic in either the aerosol (during collection of particles) or suspension (vehicle used for i.t. instillation). The particle size of UFPs is described as being less than 150 nm in diameter. Another publication from the same group summarized the results from this study in a review, including results on vasomotor function measurements (Cascio *et al.*, Inhal Toxicol 19 (Supplement): 67-76, 2007 [PMID: 17886053]). [4]This inbred strain has been developed from Swiss mice. The *Fv1*^{b} allele confers sensitive to the Friend leukemia virus B strain. It is susceptible to asthma-like airway responsiveness with generation of specific IgE. The model has been described by Taketo *et al.*, 1991 (Proc. Natl. Acad. Sci. U. S. A. 88: 2065-2069 [PMID: 1848692]). [5]There was unaltered vasomotor function in Toll-like receptor 4 deficient mice and *NOS*$^{-/-}$ mice after 20 weeks of exposure to CAPs. The publication contains information on levels of cholesterol and triglycerides in CAPs-exposed BALB/c mice, but the tissue is not specified. Pooled results from BALB/c and C57BL/6 mice have been used in the analysis. [6]There was 47% (3 days, 200 µg/m^3), 32% (3 days, 400 µg/m^3), 26% (7 weeks, 200 µg/m^3) and 14% (7 weeks, 400 µg/m^3) reduced PE-induced vasoconstriction. Statistical significance was only observed for the groups that were exposed to 400 µg/m^3 (3 days) and 200 µg/m^3 (7 weeks), which may be due to statistical power as the variation and group sizes differed. We have regarded these results as a general decreased responsiveness to PE-induced vasoconstriction.

Decreased PE-induced vasoconstriction was also report by Bai *et al*., Toxicol Appl Pharmacol 255: 184-192, 2011 [PMID: 21722660] and Bai *et al.*, Inhal Toxicol 24: 518-527, 2012 [PMID: 22746401]. The type of diesel engine has not been specified in the publication, but we have assumed that the same type of exposure system was used in this and other studies from the same group (described by Gould *et al.*, Inhal, Toxicol. 20: 49-52, 2008 [PMID: 18236222]). The results from this study are included in table 5 and 8 and dose-response relationship as group 1 and 3 (see Supplementary Table 6). [7]The study has been regarded to show unaltered vasoconstriction and reduced endothelium-dependent vasorelaxation. [8]Information on particle size in aerosol has been reported in a separate publication (McDonald *et al.* Environ Health Perspect 112: 1307-1312, 2004 [PMID: 15345344]). [9]Results from wild-type and SH rats have been included as separate studies in the analysis. [10]We have regarded the study as showing null effect in the analyses in the review because the statistically significant effects seem sporadic and inconsistent over time. [11]The original publication lacks clarity with regards to the effect of exposure to CAPs on cholesterol levels in serum. Based on the results in the publication we have calculated that the exposure to CAPs was associated with 0.92-fold (95% CI: 0.82-1.03) lower cholesterol levels as compared to filtered air exposed mice on normal chow. In the high-fat fed mice there was 1.05-fold (95% CI: 0.85-1.24) increased levels of cholesterol in the CAPs exposed mice. [12]The experiments were carried out in different batches. Vasomotor function tests were measured by different personnel. It is argued to have influenced the results. The authors conclude that the exposure to mixed vehicle exhaust was associated with a consistent PE-induced vasoconstriction. Following on, we have interpreted the results as there is no dose-response relationship and the vasoconstriction was observed in mice exposed to both mixed vehicle exhaust and gasses only. Low concentration = 16.6 µg/m^3 (gasoline exhaust) + 83.3 µg/m^3 (DE). High concentration = 25 µg/m^3 (gasoline exhaust) + 250 µg/m^3 (DE). [13]The hydrodynamic particles size was also assessed in cell culture medium (197 ± 6 nm) and water (179 ± 11 nm). The exposure vehicle (saline) to animals contained BALF to produce a stable suspension. [14]A group of *Gclm*$^{-/+}$ mice (coding for the rate limiting enzyme in glutathione synthesis) showed increased responsiveness to ACH-induced vasoconstriction. [15]Results from normal and high-fat diet have been used as separate studies in the analysis. [16]The publication cites information in the supplement, although this is not available on the journal webpage (Fe and Zn is described as being high).

Supplementary table 2. Progression on atherosclerosis in animals following exposure to particulate matter in urban air or diesel exhaust

Type	Exposure	Vascular effect (Mean ± SD, (N))	Other effects	Reference
CAPs (<2.5 µm) or UF-CAPs (<0.18 µm) from Los Angeles, CA. Information on elements, EC, OC and PAH in PM	CAPs (438 µg/m^3) or UFPs (113 µg/m^3) by whole-body exposure for 40 days (5 h/day, 3 days/week) in 6 weeks old male *ApoE*$^{-/-}$ on regular diet	Lesion area in the aortic root (cross-section, Oil Red O stain)[1]: Control: 22362 ± 10716 (14) CAPs: 26361 ± 9100 (16) **UFPs: 33011 ± 14489 (15)***	Unaltered pulmonary inflammation (results not shown). Increased plasma cholesterol after exposure to CAPs and unaltered in UFP-exposed mice	Araujo *et al.* 2008
DE (Cummings B-series engine, model 2002 turbocharged direct-injection 5.9 L, 75% load capacity). MMAD: 104 nm	200 µg/m^3 (6 h/day, 5 days/week) for 7 weeks in 30 weeks old male *ApoE*$^{-/-}$ mice on normal diet	Lesion area in the aortic root (cross-section, Movat stain): Control: 51.3 ± 11.9 (n = 10) Exposed: 48.8 ± 10.3 (n = 10)	Unaltered plasma concentration of cholesterol and triglycerides	Bai *et al.* 2011
DE (Cummings, 2000 model, 5. 9 ISB turbo engines). MMAD: 100-150 nm (GSD: 140-180 nm)	109, 305 or 1012 µg/m^3 by inhalation (6 h/day for 50 days) in 10 weeks old male *ApoE*$^{-/-}$ mice on high-fat diet	Lesion area in the aortic leaflet region (Oil Red O stain[2]: Control: 59.7 ± 7.0 (10) Low: 60.3 ± 6.6 (10) Middle: 64.2 ± 7.9 (10) High: 63.2 ± 7.0 (10) Increased trend toward accumulation of macrophages and collagen in plaques	Not reported	Campen *et al.* 2010
DE (Ingersol Rand, run at 1500 rpm with a generator load of 35 kW, fuel from a local gas station). MMAD: 82-83 nm (SD: 1.8 nm)	1700 µg/m^3 (3 h/day, 5 days/week) for 4 weeks by nose-only inhalation in 14 weeks old *ApoE*$^{-/-}$ on Western diet. Sacrifice at day 3 post-exposure	Lesion area in BCA (cross-section, US trichrome stain): Control: 43.2 ± 22.1 (10) Exposed: 57.6 ± 40.4 (10) Plaques in the DE exposed mice had developed a more complex structure. DE from combustion of fuel with CeO_2 had no effect on plaque progression	Increased number of pigmented macrophages in lungs (histopathological examination)	Cassee *et al.* 2012
Urban air (Beijing, China). Measurement of metals and organic compounds in $PM_{2.5}$ that had been collected on filters	61 µg/m^3 (filtered air = 17.6 µg/m^3) for 2 months (24 h/day, 7 days/week) in 10 weeks old male *ApoE*$^{-/-}$ mice on a Western-type diet	Lesion area in the aortic arch (cross section, H&E stain): Control: 1.06 ± 0.25 (10) **Exposed: 2.48 ± 0.59 (10)***	Pulmonary inflammation (IL-6 and TNF in BALF, histology). Systemic inflammation (CRP, TNF, but not IL-6) and oxidative stress (SOD, oxLDL). Increased levels of cholesterol and unaltered levels of plasma triglycerides and HDL	Chen *et al.* 2013b
CAPs (Tuxedo, NY). Description of the exposure	110 µg/m^3 by inhalation (6 h/day, 5 days/week for 5	Lesion area in the aortic arch (En face, Sudan IV stain) in *ApoE*$^{-/-}$ mice:	Unaltered pulmonary inflammation	Chen and Nadziejko 2005

setup has been reported in a separate publication. Particle number concentration: 135 nm (SD = 2 nm) and a bimodal volume size distribution with a mean of 389 nm, SD = 2 nm)[3]	months) in *ApoE*$^{-/-}$ (39-41 weeks) or *ApoE/LDLr* (18-20 weeks) double knockout mice on high-fat diet	Control: 42 ± 14.2 (6) **Exposed: 66 ± 15.0 (9)*** Unaltered plaque progression in double knockout mice (en face), whereas there was a slightly increased lesion area and cellularity in the aorta root (cross-section)		
EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[4]	5 mg by pharyngeal instillation (twice weekly for 4 weeks) in female 42 weeks old WHHL rabbits on regular diet. Sacrifice at day 4 after the last exposure	Lesion area in aorta: Control: 20.9 ± 7.8 (5) Exposed: 29.0 ± 28.8 (5)	Not reported	Goto *et al.* 2004
UF-CAPs (Los Angeles, CA). Information on elements, EC, OC and PAH in PM	58 µg/m^3 by inhalation (5 h/day, 4 days/week) for 8 weeks in male *ApoE*$^{-/-}$ mice on regular diet	Lesion area in BCA (cross-section): Control: 14.2 ± 12.6 (4) **Exposed: 29.0 ± 19.7 (4)***	Unaltered serum total cholesterol	Keebaugh *et al.* 2015
UFP (Los Angeles, CA). Re-aerosolized for exposure. Mode of re-aerosolized sample was below ≈50 nm (obtained from graph)	360 µg/m^3 by inhalation (5 h/day, 3 days/week) for 10 weeks in male *LDLr*$^{-/-}$ mice on high-fat diet	Lesion area in the aortic arch (%, *en face*, Sudan IV stain): Control: 7.8 ± 1.0 (8) **Exposed: 12.8 ± 1.3 (8)*** Increased plaque area when assessed by cross-section (Oil Red O)	Increased systemic inflammation (SAA and TNF). Increased level of triglycerides and decreased HDL in plasma. Unaltered LDL and total cholesterol	Li *et al.* 2013b
CAPs from five sites in USA. EC/OC and elemental composition measured	Inhalation of CAPs (6 h/day, 5 days/week) for periods up to 6 months in Manhattan, NY (122.9 µg/m^3), Tuxedo, NY (136 µg/m^3), East Lansing, MI (67.8 µg/m^3), Seattle, WA (60.5 µg/m^3) and Irvine, CA (138 µg/m^3) in 12 weeks old *ApoE*$^{-/-}$ mice (mice in Irvine and Seattle were 2 and 4 months older than the other sites) on normal diet	Lesion area in the aorta (ultrasound imaging) at 6 months exposure[5]: Manhattan: Control: 54.3 ± 2.6 (10) Exposed: 53.6 ± 5.4 (10) Tuxedo: Control: 42.5 ± 6.6 (11) **Exposed: 52.2 ± 10.7 (13)*** East Lansing: Control: 29.8 ± 4.3 (11) Exposed: 32.9 ± 4.1 (12) Seattle: Control: 54.1 ± 4.4 (11) Exposed: 57.3 ± 5.7 (11) Irvine: Control: 31.5 ± 3.7 (12) Exposed: 30.5 ± 3.0 (12) Imaging in BCA showed increased plaque area after CAPs exposure in	Unaltered serum levels of CRP, IL-6, IL-10, IL-12, IL-13, TNF, MCP-1, MIP-1, GM-CSF, MMP-9 and VEGF	Lippmann *et al.* 2013

		Manhattan, Tuxedo and East Lansing. No effect on plaque by en face Sudan IV staining in mice from Seattle and Irvine		
SRM2975. Hydrodynamic diameter: 257 nm (SD: 46 nm)	35 µg/mouse by oropharyngeal aspiration twice a week for 4 weeks in 8-9 weeks old male *ApoE*$^{-/-}$ mice on a Western-type diet	Lesion area in the aortic arch (%, *en face*, Sudan IV stain): Control: 5.3 ± 1.5 (7) **Exposed: 6.8 ± 1.7 (7)*** Increased plaque progression in BCA vessel Unaltered (low) plaque level in aorta and BCA of wild-type C57 mice	Pulmonary inflammation (BALF cells) Unaltered plasma levels of cholesterol, triglycerides, CRP, and fibrinogen	Miller *et al.* 2013
EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[4]	1 mg/kg by i.t. instillation (3 times per week for 3 weeks) in 12 weeks old male New Zealand White rabbits on high-fat diet and subjected to balloon injury in the abdominal injury prior to EHC-93 exposure	Increased atherosclerotic plaque score (i.e. indicator of complexity) by EHC-93 exposure, which was inhibited by treatment with Lovastatin	Increased plasma ET-1. Unaltered cholesterol, triglycerides, HDL and LDL	Miyata *et al.* 2013
SRM1650b No information on particle characteristics in suspension	2 µg/mouse by intra-nasal instillation (5 days/week) for 6 weeks in 10-12 weeks old *ApoE*$^{-/-}$ mice (sex not specified) on Western-type diet	Lesion area in the aortic arch (cross-section, Oil Red O)[6]: Control: 100 ± 31.8 (6) **Exposed: 157.7 ± 44.3 (6)***	Not reported	Pöss *et al.* 2013
CAPs (Tuxedo, NY, USA). CMAD: 80 nm (GSD: 1.9 nm), MMAD: 223 nm (GSD: 1.6 nm)	105 µg/m^3 by inhalation (5.2 h/day, 4 days/week) for 3 or 5 months in 12 weeks old male *ApoE*$^{-/-}$ mice on normal chow. Sacrifice at 18 h after the last exposure	Lesion area in the aortic arch (cross-section, Oil Red O) at 3 months[7]: Control: 7.2 ± 3.6 (3) Exposed: 8.0 ± 2.4 (3) At 5 months: Control: 16.0 ± 7.6 (3) **Exposed: 25.4 ± 4.6 (3)*** Increased plaque progression in BCA when assessed by ultrasound imaging (lumen size) and no effect by H&E stain	Unaltered pulmonary inflammation (PMNs in BALF). Unaltered serum IL-6, IL-10, VCAM-1, ICAM-1 and E-selectin levels in serum	Quan *et al.* 2010
DE (5500 W single-cylinder diesel engine generator). CMAD: 78 nm (GSD: 1.7 nm), MMAD: 148 nm (GSD: 1.5 nm)	485 µg/m^3 by inhalation (5.2 h/day, 4 days/week) for 3 or 5 months in 12 weeks old male *ApoE*$^{-/-}$ mice on normal chow. Sacrifice at 18 h after the last exposure	Lesion area in the aortic arch (cross-section, Oil Red O) at 3 months[8]: Control: 7.2 ± 3.6 (3) Exposed: 8.0 ± 4.0 (3) At 5 months: Control: 16.0 ± 7.6 (3) Exposed: 20.9 ± 3.6 (3) Increased plaque progression in BCA at 5 months when assessed by H&E staining, but no effect by ultrasound imaging (lumen size). Higher effect on plaque	Unaltered pulmonary inflammation (PMNs in BALF). Unaltered serum IL-6, IL-10 and E-selectin levels in serum. Increased VCAM-1 and decreased ICAM-1 in serum. Similar level of pulmonary and systemic inflammation after whole DE and DE gasses	Quan *et al.* 2010

		progression with whole DE than DE gases		
CAPs (Columbus, OH). Information on elemental composition	101.6 µg/m^3 by inhalation (6 h/day, 5 days/week) for 6 months in 8 weeks old male *ApoE*$^{-/-}$ mice on normal chow	Lesion area in the aortic arch (En face, Oil Red O). Control: 5.1 ± 3.5 (6) **Exposed: 13.1 ± 2.8 (6)***	Not reported	Rao *et al.* 2014
Urban air (Sao Paulo, Brazil). No information on particle characteristics	20.4 µg/m^3 (filtered air: 1.6 µg/m^3, $PM_{2.5}$) for 4 months in 4 weeks old male *LDLr*$^{-/-}$ mice on normal or high-fat diet	Lesion area in aorta (cross-section, Oil Red O stain). Normal diet: Control: 15.3 ± 12.3 (10) Exposed: 17.9 ± 6.5 (10) High-fat diet: Control: 47.1 ± 33.4 (10) Exposed: 50.3 ±26.0 (10) Increased arterial wall thickness in exposed mice on high-fat diet	Unaltered plasma levels of cholesterol and triglycerides	Soares *et al.* 2009
CAPs (Tuxedo, NY, USA). No information on particle characteristics	85 µg/m^3 by inhalation (6 h/day, 5 days/week) for 6 months in 6 weeks old male *ApoE*$^{-/-}$ mice on normal chow or high-fat diet. Sacrificed at day 15-16 after the last exposure	Lesion area in the aortic arch (cross-section, Oil Red O) in mice on high-fat diet: Control: 26.6 ± 8.6 (6) **Exposed: 41.5 ± 9.8 (6)*** No effect in mice on regular chow: Control: 13.2 ± 8.1 (8) Exposed: 19.2 ± 13.1 (8)	Inflammation response (CD68-positice cells, 3-nitrotyrosine and iNOS) and oxidative stress (DCFH staining) in aorta. Unaltered levels of cholesterol and triglycerides in serum[9]	Sun *et al.* 2005)
CAPs (Tuxedo, NY, USA). No information on particle characteristics	85 µg/m^3 by inhalation (6 h/day, 5 days/week) for 6 months in 6 weeks old male *ApoE*$^{-/-}$ mice on normal chow or high-fat diet. Sacrificed at day 15-16 after the last exposure	Lesion area in the aortic arch (ultrasound imaging) in mice on high-fat diet[10]: Control: 9.5 ± 4.7 (6) **Exposed: 16.0 ± 4.1 (6)*** No effect in mice on regular chow: Control: 10.6 ± 4.3 (8) Exposed: 14.2 ± 4.5 (8)	Increased number of CD68-positive cells in aorta of CAPs exposed mice on both normal chow and high-fat diet	Sun *et al.* 2008a
EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[4]	5 mg by i.t. instillation (twice weekly for 4 weeks) in female 42 weeks old WHHL rabbits on regular diet. Sacrifice at day 3 after the last exposure	Lesion area in aorta (Oil Red O staining of area): Control: 21.1 ± 5.1 (6) **Exposed: 34.5 ± 7.9 (10)*** Increased plaque progression in coronary arteries (Movat's pentachrome staining). Increased atherosclerotic score in both aorta and coronary arteries	Unaltered levels of total cholesterol, HDL and LDL in plasma	Suwa *et al.* 2002
Mixed vehicle exhaust (gasoline and diesel) Particle number mean size: 60 nm). Mass size distribution: ≈ 1 µm	100 or 300 µg/m^3 (6 h/day) for 50 consecutive days in 9-10 weeks old male *ApoE*$^{-/-}$ mice on high-fat diet. Sacrifice the day after the last exposure	Lesion area in aortic leaflet region (ross-section, MOMA-2 stain): Control: 1.03 ± 0.97 (32) Low: 2.34 ± 0.24 (8) High: 1.26 ± 0.98 (24) Similar effect by gases only. Increased monocyte/macrophage infiltration	Increased gelatinase (MMP-2/9) activity in aorta. Unaltered mRNA levels of *ET-1*, *Hmox-1*, *Timp-2*, *Mmp-2* and *Mmp-9* in aorta	Vedal *et al.* 2013

EHC-93. CMAD: 0.35 µm (GSD: 1.7 mm), MMAD: 4.6 µm (GSD: 2.3 µm). No particle characterization in suspension vehicle[4]	5 mg by i.t. instillation (twice weekly for 4 weeks) in female 42 weeks old WHHL rabbits on regular diet	Lesion area in aorta (Movat's pentachrome staining): Control: 28.7 ± 18.6 (10) **Exposed: 54.4 ± 16.4 (9)***	Increased ICAM-1 and VCAM-1 staining in plaques. Higher attachment of monocytes to plaques	Yatera *et al.* 2008
CAPs (New York, NY). Information on elemental composition, EC and OC	138.4 µg/m^3 (6 h/day, 5 days/week) for 4 months in male *ApoE*$^{-/-}$ mice fed a high-fat diet	Lesion area in aorta (H & E stain, cross-section): Control: 18.6 ± 3.7 (6) **Exposed: 35.4 ± 2.9 (6)***	Increased inflammation in aortic tissue (iNOS expression, 3-NT, NADPH oxidase subunits) and oxidative stress (superoxide radical generation)	Ying *et al.* 2009a
Urban air (Beijing, China)	63 µg/m^3 (filtered air = 19.2 µg/m^3) for 2 months (24 h/day, 7 days/week) in 10 weeks old male *ApoE*$^{-/-}$ mice on a Western-type diet	Lesion area in the aortic arch (cross section, H&E stain): Control: 1.23 ± 0.25 (10) **Exposed: 2.63 ± 0.47 (10)***	Pulmonary inflammation (IL-6 and TNF in BALF, histology). Systemic inflammation (CRP, TNF, but not IL-6) and oxidative stress (SOD, GPX, oxLDL). Increased levels of cholesterol and unaltered levels of plasma triglycerides and HDL	Wan 2014[11]

[1]Results for the two CAPs and UFP exposure has been pooled in the analysis in figure 2, whereas they are used as separate studies in the dose-response relationship analysis (figures 3 and 4). [2] This research group has published a number of papers that appears to be tied to the same project, but not necessarily the same experiments (Campen *et al.*, Environ. Health Perspect. 118: 921-927, 2010 [PMID: 20197249]; Lund *et al.*, Toxicol Sci 95: 485-494, 2007 [PMID: 176065432]; Lund *et al.*, Arterioscler. Thromb. Vasc. Biol. 29: 511-517, 2009 [PMID: 19150882]; Lund *et al.*, Am J Respir. Crit. Care Med. 184: 82-91, 2011 [PMID: 21493736]; Seilkop *et al.*, Inhal. Toxicol. 24: 270-287, 2012 [PMID: 22486345]). The experiments have mainly used 1 or 7 days of exposure and the concentrations have maximally been approximately 300 µg/m^3. Results in the three exposure groups have been pooled in figure 2. Information on particles size in aerosol has obtained from McDonald *et al.*, Environ Sci Technol 38: 2513-2522, 2004 [PMID: 151800045] and Reed *et al.*, Inhal Toxicol 16: 177-193, 2004 [PMID: 15204765]. [3]Description of the exposure setup and particle characterization has been published in a parallel publication, although with data that over a wider exposure period than the CAPs exposure for vascular effects (Maciejczyk *et al.* 2005). [4]CMAD and MMAD have been reported in Vincent *et al.* 1997. [5]Results from the five locations have been pooled in figure 2. Each location has been used as separate study in the dose-response assessment. [6]The study is not included in the analysis because it has used intra-nasal instillation. [7]Results from 3 and 5 months exposure have been pooled in the analysis. [8]Results from 3 and 5 months exposure have been pooled in the analysis. [9]The results have been re-calculated as normalized mean and standard deviation from results in the normal and high-fat diet groups in figure 2. The original publication lacks clarity with regards to the effect of exposure to CAPs on cholesterol levels in serum. Based on the results in the publication we have calculated that the exposure to CAPs was associated with 0.92-fold (95% CI: 0.82-1.03) lower cholesterol levels as compared to filtered air exposed mice on normal chow. In the high-fat fed mice there was 1.05-fold (95% CI: 0.85-1.24) increased levels of cholesterol in the CAPs exposed mice. [10]For the analysis in figure 2, we have calculated normalized mean and standard deviation from results in the groups that have been fed a normal or high-fat diet. [11]The details are shown in this table, but the results have not been used in the review due to suspected replicate results from Chen *et al.* 2013b. (Full reference: Wan *et al.*, Cell Stress Chaperons 19: 715-724 [PMID: 24534034]).

Supplementary table 3. Vasomotor function in vessels from animals following *in vivo* exposure to nanomaterials

Type	Exposure	Vascular effect	Other effects	Reference
TiO_2 (primary size: 15 nm)	100 µg/rat (saline) by i.t. instillation in male 10-14 weeks old Wistar rats and sacrifice at day 21 after the exposure	Unaltered ACH-induced vasorelaxation in second order branch intralobar pulmonary arteries	Not assessed	Courtois *et al.* 2010
Carbon black (primary size: 13 nm)	100 µg/rat (saline) by i.t. instillation in male 10-14 weeks old Wistar rats and sacrifice at day 21 after the exposure	Unaltered ACH-induced vasorelaxation in second order branch intralobar pulmonary arteries	Not assessed	Courtois *et al.* 2010
Nickel hydroxide (5 nm). Impurities below detection limit. CMAD: 40 nm (GSD: 1.5 nm)	100, 150 or 900 µg/m^3 (5 h/day) for 1, 3 or 5 days and sacrifice at 24 h after the last exposure in 12 weeks old male C57BL/6 mice	Blunted ACH-induced vasorelaxation response in carotid arteries (all exposure models). Decreased PE-induced vasoconstriction	Not assessed	Cuevas *et al.* 2010
Carbon black (Printex 90). Hydrodynamic size: 104 nm (SD = 53 nm). The count median particle diameter in suspension was 86 nm	0.064, 0.64 or 6.4 mg/kg as single oral gavage, or 0.0.64 or 0.64 once a week for 10 weeks old female lean or obese 14 weeks old lean or obese Zucker rats on regular diet	Dose-dependent decrease in ACH-induced vasorelaxation in aorta rings after repeated exposures. Unaltered vasorelaxation following exposure to nitroglycerin or felodipine. Unaltered PE-induced vasoconstriction response	Unaltered TNF in serum. Unaltered levels of triglycerides, cholesterol insulin and glucose in plasma	Folkmann *et al.* 2012
Fe-SWCNT (D 1-3 nm, L: 1.5-3 µm) or Gd-SWCNT (D: 1-3 nm, L: 0.6-0.8 µm) in suspensions as aggregates or non-aggregated	12.7 – 126.8 pg per arteriole location in male mice (101 days old) or hamsters (64 days old) by topical injection in the left cheek pouch (hamster) or right cremaster muscle (mice) [type of mouse and hamster strain has not been reported]	Immediate vasodilation (aggregated SWCNTs) and vasoconstriction (non-aggregated) that subsided within one min. Reduced ACH response (15-30 min post-exposure). Unaltered PE response in arcade and terminal arterioles (intravital miscroscopy)[1]	Not assessed	Frame *et al.* 2014
Carbon black (mean aerodynamic diameter ≈ 85 nm, GSD: 1.5 nm)	Nose-only inhalation (4 h/d, 5 d/week) for 4 weeks to low (1.3 x 10^5 particles/cm^3), middle (6.2 x 10^5 particles/cm^3) or high (42 x 10^5 particles/cm^3) in 9 weeks old Sprague-Dawley rats. Sacrifice the day after the last exposure	Unaltered vasorelaxation (ACH) and vasoconstriction (PE or 5-HT) responses in aorta rings	Mainly unaltered cytokine levels in BALF (INFγ, IL-1β, IL-4, IL-6 and TNF [increased IL-10 levels])[2]	Kim *et al.* 2011
TiO_2 (21 nm, P25	10 µg/rat deposited	Reduced active	Not reported (refer to	Knuckles *et al.*

from DeGussa). Information on particle characteristic in Nurkiewicz *et al.* 2008	dose, delivered by inhalation and sacrifice at post-exposure 24 h in male 7-9 weeks old Sprague-Dawley rats	hyperemia-induced vasodilation in spinotrapezius muscle arterioles (intravital microscopy), which was attenuated by inhibition of COX. Enhanced U46619-induced vasoconstriction. Enhanced adrenergic[3] receptor sensitivity	earlier observations of unaltered pulmonary inflammation)	2012
TiO_2 (21 nm, P25 from DeGussa). Information on particle characteristic in Nurkiewicz et al. 2008	10 µg/rat deposited dose, delivered by whole-body inhalation (6 mg/m^3, 4 h) and sacrifice at post-exposure 24 h in male 10-12 weeks old Sprague-Dawley rats	Impaired vasodilation by ACH or A23187 in subepicardial arterioles. No difference in SNP-induced vasodilation or myogenic response	Not assessed[4]	LeBlanc *et al.* 2009
TiO_2 (21 nm, P25 from DeGussa). Information on particle characteristic in Nurkiewicz et al. 2008	10 µg/rat deposited dose, delivered by whole-body inhalation (6 mg/m^3, 4 h) and sacrifice at post-exposure 24 h in male 10-12 weeks old Sprague-Dawley rats	Impaired by ACH-induced vasodilation, which was restored by pretreatment with tempol in subepicardial arterioles. Modest vasoconstriction response to arachidonic acid and unaltered response to U46619 (thromboxane analogue)	Oxidative stress (DHE staining) in coronary arteries	LeBlanc *et al.* 2010
TiO_2 (as ingredient in a commercial antimicrobial spray). CMAD: 110 nm. SEM analysis showed that particles had a spherical shape with a physical diameter between 80 and 130 nm	2.6 mg/m^3 (2 h), 1.7 mg/m^3 (4 h/day for 2 days) and 3.8 mg/m^3 (4 h/day for 4 days) in 10 weeks old male Sprague-Dawley rats. Sacrifice at 24 h post-exposure	Unaltered ACH-induced vasorelaxation and PE-induced vasoconstriction in pressurized tail arteries[5]	Increased pulmonary inflammation (PMNs in BALF) and cytotoxicity (LDH in BALF) at the highest dose level	McKinney *et al.* 2012
Rutile TiO_2 (primary size 20.6 nm, SSA: 108 m^2/g). Hydrodynamic diameter: 518 nm (SD: 118 nm) Photocatalytic TiO_2 (primary size: 12 nm). Hydrodynamic diameter: 2321 nm (SD: 272 nm)	0.5 mg/kg by i.t. instillation twice during 24 h and sacrifice at 2 h post-exposure (total dose = 1 mg/kg) in 11-13 weeks old female *ApoE*$^{-/-}$ mice on a normal diet	Unaltered vasorelaxation in aorta rings (assessed by *ex vivo* treatment with ACH, CGRP, NTG or filodipine). Unaltered vasorelaxation response by *ex vivo* pre-treatment with tempol (SOD mimic)[6]	Unaltered gene expression levels (*Mcp-1*, *Mip-2*, *Icam-1*, *Vcam-1*, *Vegf*) in lungs	Mikkelsen *et al.* 2011
CeO_2 (primary size: 4-6 nm, SSA: 81 m^2/g). Hydrodynamic size in suspension show peaks at 191, 900 and 5081 nm	10, 50, 100, 200 or 400 µg by i.t. instillation (saline with 5% FBS) and sacrifice at 24 h post-exposure in 8-11 weeks old male Sprague-Dawley rats	Decreased endothelium-dependent (ACH and A23187) and endothelium-independent (SNP and spermine NONOate) vasorelaxation in pressurized coronary and mesenteric arterioles. Augmented	Increased pulmonary inflammation (PMN in BALF) and cytotoxicity (LDH in BALF) at 100 and 400 µg/rat [200 µg/rat not assessed]. Unaltered levels at 10 µg/rat	Minarchick *et al.* 2013

		vasoconstriction response in coronary arteries (serotonin-induced) and unaltered response in mesenteric arterioles (PE-induced). Unaltered myogenic response		
CeO_2 (information on particle characteristic in Minarchich *et al.* 2013)	50, 100 or 900 µg/rat (i.v.) or 100, 300 or 600 µg/rat (oral), or 65 µg/rat (i.t.) (saline with 5% FBS) in 8-11 weeks old male Sprague-Dawley rats and sacrifice at 24 h post-exposure	Reduced ACH-induced vasorelaxation in mesenteric arterioles following i.v. (all doses), gastrointestinal (600 µg) and i.t. (65 µg) exposure. Impaired endothelium-independent (spermine NONOate) vasorelaxation following i.v. exposure, whereas gastrointestinal exposure augmented (100 µg) and reduced (600 µg) the response. Inconclusive results on PE-induced vasoconstriction and unaltered myogenic response[7]	Not reported	Minarchick *et al.* 2015
TiO_2 (21 nm, P25 from DeGussa). SSA: 48 m^2/g, 80% anatase, 20% rutile. Bimodal size distribution with peaks at 100 and 400 nm. CMAD: 138 nm (GSD = 2.4 nm)	4 - 38 µg/rat deposited dose, delivered by whole-body inhalation (1.5 – 12 mg/m^3 for 2-8 h) and sacrifice at post-exposure 24 h in male 6-7 weeks old Sprague-Dawley rats	Impaired A23187-induced vasodilation in spinotrapezius muscle arterioles (dose-dependent with significant effect at 10 µg/rat)	No pulmonary inflammation (histophathology, H&E stain)	Nurkiewicz *et al.* 2008
TiO_2 (21 nm, P25 from DeGussa). Information on particle characteristic in Nurkiewicz *et al.* 2008	10 µg/rat deposited dose, delivered by whole-body inhalation (240-720 min) and sacrifice at post-exposure 24 h in male 6-7 weeks old Sprague-Dawley rats	Impaired A23187-induced vasodilation in spinotrapezius muscle arterioles (intravital microscopy). No difference in SNP-induced vasodilation response	Increased oxidative stress in vessel wall (hydroethidine) and 3-NT	Nurkiewicz *et al.* 2009
TiO_2 (21 nm, P25 from DeGussa). Information on particle characteristic in Nurkiewicz *et al.* 2008	10 µg/rat deposited dose, delivered by inhalation and sacrifice at post-exposure 24 h in male 48-49 days old Fisher 344 rats	Impaired A23187-induced vasodilation in spinotrapezius muscle arterioles (intravital microscopy). Impaired vasodilation also in cyclophosphamide pre-treated rats (reduce neutrophils)	Unaltered pulmonary inflammation. Unaltered circulating levels of cytokines (26 different mediators measured by Multiplex analysis). [Exposure to fine size TiO_2 was associated with altered levels of some cytokines]	Nurkiewicz *et al.* 2011
Quantum dots (mercaptoundecanoic acid coated). Size of particles in	100 µg (in PBS) by i.v. injection in male Wistar rats and sacrificed at 2 h post	Unaltered PE-induced vasoconstriction in pressurized 4^{th} order mesenteric arteries. ACH-	Not reported	Shukur *et al.* 2013

suspension is reported to be 5.0 ± 0.9 nm, although TEM images indicate agglomeration to larger particles	exposure (age not reported)	induced vasorelaxation was unaltered, whereas SNP-induced response was reduced. Essentially similar vasorelaxation response by *ex vivo* exposure to quantum dots (15 µg/ml), although the SNP response did not reach statistical significance		
MWCNT (width: 49 nm, length: 3.9 µm, Mitsui)	13.5 µg (lung burden, administered by inhalation of 5 mg/m^3 for 5 h) and sacrifice at 24-168 h after exposure in male 7-8 weeks Sprague-Dawley rats	Blunted ACH- and A23187 vasodilation in pressurized subepicardial arterioles. No effect on SNP-induced vasodilation or myogenic response. PE-response unaltered	Increased lung inflammation and cytotoxicity (PMNs and LDH in BALF)	(Stapleton *et al.* 2012a)
TiO_2 (21 nm, P25 from DeGussa). Information on particle characteristic in Nurkiewicz *et al.* 2008	10 mg/m^3 (5 h/day) for 6.8 days (average) in female Sprague-Dawley rats on gestation day 6 (average deposited daily dose = 43.8 µg). Vascular effects measured in adult female rats in the F1 generation	Reduced vasorelaxation response to ACH and spermine NONOate in coronary arterioles. Reduced ACH-induced vasorelaxation in uterine arterioles (spermine NONOate response lowered, although not statistically significant). Unaltered vasoconstriction response to 5-HT. Assessed in pressurized vessels[8]	Not reported	Stapleton *et al.* 2014
MWCNT (bimodal diameter with peaks at 12.5 and 25 nm. Up to several microns long. 5% Fe impurities, SAA: 113 m^2/g). Bimodal hydrodynamic size of 200 and 1000 nm (TEM)[9]	100 µg by i.t. instillation (saline with 10% pulmonary surfactant) and sacrifice at 24 h post-exposure in 13-14 weeks old male Sprague-Dawley rats	Unaltered ACH-induced vasorelaxation in left anterior descending coronary arteries. Unaltered response to SNP, ET-1 and serotonin	Unaltered pulmonary inflammation (total cells in BALF). Increased protein content in BALF	Thompson *et al.* 2014a
Fullerenes C_{60} (size 115 ± 32 nm (TEM)). Hydrodynamic size (370 ± 1.2 nm, Z-average)	28 µg (in 1.4% PVP) by i.t. instillation or i.v. injection in 10-12 weeks old male or female Sprague-Dawley rats and sacrifice at 24 h post-exposure	Increased ET-1 induced vasoconstriction response in coronary arteries (ameliorated by indomethacin pre-treatment) in male rats after i.t. exposure. Borderline statistical effect on serotonin-induced vasoconstriction in the same group. No effect on vasorelaxation response (ACH or SNP in wire myograph)	Little evidence of pulmonary inflammation (eosinophilic influx in females after i.t. instillation). Increased concentration of protein in BALF. Increased serum levels of IL-6 and MCP-1 after i.v. injection and unaltered levels after i.t. exposure	Thompson *et al.* 2014b

Fullerenes C_{60} (primary size: 0.7 nm, SSA: 20 m^2/g). Assessment of hydrodynamic size indicated a large degree of agglomeration (diameter above 1 µm)	0.05 or 0.5 mg/kg (saline with 10% BALF) by i.p. injection and sacrificed at 1 h post-exposure in 11-13 or 40-42 weeks old male or female *ApoE*$^{-/-}$ mice	Decreased ACH-induced vasorelaxation in aorta arch (11-13 weeks old mice) and descending aorta (40-42 weeks old). Unaltered ACH-induced vasorelaxation in aorta arch of 40-42 weeks old mice (attributed to severe vasomotor dysfunction in this aorta segment at old age). Signs of impaired SNP-induced vasorelaxation. Unaltered PE-induced vasoconstriction	Not reported	Vesterdal *et al.* 2009
Carbon black (Printex 90). Primary size: 14 nm, SSA: 300 m^2/g). Bimodal hydrodynamic size distribution in exposure vehicle with peaks at 1.2 and 5.5 µm	0.05, 0.5, 0.9, or 2.7 mg/kg, or 0.5 mg/kg twice during 24 h by i.t. instillation (saline with 10% BALF) and sacrifice at 2 h post-exposure (total dose = 1 mg/kg) in 11-13 weeks old female *ApoE*$^{-/-}$ mice on a normal diet	Unaltered vasomotor function in aorta rings following a single i.t. instillation. Reduced ACH-induced vasorelaxation following two instillations and unaltered SNP-induced relaxation and PE-induced vasoconstriction	Dose-dependent increase in *Mcp-1* expression in lung tissue at 24 h (0.9 and 2.7 mg/kg). Unaltered expression after two instillations. Unaltered levels of 3-NT in BCA and aorta tissue	Vesterdal *et al.* 2010
SWCNT (diameter: 0.9-1.7 nm, length: < 1 µm assessed by TEM. 2% iron impurities[10]	0.5 mg/kg by i.t. instillation twice during 24 h and sacrifice at 2 h post-exposure (total dose = 1 mg/kg) in 11-13 weeks old female *ApoE*$^{-/-}$ mice on a normal diet	Unaltered ACH-induced vasorelaxation in prostaglandin $F_{2\alpha}$ pre-contracted aorta rings. No effect of L-sepiapterin supplementation to aorta rings	Increased expression of *Ccl2* (approximately 7-fold). Unaltered levels of *Vcam-1*, *Icam-1* and *Hmox-1* in lungs	Vesterdal *et al.* 2014
Fullerenes C_{60} Hydrodynamic diameter: 371 nm (SD = 1.2 nm)	28 µg (in 1.4% PVP) or PVP vehicle by i.v. injection in 11-13 weeks female non-pregnant or pregnant (gestation day 17-19) Sprague-Dawley rats and sacrifice at 24 h post-exposure	Unaltered vasoconstriction response in non-pregnant rats (PE, ET-1, angiotensin II or 5-HT stimulated). Increased ACH-induced vasorelaxation in uterine and mesenteric arteries; unaltered response in aorta. Increased vasoconstriction in pregnant rats (generally unaltered ACH-induced vasorelaxation)[11]	Unaltered levels of cytokines in serum (IL-1β, IL-6, IL10, INFγ, MCP-1 and TNF)	Vidanapathirana *et al.* 2014
SWCNT (diameter: 50 nm, length: 1.8 µm). Geometric mean hydrodynamic diameter: 117 nm	5 mg (in dimethyl sulfoxide) by i.v. injection in male 8 weeks old Wistar rats and sacrifice at 3 h post-exposure	Unaltered vasorelaxation response to ACH and SNP, and vasoconstriction response to PE, in aorta rings. *Ex vivo* exposure (200 µg/ml) of pressurized PE-precontracted mesenteric	Not reported	Vlasova *et al.* 2014

		arteries increased vasorelaxation, which was abolished by blockage of NO synthesis (L-NAME treatment)		
Mesoporous silicon nanoparticles (thermally hydrocarbonized). Geometric mean hydrodynamic diameter: 90 nm	5 mg (in dimethyl sulfoxide) by i.v. injection in male 8 weeks old Wistar rats and sacrifice at 3 h post-exposure	Reduced ACH-induced vasorelaxation in aorta rings and unaltered response to SNP. Increased vasoconstriction response to PE. Unaltered response by e*x vivo* exposure (200 µg/ml) in pressurized PE-pre-contracted mesenteric arteries	Not reported	Vlasova *et al.* 2014

[1]We have only used the results obtained at 15 min post-exposure in the analysis. Thus the study is regarded as showing reduced ACH-induced vasodilation and unaltered PE-induced vasorelaxation. [2]The study has been regarded as showing unaltered pulmonary inflammation. The particle concentrations in aerosol have not been reported in mass concentration, whereas there is information on the surface area concentration. For the conversion of surface area concentration to mass concentration, we have assumed that oil-furnace with a size range of 10-400 nm has a surface area of 12-240 m2/g (IARC, Volume 93, 2010). Assuming an inverse linear relationship between particle size and surface area, carbon black particles with an aerodynamic diameter of 85 nm have a surface area of 196 m^2/g. The surface area concentration (1.1, 2.7 and 14 nm^2/cm^3) correspond to mass concentrations of 56.1 (low), 138 (middle) and 714 $\mu g/m^3$ (high). [3]We have regarded this study as showing reduced vasorelaxation and augmented vasoconstriction. [4]Nurkiewicz and co-workers have generally used doses of TiO_2 that have not caused pulmonary inflammation (assessed by influx of cells in BALF), whereas there are indices of oxidative stress in the lungs and microcirculation. A through description of studies is reported in Nurkiewicz *et al.* 2011. [5]The exposures have been regarded to be associated with either pulmonary inflammation (high-dose level) or no effect (low-dose level) in table 8. [6]Results on rutile and photocatalytic TiO_2 have been used in the analysis in table 4 and 5 and dose-response assessment. [7]We have judged that i.t. instillation of 65 µg/rat could elicit pulmonary inflammation. Based on dose-response relationship in Minarchick *et al.* 2013, using log-linear dose scale, there would be 6% PMNs in BALF, which would be higher than the control group (1% PMNs). [8]The results from this study have not been used in quantitative analysis because the vasomotor responses occur in adult outcomes following *in utero* exposure. [9]Fiber characteristics have been described in an earlier publication (Wang *et al.* Part. Fibre Toxicol. 8: 24, 2011 [PMID: 21851604]). [10]Fiber characteristics have been described in earlier publications (Jacobsen et al. Environ. Mol. Mutagen. 49: 476-487, 2008 [PMID: 18618583]; Jacobsen *et al.* Part. Fibre Toxicol. 6:2, 2009 [PMID: 19138394]). Analysis of particle size of SWCNTs in suspension was not possible due to technical problems. [11]Only results from pregnant rats have been used in the analysis. The study has been regarded as showing null effect in terms of vasoconstriction and vasorelaxation.

Supplementary table 4. Plaque progression in atherosclerosis-prone animals following exposure to nanomaterials

Type	Exposure	Vascular effect (Mean ± SD, (N))	Other effects	Reference
MWCNTs (NM400: diameter: 5-35 nm, length: 0.7-3.0 µm; NM402: diameter: 6-20 nm, length: 0.4-4.0 µm). Particle sized analyzed in suspension (median sizes: 116-147 nm)	6.4 or 25.6 µg/mouse (water with 2% mouse serum) once a week for 5 weeks (total dose = 32 or 128 µg/mouse) and sacrifice at 24 h or 4 weeks after the last exposure in 9-10 weeks old female *ApoE*$^{-/-}$ mice on a Western-type diet	Lesion area in the aortic arch (%, *en face*). Increased plaque progression at 24 h after the last exposure[1]. Control: 5.4 ± 1.1 (6) **NM400: 9.7 ± 5.1 (6)*** **NM402: 9.4 ± 1.3 (6)*** Unaltered levels at 4 weeks after the last exposure Control: 8.4 ± 3.6 (10) NM400 (L): 8.3± 2.6 (10) NM400 (H): 8.1 ± 2.7 (9) Control: 8.5 ± 3.7 (10) NM402 (L): 8.4 ± 2.7 (10) NM402 (H): 12.9 ± 6.7 (6)	Pulmonary inflammation (PMNs in BALF, cytokines). Unaltered levels of cytokines in plasma	Cao *et al.* 2014
TiO_2 (primary size: 5-10 nm, anatase, SSA: 210 m^2/g, 1% impurities)[2]	5, 25 or 50 µg by i.t. instillation (PBS) twice a week for 6 weeks in 11 weeks old male *ApoE*$^{-/-}$ mice on regular diet (total dose = 3-30 mg/kg)	Lesion area in aorta (%, en face, Oil red)[3]. Control: 19.0 ± 10.9 (5) 5 µg: 16.1 ± 8.0 (5) 25 µg: **49.8 ± 12.6 (5)*** 50 µg: 25.6 ± 9.4 (5) Increased lipid content per plaque area	Increased cholesterol and decreased HDL in plasma. Increased plasma concentration of mouse CRP in plasma	Chen *et al.* 2013a
MWCNTs (own production, acid functionalized). Length (20 µm, up to 50 µm), diameter (21 nm), SSA (50 m^2/g). Size of agglomerated particles in suspension: 98 nm ± 10 nm[4]	40 µg (in PBS) by pharyngeal aspiration per week for 16 weeks (total dose = 640 µg/mouse) in 9 weeks old female *ApoE*$^{-/-}$ mice on high-fat diet	Lesion area in the aortic arch (%, *en face*). Control: 33.9 ± 6.3 (9) Exposed: 31.7 ± 3.9 (10)	Pulmonary inflammation (PMNs in BALF) and cell damage (protein, LDH) increased. Unaltered level of cholesterol in plasma (increased level if one outlier is removed)	Han *et al.* 2015
Nickel hydroxide (primary size: 5 nm). CMAD: 40 nm (GSD = 1.5). SAA: 37 m^2/g[5]	79 µg/m^3 (5 h/day, 5 days/week) for 5 months in 5 months old male *ApoE*$^{-/-}$ mice on standard chow by whole-body inhalation and sacrifice at 24 h post-exposure	Lesion area in aorta (H & E strain, cross-section). Control: 22.7 ± 6.73 (7) Exposed: **40.4 ± 9.7 (7)***	Pulmonary inflammation assessed by increased total (and neutrophils) in BALF. Increased expression of *Il-6* and *TNF-α* in lungs. Increased protein content in BALF. Increased *Hmox-1* expression in lungs. Increased CCL2, VCAM-1 and CD68 expression in aorta	Kang *et al.* 2011
SWCNT from CNI Huston, TX, USA. Diameter (1-4 nm by TEM analysis), SSA	20 µg by pharyngeal aspiration every other week for 8 weeks (total dose = 80 µg/mouse or ≈3.2 mg/kg) in 2-3	Lesion area in thoracic part of aorta (%, *en face*, Sudan IV). Results on mice on regular diet were not reported because of too low	Increased VCAM-1 and Mac in BCA. Unaltered plasma levels of cholesterol and triglycerides[6]	Li *et al.* 2007

(1040 m^2/g)	months male *ApoE*$^{-/-}$ mice on regular or high-fat diet	response. Increased plaque area in BCA. Control: 5.7 ± 3.5 (10) Exposed: **9.1 ± 2.9 (10)***		
TiO_2 (primary particle size: 20.6 nm). Hydrodynamic diameter: 518 nm (SD: 118 nm)	0.5 mg/kg (90% saline and 10% BAL fluid) by i.t. instillation per week for 4 weeks and sacrifice 5 weeks later in 11 weeks old female *ApoE*$^{-/-}$ mice on normal chow (total dose = 2 mg/kg)	Lesion area in aorta (%, en face). Control: 4.1 ± 2.3 (8) Exposed: **5.5 ± 3.4 (8)***	Unaltered gene expression levels (*Mcp-1*, *Mip-2*, *Icam-1*, *Vcam-1*, *Vegf*) in lungs	Mikkelsen *et al.* 2011
Carbon black (described as nanosized although). MMAD: 121 nm CMAD: 111 nm (GSD: 1.7 nm)	1 mg/mouse per week for 10 weeks in 10-14 weeks old male *Ldlr*$^{-/-}$ mice on regular or cholesterol-rich diet	Lesion area in thoracic part of aorta (%, *en face*, Sudan IV). No effect in mice on regular diet[7]: Control: 2.2 ± 1.0 (5) Exposed: 3.0 ± 1.2 (5) Increased plaque progression in mice on a cholesterol-rich diet: Control: 7.3 ± 3.4 (5) Exposed: **13.5 ± 5.0 (5)***	Increased blood levels of IL-6, CRP and MCP-1	Niwa *et al.* 2007
Carbon black (Printex 90, 14 nm)	0.5 mg/kg by i.t. instillation (saline with 10% BALF) once a week for two weeks (total dose = 1 mg/kg) and sacrifice at 5 weeks post-exposure in 48-49 weeks old female *ApoE*$^{-/-}$ mice on a normal diet	Lesion area in thoracic part of aorta (%, *en face*) and BCA. Control: 16.3 ± 3.0 (11) Exposed: 16.8 ± 3.5 (11)	Unaltered gene expression of *Mcp-1* in lung tissue	Vesterdal *et al.* 2010

[1]For assessment of effect size, results has been pooled on the two types of MWCNTs in figure 2. [2] The publication contains a relatively detailed description of physicochemical characteristic of TiO_2. However, the hydrodynamic particles size does not appear to have been determined in the exposure vehicle (i.e. phosphate buffer saline). [3]The doses have been pooled in figure 2. We have judged that the low dose (5 µg) would not be associated with pulmonary inflammation, whereas the middle (25 µg) and high (50 µg) doses are likely to be associated with inflammatory responses by bolus i.t. injections as has been reported in other studies (Oberdörster *et al.* 2000). [4]Characterization of MWCNTs have reported in Han *et al.* Inhal Toxicol 20: 391-398, 2008 [PMID: 183020479], Han *et al.* Inhal Toxicol 22: 340-347, 2010 [PMID: 20064106] and *Han et al.* Inhal Toxicol 26: 327-332, 2014 [PMID: 24655089]. The MWCNTs in suspension are described as agglomerated and entangled (assessed by scanning electron microscope). [5]Particle characteristics have been described in an earlier publication (Gillespie *et al.* Nanotoxicology 4: 106-119, 2010 [PMID: 20730025]). [6]An earlier study showed persistent pulmonary inflammation in C57BL/6 mice after exposure to 40 µg by oropharyngeal aspiration (Shvedova *et al.* Am. J. Physiol. Lung Cell Mol. Physiol. 289: L698-L708, 2005 [PMID: 15951334]). Thus we have judged that it is likely that the dose in the present would be sufficiently high to produce a pulmonary inflammation reaction. [4]We have calculated normalized mean and standard deviation from groups on normal chow and high-fat diet in figure 2. Results on systemic inflammation markers have obtained from Niwa *et al.* (Circ. J. 72: 144-149, 2008 [PMID: 18159116]). *Denote statistically significant effect in the original publication.

Supplementary Table 5. Available information of particle size, shape and chemical composition of air pollution particles, diesel exhaust and nanomaterials in studies on vasomotor function responses

Reference	Type of exposure	Mode of exposure	Dose score[1]	Particle characterization score[2]	Effect[3]
Chen and Nadziejko 2005	CAPs	Inhalation	0	0	1 (plaque)
Courtois 2010	TiO_2	Instillation	0	0	0 (vasomotor)
Courtois 2010	Carbon black	Instillation	0	0	0 (vasomotor)
Cozzi 2006	UFP	Instillation	0	0	1 (vasomotor)
Kampfrath 2011	CAPs	Inhalation	0	0	1 (vasomotor)
Kido 2011a	DE	Inhalation	0	0	0 (vasomotor)
Liu 2014	CAPs	Inhalation	0	1	1 (vasomotor)
Soares 2009	Urban air	Inhalation	0	0	0 (plaque)
Sun 2005	CAPs	Inhalation	0	0	1 (plaque) 1 (vasomotor)
Sun 2008a	CAPs	Inhalation	0	0	1 (plaque)
Sun 2008b	CAPs	Inhalation	0	0	1 (vasomotor)
Sun 2009	CAPs	Inhalation	0	0	1 (vasomotor)
Weldy 2015	DE	Inhalation	0	0	0 (vasomotor)
Araujo 2008	UF-CAPs/CAPs	Inhalation	0	1	1 (plaque)
Chen 2013b	Urban air	Inhalation	0	1	1 (plaque)
Cuevas 2015	Air pollution	Instillation	0	1	1 (vasomotor)
Davel 2012	CAPs	Inhalation	0	1	1 (vasomotor)
Keebaugh 2015	UF-CAPs	Inhalation	0	1	1 (plaque)
Lippmann 2013	CAPs	Inhalation	0	1	1 (plaque)
Rao 2014	CAPs	Inhalation	0	1	1 (plaque)
Xu 2010	CAPs	Inhalation	0	1	1 (vasomotor)
Ying 2009a	CAPs	Inhalation	0	1	1 (vasomotor) 1 (plaque)
Ying 2009b	CAPs	Inhalation	0	1	1 (vasomotor)
Ying 2014	CAPs	Inhalation	0	1	1 (vasomotor)
Ying 2015	CAPs	Inhalation	0	1	1 (vasomotor)
Bagate 2004	EHC-93	Instillation	0	2	1 (vasomotor)
Bai 2011	DE	Inhalation	0	2	0 (plaque)
Chen 2013a	TiO_2	Instillation	2	2	1 (plaque)
Courtois 2008	SRM1648	Instillation	0	2	1 (vasomotor)
Goto 2004	EHC-93	Instillation	0	2	1 (plaque)
Kido 2011b	EHC-93	Instillation	0	2	1 (vasomotor)
Knuckles 2008	DE	Inhalation	0	2	1 (vasomotor)
Cherng 2009	DE	Inhalation	0	2	1 (vasomotor)
LeBlanc 2009	TiO_2	Inhalation	0	2	1 (vasomotor)
LeBlanc 2010	TiO_2	Inhalation	0	2	1 (vasomotor)
Li 2007	SWCNT	Instillation	0	2	1 (plaque)
Miyata 2013	EHC-93	Instillation	0	2	1 (vasomotor) 1 (plaque)
Niwa 2007	Carbon black	Instillation	0	2	1 (plaque)
Nurkiewicz 2008	TiO_2	Inhalation	2	2	1 (vasomotor)
Nurkiewicz 2009	TiO_2	Inhalation	0	2	1 (vasomotor)
Nurkiewicz 2011	TiO_2	Inhalation	0	2	1 (vasomotor)
Quan 2010	CAPs	Inhalation	0	2	1 (plaque) 1 (vasomotor)
Quan 2010	DE	Inhalation	0	2	1 (plaque) 1 (vasomotor)
Robertson 2012	SRM2975	Instillation	0	2	1 (vasomotor)

Stapleton 2012	MWCNT	Inhalation	0	2	1 (vasomotor)
Suwa 2002	EHC-93	Instillation	0	2	1 (plaque)
Tamagawa 2008	EHC-93	Instillation	0	2	1 (vasomotor)
Vesterdal 2014	SWCNT	Instillation	0	2	0 (vasomotor)
Yatera 2008	EHC-93	Instillation	0	2	1 (plaque)
Campen 2010	DE	Inhalation	2	3	0 (plaque)
Cao 2014	MWCNT	Instillation	2	3	1 (plaque)
Cassee 2012	DE (± CeO_2)	Inhalation	0	3	0 (plaque)
Cherng 2011	DE	Inhalation	0	3	1 (vasomotor)
Cuevas 2010	Nickel hydroxide	Inhalation	2	3	1 (vasomotor)
Gerlofs-Nijland 2010	DE	Inhalation	0	3	0 (vasomotor)
Gerlofs-Nijland 2010	CAPs	Inhalation	0	3	0 (vasomotor)
Han 2015	MWCNT	Instillation	0	3	0 (plaque)
Kang 2011	Nickel hydroxide	Inhalation	0	3	1 (plaque)
Kim 2011	Carbon black	Inhalation	2	3	0 (vasomotor)
Knuckles 2012	TiO_2	Inhalation	0	3	1 (vasomotor)
Labranche 2012	SRM2975	Instillation	0	3	1 (vasomotor)
Li 2013	UFP	Inhalation	0	3	1 (plaque)
McKenney 2012	TiO_2	Inhalation	2	3	0 (vasomotor)
Mikkelsen 2011	TiO_2	Instillation	0	3	0 (vasomotor) 0 (plaque)
Miller 2013	SRM2975	Instillation	0	3	0 (vasomotor) 1 (plaque)
Minarchick 2013	CeO_2	Instillation	2	3	1 (vasomotor)
Minarchick 2015	CeO_2	Instillation	0	3	1 (vasomotor)
Thompson 2014a	MWCNT	Instillation	0	3	1 (vasomotor)
Thompson 2014b	Fullerene C_{60}	Instillation	0	3	1 (vasomotor)
Vedal 2013	DE	Inhalation	1	3	0 (plaque)
Vesterdal 2010	Carbon black	Instillation	2	3	1 (vasomotor)
Vesterdal 2014	SRM2975	Instillation	0	3	0 (vasomotor)
Vesterdal 2014	SRM1649b	Instillation	0	3	0 (vasomotor)

[1]The numbers refer to differences in dose levels (0 = one exposure group; 1 = two exposure groups; 2 = more than two exposure groups). The dose groups have been dichotomized for the logistic regression in table 6 (i.e. groups 1 and 2 have been pooled). [2]The score refers levels are 0 = "None" (i.e. no information except the mass concentration or dose of PM); 1 = "Some" (i.e. information on chemical composition, shape or primary particle size in dry form (e.g. elemental composition in CAPs exposure studies)); 2 = "Well-characterized sample" (i.e. information on both particle size (or shape) and chemical composition in dry sample (e.g. EHC-93)); 3 = "Well-characterized sample in vehicle" (i.e. information on aerodynamic or hydrodynamic diameter in the suspension vehicle (air or suspension)). [3]The effect refers to 0 = no statistical significance of the endpoint; 1 = statistical significance of the endpoint. The vascular endpoints (i.e. vasomotor function and atherosclerosis) have been regarded as independent outcomes for the logistic regression analysis in table 6.

Supplementary table 6. Segregation of publications into different dose groups for assessment of effects on vasomotor function (VMF) and plaque progression after pulmonary exposure to particulate matter

Group	Description	Studies
Short-term. Few high doses (1)	Causes pulmonary inflammation <1 week exposure Typically i.t. instillation	Bagate *et al.* 2004b: VMF Courtois *et al.* 2008: VMF Cozzi *et al.* 2006: VMF Kido *et al.* 2011b: VMF McKinney *et al.* 2012: VHF (high dose) Minarchick *et al.* 2015: VMF (100/400 µg) Minarchick *et al.* 2013: VMF (high dose) Robertson *et al.* 2012: VMF Stapleton *et al.* 2012a: VMF Vesterdal *et al.* 2010: VMF (high dose) Vesterdal *et al.* 2014: VMF (SWCNT) Weldy *et al.* 2013: VMF
Long-term. Repeated high doses (2)	Causes pulmonary inflammation Weeks to months of exposure Typically i.t. instillation and inhalation	Cao *et al.* 2014: Plaque Cassee *et al.* 2012: Plaque Chen *et al.* 2013b: Plaque Chen *et al.* 2013a: Plaque (high dose) Cuevas *et al.* 2015: VMF (Jinchang) Cuevas *et al.* 2015: VMF (Zhangye) Goto *et al.* 2004: Plaque Han *et al.* 2015: Plaque Kampfrath *et al.* 2011: VMF Kang *et al.* 2011: Plaque Labranche *et al.* 2012: VMF (wild-type rats) Labranche *et al.* 2012: VMF (SH rats) Li *et al.* 2007: Plaque Miller *et al.* 2013: Plaque, VMF Niwa *et al.* 2007: Plaque Suwa *et al.* 2002: Plaque Yatera *et al.* 2008: Plaque Ying *et al.* 2015: VMF
Short-term. Few low doses (3)	Does not cause pulmonary inflammation <1 week exposure Short-term inhalation Low dose i.t. instillation	Cherng *et al.* 2009: VMF Cherng *et al.* 2011: VMF Courtois *et al.* 2010: VMF (carbon black) Courtois *et al.* 2010: VMF (TiO_2) Kido *et al.* 2011a: VMF (3 days exposure) Knuckles *et al.* 2008: VMF Knuckles *et al.* 2012: VMF LeBlanc *et al.* 2010: VMF LeBlanc *et al.* 2009: VMF McKinney *et al.* 2012: VMF (low dose) Minarchick *et al.* 2013: VMF (low dose) Nurkiewicz *et al.* 2009: VMF Nurkiewicz *et al.* 2008: VMF Nurkiewicz *et al.* 2011: VMF Tamagawa *et al.* 2008: VMF Thompson *et al.* 2014a: VMF Thompson *et al.* 2014b: VMF Vesterdal *et al.* 2010: VMF Vesterdal *et al.* 2014: VMF (SRM2975) Vesterdal *et al.* 2014: VMF (SRM1649b)
Long-term. Repeated low doses (4)	Does not cause pulmonary inflammation Weeks to months of exposure Typically inhalation (of CAPs)	Araujo *et al.* 2008: Plaque Bai *et al.* 2011: Plaque Campen *et al.* 2010: Plaque

		Chen and Nadziejko 2005: Plaque Chen *et al.* 2013a: Plaque (low dose) Cuevas *et al.* 2010: VMF Davel *et al.* 2012: VMF Gerlofs-Nijland *et al.* 2010: VMF (DE) Gerlofs-Nijland *et al.* 2010: VMF (CAPs) Keebaugh *et al.* 2015: Plaque Kido *et al.* 2011a: VMF (7 weeks exposure) Kim *et al.* 2011: VMF Li *et al.* 2013b: Plaque Lippmann *et al.* 2013: Plaque Liu *et al.* 2014: VMF Mikkelsen *et al.* 2011: Plaque, VMF(photocat.) Mikkelsen *et al.* 2011: Plaque, VMF (rutile) Miyata *et al.* 2013: VMF Quan *et al.* 2010: Plaque, VMF (DE) Quan *et al.* 2010: Plaque, VMF (CAPs) Rao *et al.* 2014: Plaque Soares *et al.* 2009: Plaque Sun *et al.* 2005: Plaque, VMF (normal diet) Sun *et al.* 2005: Plaque, VMF (high-fat diet) Sun *et al.* 2008b: VMF Sun *et al.* 2008a: Plaque Sun *et al.* 2009: VMF Vedal *et al.* 2013: VMF Vesterdal *et al.* 2010: Plaque Ying *et al.* 2009a: Plaque, VMF Ying *et al.* 2009b: Plaque, VMF Ying *et al.* 2014: VMF Xu *et al.* 2010: VMF (normal diet) Xu *et al.* 2010: VMF (high-fat diet)

Supplementary Table 7. Association between studies on cardiovascular disease outcomes and systemic inflammation in studies on airway exposure to particulate matter

Outcome	**Response to systemic inflammation markers and cardiovascular outcome**	
	Similar response	***Different response***
Vasomotor dysfunction	Cherng *et al.* 2009 - Null	Davel *et al.* 2012 – No inflammation
	Cuevas *et al.* 2015 – Effect	Liu *et al.* 2014 - No inflammation
	Kampfrath *et al.* 2011 - Effect	Nurkiewicz *et al.* 2011 – No inflammation
	Kido *et al.* 2011b – Effect	Quan *et al.* 2010 – No inflammation (DE)
	Miller *et al.* 2013 – Null	Quan *et al.* 2010 – No inflammation (CAPs)
	Robertson *et al.* 2012 - Null	Thompson *et al.* 2014b – No inflammation
	Sun *et al.* 2009 – Effect	
	Tamagawa *et al.* 2008 – Effect	
	Xu *et al.* 2010 - Effect	
Atherosclerosis	Chen *et al.* 2013b – Effect	Cao *et al.* 2014 – No inflammation
	Chen *et al.* 2013a – Effect	Lippmann *et al.* 2013 – No inflammation
	Li *et al.* 2013b – Effect	Miller *et al.* 2013 – No inflammation
	Miller *et al.* 2013 – Null	Quan *et al.* 2010 – No inflammation
	Niwa *et al.* 2007 – Effect	
	Quan *et al.* 2010 – Null	

Supplementary Table 8. Association between studies on cardiovascular disease outcomes and blood levels of cholesterol and triglycerides in long-term PM exposure studies

Outcome	**Similar response**		**Different response**	
	Cholesterol	Triglycerides	Cholesterol	Triglycerides
Vasomotor dysfunction	Folkmann *et al.* 2012	Folkmann *et al.* 2012		
	Miller *et al.* 2013	Miller *et al.* 2013		
	Miyata *et al.* 2013	Miyata *et al.* 2013		
	Sun *et al.* 2005	Sun *et al.* 2005		
	Sun *et al.* 2009	Sun *et al.* 2009		
Atherosclerosis	Bai *et al.* 2011	Bai *et al.* 2011	Araujo *et al.* 2008	Chen *et al.* 2013b
	Chen *et al.* 2013b	Li *et al.* 2013b	Li *et al.* 2007	Li *et al.* 2007
	Chen *et al.* 2013a	Soares *et al.* 2009	Li *et al.* 2013b	Miller *et al.* 2013
	Soares *et al.* 2009		Miller *et al.* 2013	Miyata *et al.* 2013
			Miyata *et al.* 2013	Sun *et al.* 2005
			Han *et al.* 2015	Suwa *et al.* 2002
			Sun *et al.* 2005	
			Keebaugh *et al.* 2015	

Legends to Supplementary figures

Supplementary Figure 1. Funnel plot of studies segregated by group (all studies including Chen *et al.*, 2013b, Li *et al.*, 2013b, Rao *et al.*, 2014, Yin *et al.*, 2009a). The Funnel plot depicts an asymmetrical distribution of studies. Certain studies have both high SMD and SE(SMD). This is mainly driven by a high effect size because the studies have a similar number of animals per group The SE(SMD) is an inverse measure of study size (i.e. small studies tend to have high SE(SMD)).

Supplementary Figure 2. Forrest plot of studies segregated by group (excluded studies: Chen *et al.*, 2013b, Li *et al.*, 2013b, Rao *et al.*, 2014, Ying et al., 2009a)

Supplementary Figure 3. Funnel plot of studies segregated by group (excluded studies: Chen et al., 2013b, Li et al., 2013b, Rao *et al.*, 2014, Ying *et al.*, 2009a). The plot corresponds to the Forrest plot in Supplementary Figure 2.

Supplementary figure 4. Dose-response relationships across studies after instillation (A, C, E) or inhalation (B, D, F). Results on vasomotor function is reported as ”altered” (upper row of symbols) or unaltered (lower row of symbols) after exposure to ambient air pollution particles (diamond), diesel exhaust (square) or nanomaterials (triangle). Vasomotor function is segregated into vasoconstriction (A and B), endothelium-depedent vasorelaxation (C and D) and endothelium-independent vasorelaxation (E and F). Each symbol represents one dose.

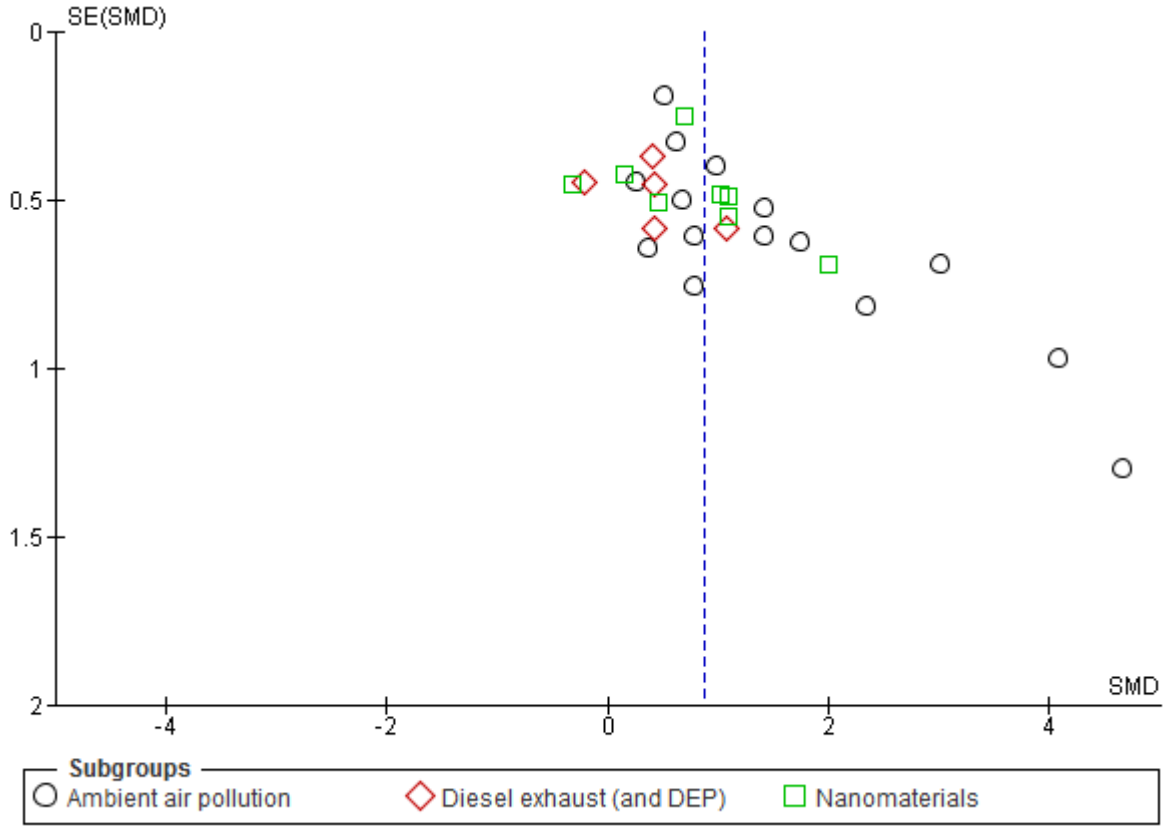
Supplementary Figure 5. Forrest plot of studies segregated by dose group and diet (normal chow or high-fat diet (HFD)). All studies are included. Certain publications are included twice because they have used different doses, diets or samples.

Supplementary Figure 6. Funnel plot of studies segregated by dose group and diet (normal chow or high-fat diet (HFD)). All studies are included. The plot corresponds to the Forrest plot in Supplementary Figure 5.

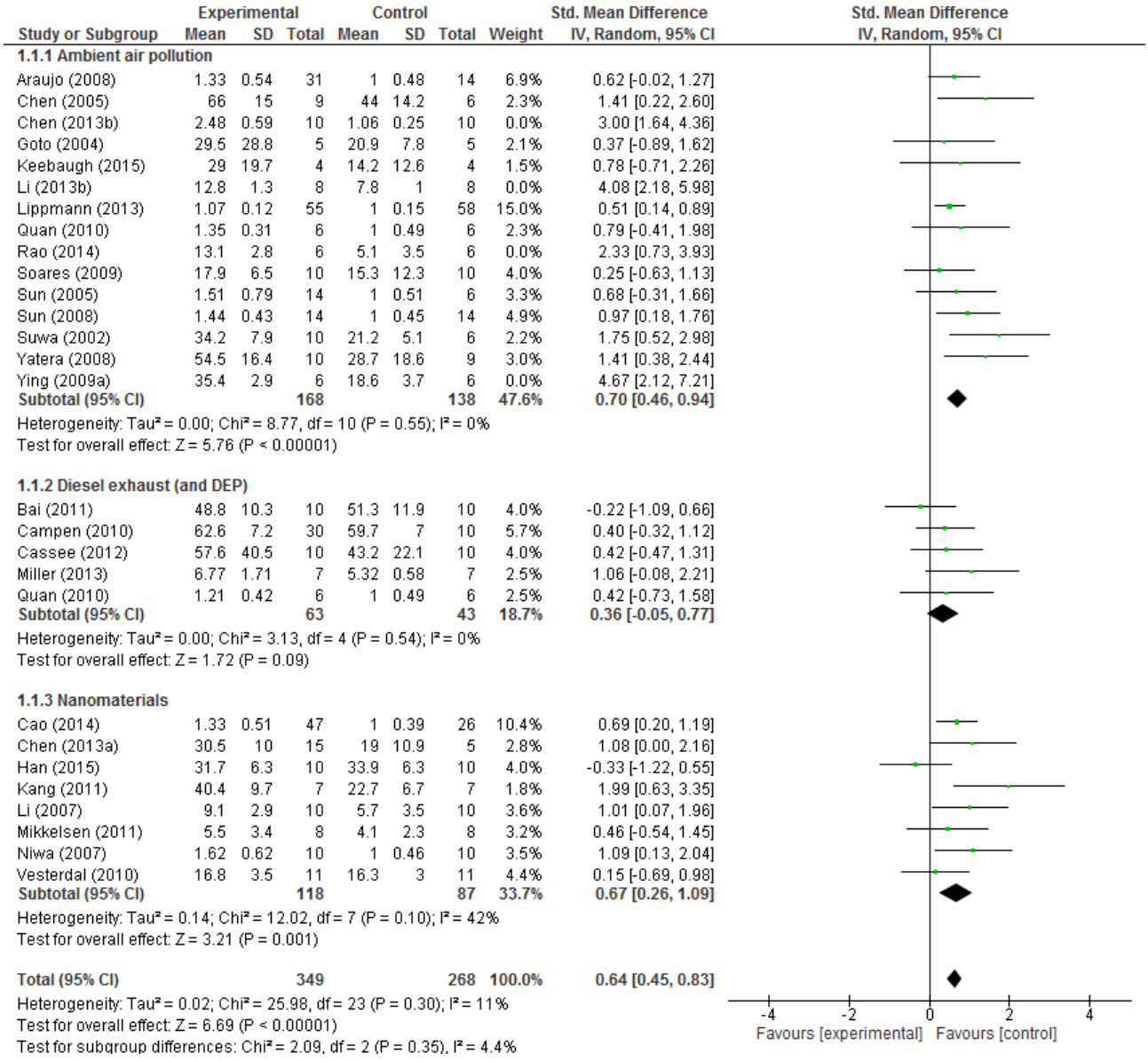
Supplementary figure 7. Forrest plot of studies segregated by dose group and diet (normal chow or high-fat diet (HFD)). Excluded studies: Chen *et al.*, 2013b, Li *et al.*, 2013b, Ying *et al.*, 2009a) All studies are included. Certain publications are included twice because they have used different doses, diets or samples.

Supplementary figure 8. Funnel plot of studies segregated by dose group and diet (normal chow or high-fat diet (HFD)). All studies are included. The plot corresponds to the Forrest plot in Supplementary Figure 7.

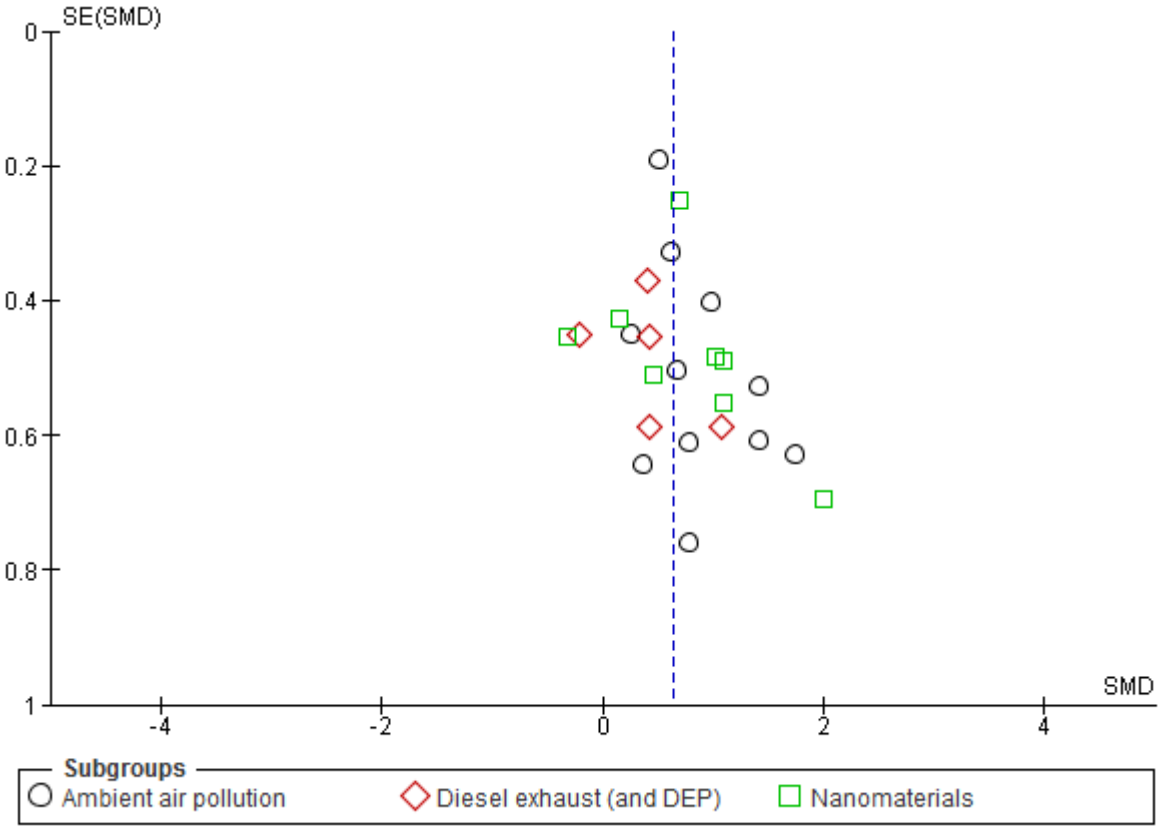
Supplementary Figure 1



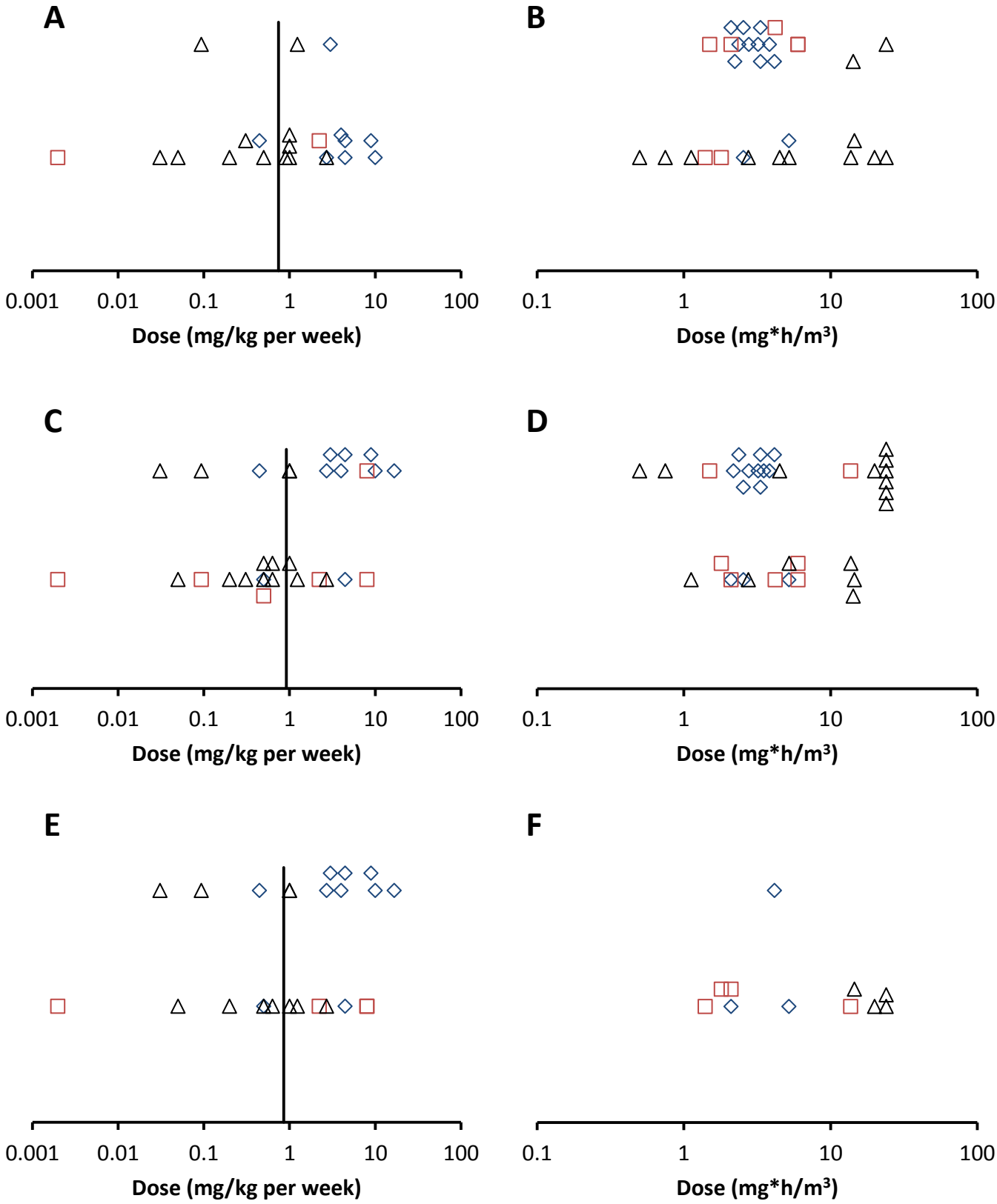
Supplementary Figure 2.



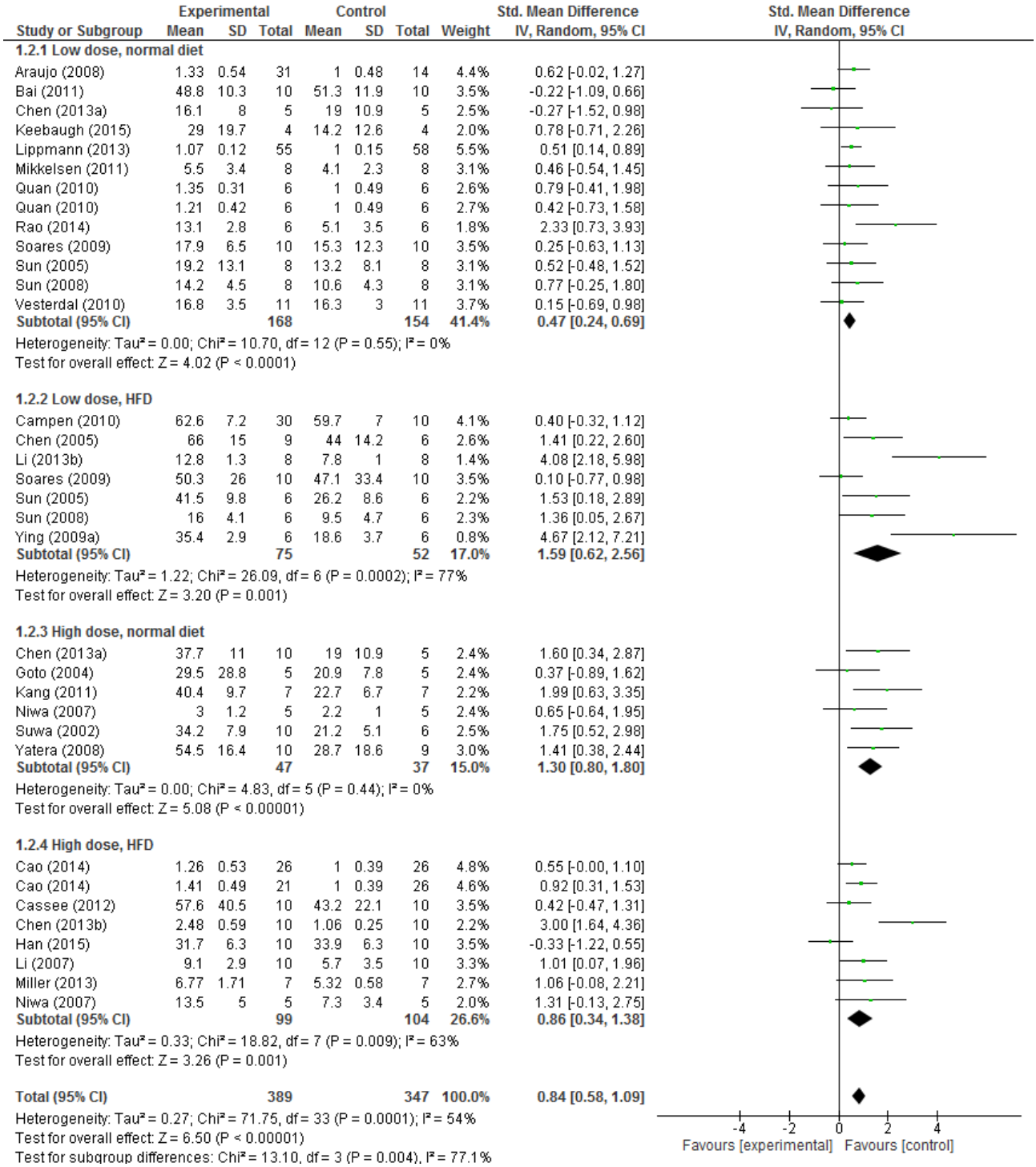
Supplementary Figure 3



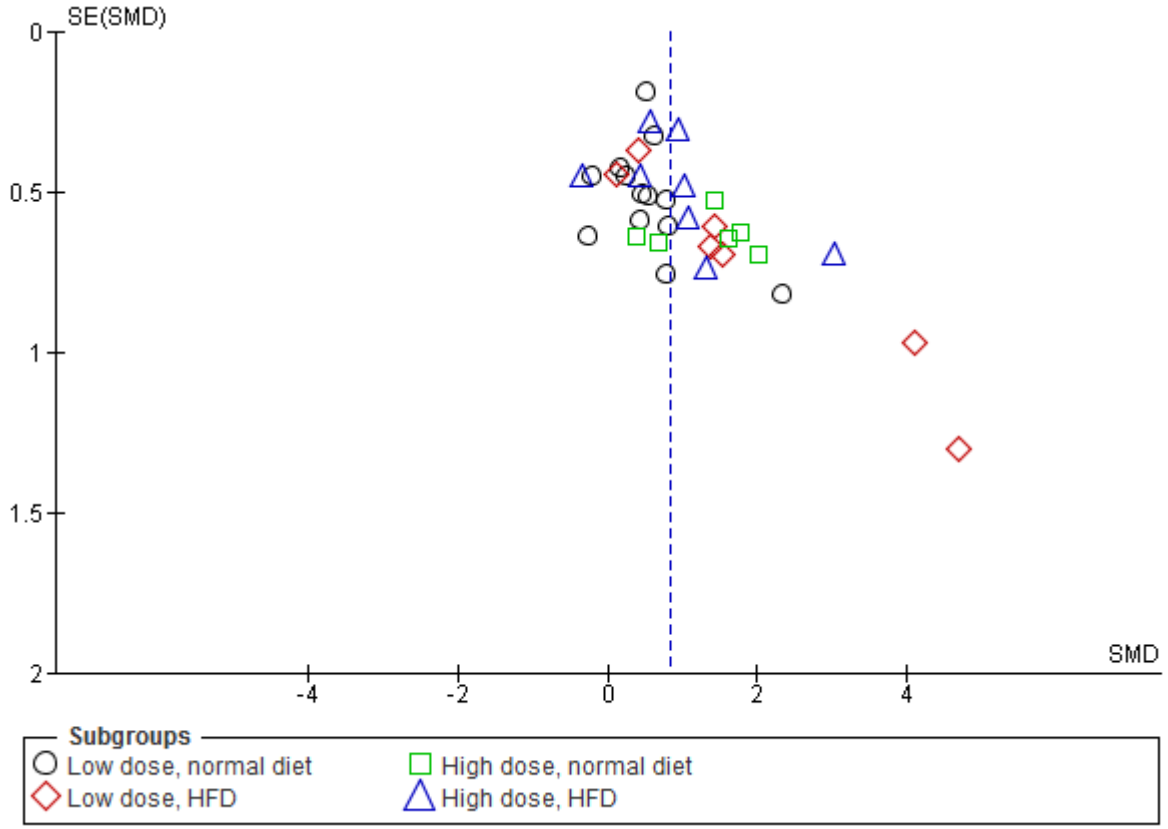
Supplementary Figure 4



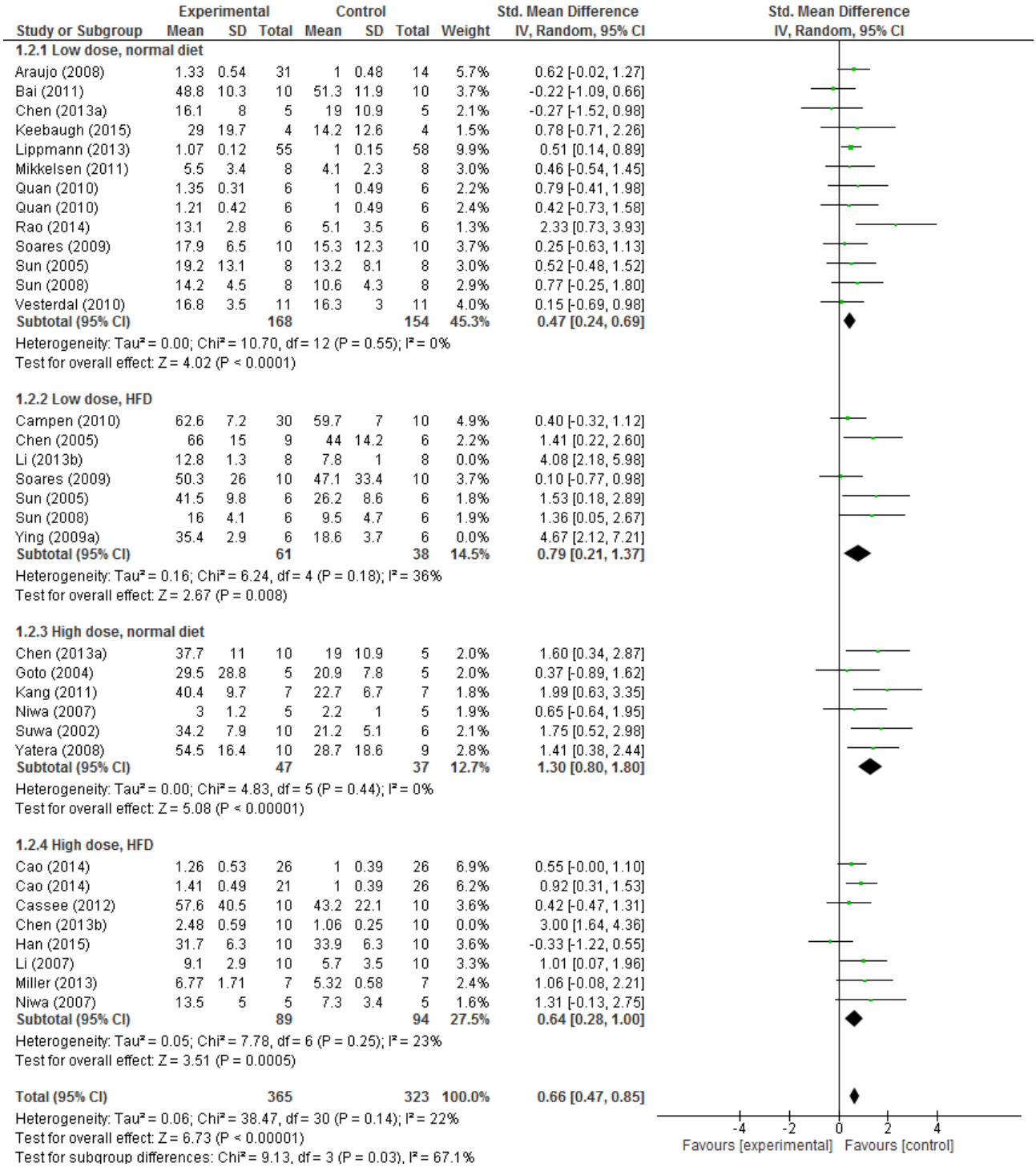
Supplementary Figure 5



Supplementary Figure 6



Supplementary Figure 7



Supplementary Figure 8