Supplemental Table 1. In vitro/ex-vivo studies on association of endothelial dysfunction, inflammation or oxidative stress with air pollution.

Study	Tissue or cells	Air pollutant	Major outcome	Ref
Courtois 2008	Male Wistar rats (12–14 weeks old) exposed to PM particles with assessment of endothelial function in pulmonary artery branches	Intra-tracheal exposure to SRM1648 (urban PM) and	Endothelial dependent relaxation and cGMP accumulation induced by acetylcholine (ACh) decreased 24 hr after exposure of rat intrapulmonary arteries to standard reference material 1648 (SRM1648; urban PM). Relaxation due to NO donors also decreased whereas responsiveness to cGMP analogue remained unaffected. SRM1648, ultrafine carbon black and ultrafine and fine titanium dioxide (TiO2) manufactured particles did not impair NO-mediated relaxation.	(1)
Miller 2009	Thoracic aorta of male Wistar rats	Diesel exhaust particles (10-100 µg/ml for 20 min ex vivo)	Ex vivo incubation of thoracic aortic ring segments with diesel exhaust particles impaired endothelium-dependent (Ach) relaxation and to a minor extent also nitric oxide-dependent (SNP) relaxation in a concentration-dependent fashion (measured by isometric tension recording), all of which was mostly corrected by superoxide dismutase. Likewise, nitric oxide bioavailability (measured by NO electrode) was decreased and superoxide formation (measured by electron paramagnetic resonance spectroscopy) was increased by diesel exhaust particles.	(2)
Mo 2009	Mouse pulmonary microvascular endothelial cells (MPMVEC)	Ultrafine PM <160 nm collected with a nano-MOUDI cascade impactor (10-200 µg/ml)	Ultrafine PM decreased cell viability at the highest concentrations and longer incubation times (>48 h). PM elevated ROS formation (DCF-DA) in a concentration- and time-dependent manner and the signal was inhibited by catalase, diphenyliodonium (DPI), N-acetylcysteine and partially by $p47^{phox}$ depletion by siRNA. The increase in ROS signal was also not observed in endothelial cells isolated from $gp91^{phox-/-}$ mice. PM caused translocation of $p67^{phox}$ to the membrane and association with $gp91^{phox}$ and Rac1.	(3)
Li 2009	Human aortic endothelial cells (HAEC)	Ultrafine PM from diesel exhaust (12.5-50 µg/ml)	Ultrafine PM treatment caused a concentration-dependent increase in cellular superoxide formation (nitroblue tetrazolium) and expression of the stress-response protein heme oxygenase-1 and the pro-coagulant tissue factor, which was partially prevented by N-acetylcysteine. PM also elevated mitochondrial superoxide formation (mitoSOX) and protein carbonyl groups. PM also lead to a time-dependent increase in JNK activation and superoxide formation and expression of heme oxygenase-1 and tissue factor were prevented by a JNK inhibitor and depletion of JNK by siRNA.	(4)
Frikke-Schmidt 2011	Human umbilical endothelial cells (HUVEC)	Diesel exhaust particles, SRM2975 and carbon black (1-100 µg/ml)	All particles caused a moderate decrease in cell viability at higher concentrations and 24 h incubation. Carbon black and diesel exhaust particles induced ROS formation (DCF-DA) and inflammation (ICAM-1 and VCAM-1) in a concentration-dependent manner that was partially blocked by vitamin C, desferrioxamine or the combination of both compounds. The combination treatment also prevented carbon black and SRM2975-induced DNA strand breaks and 8-	(5)

			hydroxydeoxyguanosine lesions.	
Labranche 2012	Male Wistar rats, spontaneously hypertensive rats (SHR)	Intra-tracheal administration of diesel exhaust particles using an aerosolizing System, 3x per week for 4 weeks	Diesel exhaust particles induced endothelial dysfunction (ACh) upon in vitro exposure of aortic rings corrected by superoxide dismutase. In contrast, vasodilation by sodium nitroprusside (SNP) was only marginally impaired by in vitro diesel exhaust exposure. In vivo exposure to diesel exhaust particles only induced endothelial dysfunction in SHR but not control rats, mirrored by increased $p22^{phox}$ expression levels in the aorta of SHR.	(6)
Forchhammer 2012	Human umbilical endothelial cells (HUVEC)	Diesel exhaust particles SRM2975 and wood smoke particles (0.1-100 µg/ml)	Wood smoke but not diesel exhaust particles increased the adhesion of THP-1 cells onto HUVEC, whereas both PM species induced VCAM-1 expression, strand breaks (SB) and formamidopyrimidine DNA glycosylase (FPG)-sensitive sites in DNA (8-oxo-dG) and slightly decreased cell viability in a concentration-dependent manner. The wood smoke particles were more potent in inducing inflammatory cytokines IL-8 and TNF-α.	(7)
Du 2013	Human aortic endothelial cells (HAEC)	Ambient ultrafine particles < 200 nm (12.5-50 µg/ml)	Ultrafine particles reduced nitrite/nitrate levels in a concentration-dependent fashion, which was prevented by JNK inhibition (SP600125), NADPH oxidase inhibition by apocynin and antioxidant treatment (TEMPOL, MnTMPyP and N-acetylcysteine). Ultrafine particles decreased the GSH/GSSG ratio and increased eNOS S-glutathionylation (a mechanism of uncoupling). eNOS dysfunction upon ultrafine particles exposure was normalized by overexpression of glutaredoxin-1, an enzyme that “repairs” protein S-glutathionylation.	(8)
Cao 2014	Human umbilical endothelial cells (HUVEC) and assessment of adhesion molecule expression and ROS	Synthetic carbon black nanoparticles (2.5-100 µg/ml)	Nanoparticles decreased cell viability of THP-1 cells in a concentration-dependent fashion and that of HUVEC at the highest concentration. Nanoparticles induced ROS formation in all cell types, which was even more pronounced upon depletion of cellular glutathione. Nanoparticles augmented VCAM-1 expression in HUVEC and adhesion of THP-1 cells onto HUVECs in a concentration-dependent fashion. Nanoparticles triggered lipid accumulation in THP-1a cells.	(9)
Tseng 2015	Human umbilical endothelial cells (HUVEC) and expression of inflammatory genes and NFκB.	Diesel exhaust particles (1-100 µg/ml)	Diesel exhaust particles induced inflammation (TNF-α, IL-6), ROS formation (DCF-DA) and impaired GSH/GSSG ratio in a concentration-dependent fashion, all of which was normalized by N-acetylcysteine. PM exposure also increased the stress-response protein heme oxygenase-1, decreased IκB-α and increased nuclear translocation of p65 (NF-κB activation). These processes contribute to VEGF-A secretion and disruption of cell-cell borders and increased vasculature permeability.	(10)
Rui 2016	Human endothelial hybridoma cell line (EA.hy926)	PM2.5 collected from traffic air pollution (25-200 µg/ml)	$PM_{2.5}$ decreased cell viability at 50-200 µg/ml and longer incubation times (12 and 24 h). ROS formation (DCF-DA) was maximal at 12 h and was increased in a concentration-dependent fashion and suppressed by N-acetylcysteine. A similar concentration and time dependence was observed for ICAM-1 and VCAM-1 expression as well as THP-1 cell adhesion, all of which was prevented by N-	(11)

			acetylcysteine. JNK/p38 MAPK/ERK signaling was activated in a concentration- and time-dependent manner. Inhibition of ERK (U0126), AKT (LY294002), NF-κB (BAY11-7082) prevented PM2.5-dependent induction of VCAM-1 and ICAM-1 expression and THP-1 adhesion onto endothelial cells, whereas inhibition of JNK (SP600125) and p38 MAPK (SB203580) showed no effect.	

Supplemental Table 2. In vivo animal studies on endothelial function, inflammation and/or oxidative stress with inhalational air pollution exposures.

Study	Animals and model	Air pollutant	Major outcome	Ref
CONCENTRATED AMBIENT $PM_{2.5}$ (CAP) USING A WHOLE BODY EXPOSURE SYSTEM				
Sun et al. 2005	Apo $E^{-/-}$ model fed high fat chow	Whole body concentrated ambient particles (CAP) $PM_{2.5}$ or filtered air (FA) for 10 weeks	Plaque area of $PM_{2.5}$ vs FA was 41.5% vs 26.2% in the high fat diet groups but $PM_{2.5}$ also increased the plaque area in normal diet mice. Lipid content in the aortic arch measured by oil red-O staining revealed a 1.5-fold increase in mice fed the high-fat chow and exposed to $PM_{2.5}$ vs FA (30.0 vs 20.0). In addition, $PM_{2.5}$ exposure amplified vasoconstrictor responses to phenylephrine and serotonin challenge and impaired the acetylcholine-dependent relaxation in the thoracic aorta of mice fed high-fat chow along with marked increases in macrophage infiltration, iNOS expression, ROS generation and 3-nitrotyrosine levels.	(12)
Sun et al. 2008	Male Sprague-Dawley rat	Whole body CAP $PM_{2.5}$ or FA for 10 weeks	Endothelial function decreased in response to $PM_{2.5}$. O_2•− production in aortic rings was markedly enhanced in $PM_{2.5}$ exposed rat compared with the FA group, abolished by PEG-SOD or NADPH oxidase inhibitor treatment. mRNA level of NAPDH oxidase subunit p22phox and p47phox significantly increased in the aortic tissues of PM exposed rats.	(13)
Xu et al. 2010	C57BL/6 and p47($phox^{-/-}$) mice	Whole body CAP $PM_{2.5}$ or FA for 10 weeks	$PM_{2.5}$ exposed mice developed insulin resistance and adipose inflammation with expression of inflammatory genes in stromal vascular fraction. $O_2^{\bullet-}$ production was significantly increased in the epididymal fat (visceral fat), but not in the subcutaneous fat location of the mice exposed to $PM_{2.5}$ compared with the FA group. This effect was abolished in $p47phox^{-/-}$ mice.	(14)
Xu et al. 2011	C57BL/6 mice	Whole body CAP $PM_{2.5}$ or FA exposure for 9 months	Long-term $PM_{2.5}$ exposure significantly induced superoxide production as determined by DHE staining and increased 3-nitrotyrosine expression in BAT depots, increased *Nrf2, Nqo1* and *Gclm gene expression in both WAT and BAT.*	(15)
Kampfrath 2011	Wildtype mice, Nox2- and TLR4-deficient mice	Whole body CAP $PM_{2.5}$ or FA for 20 weeks	Exposure of mice to $PM_{2.5}$ impairs endothelial function (ACh), triggers infiltration of immune cells ($Ly6C^{high}$ monocytes) into the vasculature and induces cytokines (TNF-α, MCP-1), and formation of oxidized phospholipid derivatives in lungs, all of which is normalized by TLR4 deficiency. PM2.5 exposure also increased NADPH oxidase-dependent superoxide formation in the aorta that was abolished in Nox2- and TLR4-deficient mice. $PM_{2.5}$ increases release of “inflammatory” monocytes from the bone marrow into the circulation.	(16)
Wold et al. 2012	C57BL/6 mice	Whole body CAP $PM_{2.5}$ exposure (70-90)	Exposure of mice to $PM_{2.5}$ over a prolonged period induces hypertension, LV fibrosis and alterations in diastolic function. Total antioxidant capacity in	(17)

		$\mu g/m^3$) for 9 months	the plasma was significantly decreased in the plasma of $PM_{2.5}$ mice	
Davel et al. 2012	Male Wistar rats	Whole body CAP $PM_{2.5}$ for 2 weeks using Harvard Concentrator	DHE fluorescence density and protein expression of Cu/Zn- and Mn-SOD increased in the pulmonary artery, while eNOS decreased in the artery after $PM_{2.5}$ exposure.	(18)
Haberzettl 2012	Male C57BL/6J mice exposed to CAP	Whole body CAP $PM_{2.5}$ (30–100 $\mu g/m^3$) for 6 h/d for 4-30 d or FA	Exposure to ambient fine particulate matter (PM2.5) impaired the mobilization of endothelial progenitor cells ($Flk\text{-}1^+/Sca\text{-}1^+$) from bone marrow to the circulation by interfering with the VEGF-dependent activation of Akt and eNOS. These observations could explain the deficits in vascular repair or regeneration observed in response to particulate matter exposures.	(19)
Ying 2013	Male $ApoE^{-/-}$ mice	Whole body CAP (68 $\mu g/m^3$) and/or Ni (450 ng/m^3) for 6 h/d, 5d/w	Exposure of mice to concentrated ambient PM2.5 induced a strong inflammatory response (TNF-α, IL-6, MCP-1, E-selectin, VCAM-1). Ni exposure caused impaired endothelial function (ACh) by diminished eNOS dimerization and increased markers of oxidative stress. The authors propose that Ni in ambient PM2.5 synergistically induce vascular damage.	(20)
Rao et al. 2014	$ApoE^{-/-}$ or $LDLR^{-/-}$ mice	Whole body CAP (70–90 $\mu g/m^3$) or FA exposure for 3 or 6 months	$PM_{2.5}$ increased 7-ketocholesterol in plasma IDL/LDL fraction and in aortic plaque concomitant with progression of atherosclerosis. CD36 expression increased in peritoneal macrophages concomitant with increased 7-KC intake without alterations in efflux.	(21)
Haberzettl 2016	C57Bl/6 mice treated with 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL) OR mice overexpressing lung-extracellular superoxide dismutase (ecSOD) exposed to CAP	Whole body CAP $PM_{2.5}$ or FA for 9 or 30 days,	In control diet-fed mice, a 9-day CAP exposure was sufficient to suppress insulin-stimulated Akt and eNOS phosphorylation and to decrease IκBα (inhibitor of the transcription factor NF-κB levels in the aorta). Treatment with the antioxidant TEMPOL or lung-specific overexpression of ecSOD prevented CAP-induced vascular insulin resistance and inflammation.	(22)
DIESEL EXHAUST (DE) EXPOSURE (ULTRAFINE PARTICLES)				
Cherng 2009	Sprague-Dawley rats exposed to whole body CAPS exposure for 5 hours	300 $\mu g/m^3$ diesel exhaust or FA in a sealed chamber for 5 h.	Increased constrictor sensitivity to ET-1 in PM versus FA exposure. Nitric oxide synthase (NOS) inhibition [N^{ω}-nitro-l-arginine (L-NNA), 100 μM] and endothelium inactivation augmented ET-1 responses in arteries from Air but not DE rats so that after either treatment responses were not different between groups.	(23)
Cherng 2011	Male Sprague-Dawley rats	Diesel exhaust (300 $\mu g/m^3$ for 5 h/d)	Diesel exhaust inhalation impaired endothelium-dependent (ACh) relaxation (measured by isometric tension recording), all of which was mostly corrected in the presence of the eNOS cofactor tetrahydrobiopterin or superoxide dismutase. Likewise, superoxide formation (measured by dihydroethidium fluorescence) was increased by diesel exhaust inhalation in coronary arteries and normalized by eNOS inhibition or	(24)

			tetrahydrobiopterin.	
OZONE AND OTHER GAS MIXTURES				
Chuang 2009	C57BL/6 and ApoE$^{-/-}$ mice on normal diet, rhesus monkeys	Ozone (O_3, 0.5 ppm) for 8 h/d for 1 or 5 d	Ozone induced endothelial dysfunction (ACh) in wildtype mice, whereas no effect was observed on phenylephrine-dependent vasoconstriction and only a marginal impairment was seen for sodium nitroprusside-dependent relaxation. Blood pressure and heart rate slightly increased, eNOS protein / $^{\bullet}$NO-products decreased and isoprostane levels in lung / aorta increased, whereas mitochondrial aconitase activity was impaired upon ozone exposure of wildtype mice. Ozone exposure induced mtDNA lesions in lung and aorta of wildtype mice and monkeys as well as atherosclerotic plaques in the aorta of ApoE$^{-/-}$ mice.	(25)
Robertson 2013	Female C57BL/6 WT mice and CD36$^{-/-}$ mice aged 8–10 weeks were used in the study. Acetylcholine responses in myograph of aortic ring segments.	Filtered air (FA) or 1 ppm O_3 for 4h.	O_3-induced a reduction (85% reduction) in Ach dependent relaxation compared to identical exposure to FA in WT mice. CD36$^{-/-}$ mice were protected against the O_3-induced impairments of ACh-dependent vasorelaxation in aortic rings. However ex-vivo incubation of WT aortic rings with serum from CD36-/- mice exposed to ozone induced the same degree of vasodilatory impairment when compared with serum from WT mice exposed to a single dose of ozone. These experiments suggest that CD36 may be downstream of f	(26)
Pafett 2015	Male Sprague-Dawley rats	Ozone (1 ppm) for 4 h	Ozone exposure augmented broncho-alveolar lavage cellularity and neutrophil count and numbers of circulating neutrophils and macrophages. The baseline coronary artery internal diameter was decreased and the percent increase in tone following isolation and mounting was higher in vessels obtained from rats exposed to ozone. Coronary artery constriction in response to serotonin was more pronounced in the ozone group. Likewise, ozone exposure produced a dramatic endothelial dysfunction (ACh) that was partially corrected in the presence of superoxide dismutase and completely prevented by a mixture of SOD and catalase as well as the NADPH oxidase inhibitor apocynin.	(27)
Murnaw 2015	Male Sprague-Dawley rats exposed to one O3 exposure. Young or aged rats exposed for 50 days to mixed motor vehicle emissions.	Ozone (1 ppm) for 4 hours. Responses tested from serum obtained 24 hours later.	Serum from ozone exposure augmented a proinflammatory response in cultured microglial cells to agents such as beta-amyloid 42 (Abeta42) neurotoxicity independent of traditional circulating cytokines. MVE exaggerated inflammation in cortical cells from aged mice. Ozone exposed serum amplified inflammatory responses.	(28)
Zhong 2016	Diabetes prone KK mice exposed to ozone or	O_3 (0.5 ppm for 13 consecutive weekdays	O_3 increased monocytes/macrophages in both blood and visceral adipose tissue. Systemic CD4 + T cell activation enhanced by the exposure of O3.	(29)

	filtered air sub-chronically. Insulin resistance and inflammation measures in lung and insulin responsive tissues.	(Monday to Friday, 4 h/day).	Multiple inflammatory genes including CXCL-11, IFN-gamma, TNFalpha, IL-12, and iNOS up-regulated in visceral adipose tissue.	
Ying 2016	Male KKAy mice were exposed to ozone or filtered air for 13 consecutive days	0.5 ppm ozone or FA for 13 consecutive weekdays	Pro-inflammatory CD11b(+)Gr-1^{lo}7/4^{hi} macrophages increased in adipose but unchanged in blood. Fasting insulin and HOMA-IR in ozone-exposed animals reduced without change in glucsoe. Paradoxic increased insulin signaling in skeletal muscle/liver. Ozone associated with weight loss and reduced plasma leptin that may have confounded results.	(30)
Lund 2009	Male ApoE$^{-/-}$ mice on high fat diet exposed for 1 or 7 days. Parallel human study (n=10) with diesel exhaust exposure versus filtered air for 2 hours repeated twice per person	Gasoline engine exhaust (60 µg/m^3) for 6 h/d for 1-7 d. In a parallel study, diesel exhaust exposure 100 µg/m^3 or HEPA filtered "clean" air	Exposure lead to MMP-2/9 activation and endothelin-1 induction in the aorta. Aortic MMP-9 expression and MDA formation by exhaust exposure was prevented by the free radical scavenger TEMPOL, whereas the ET_A receptor antagonist BQ-123 prevented these adverse effects but also endothelin-1 expression by PM2.5. Significant increases in plasma ET-1 and MMP-9 expression and activity in response to ozone exposure.	(31)
Li 2011	Male Wistar rats	$^{\bullet}NO_2$ (5, 10 and 20 mg/m^3) for 6 h/d for 7 d	$^{\bullet}NO_2$ dose-dependently induced cardiac morphological changes and increased oxidative stress markers (MDA and protein carbonyl groups), triggered adverse regulation of antioxidant proteins and triggered an inflammatory cardiac phenotype (TNF-α, IL-1β, ICAM-1) and vasoconstriction via endothelin-1. Apoptotic pathways were also initiated by $^{\bullet}NO_2$ (p53, bax/bcl-2 and TUNEL-positive myocytes).	(32)
COMPARATIVE STUDIES				
Kodavanti 2011	Male Wistar Kyoto rats	Ozone (0.4-1 ppm) and diesel exhaust particles (2.1 mg/m3) or a mixture for 5 h/d, 1 d/w for 16 weeks or for 2 d	Ozone and diesel exhaust particles induced aortic expression of biomarkers of oxidative stress, thrombosis, vasoconstriction and fibrosis (HO-1, tissue factor, tPA, PAI-1, vWF, endothelin-1, ET_AR, MMP-2, TIMP-2). The levels of polyunsaturated fatty acids (PUFA) were decreased by both pollutants. The mixture showed no synergistic effects on these parameters, whereas LOX-1, RAGE and HMGB-1 showed an additive increase.	(33)
Lund 2011	ApoE$^{-/-}$ mice on high fat diet	Gasoline engine exhaust (60 µg/m^3) or PM from diesel exhaust (300 µg/m^3) or a mixture for 6 h/d for 7 or 50 d	Aortic lectin-like oxidized low-density lipoprotein receptor (LOX-1) and lipid peroxidation was increased by all exhaust exposures and higher particle exposures caused more pronounced effects, whereas the exposure time had no effect. Filtration of the exhaust volume stream diminished the effect. Induction of vascular oxLDL, MDA, LOX-1, endothelin-1 and MMP-9 expression and monocyte / macrophage infiltration by exhaust exposure was prevented by treatment with a LOX-1 antibody.	(34)
Campen 2010	ApoE-/- mice exposed to a variety of particles, gases and	Exposures to gasoline, diesel, coal, hardwood),	Increased aortic *MMP-9*, *ET-1*, and tissue inhibitor of metalloproteinase (*TIMP-2*) with GEE. Diesel exhaust increased ET-1 but not other	(35)

	mixtures for for 6 hr/day for 7 days.	secondary coal derived combustion particles and aerosols (SOAs), or combustion-source gases [O3, NO2, CO]	transcripts. Increase in ET-1 and MMP-9 by gasoline and diesel exhaust recreated by CO and NO. Aortic lipid peroxidation (LPO) significantly enhanced by both gasoline and diesel engine emissions. No significant change in aortic LPO for any of the principal gases. In a parallel study, volunteer human subjects exposed to 2-h of 100 $\mu g/m^3$ diesel (DE) or clean air for 2 hrs induced increases in plasma ET-1 and MMP-9.	

Supplemental Table 3. Human studies on association of endothelial dysfunction inflammation or oxidative stress with air pollution.

Study	Population / cohort	Air pollutant	Major outcome	Ref
PANEL STUDIES				
O'Neill 2005 (Massachussets, USA)	270 adults with Diabetes or at risk for diabetes and who had undergone FMD measurements as part of clinical trials	24-hour average ambient levels of air pollution (fine particles **[$PM_{2.5}$], particle number, black carbon, and sulfates [$SO4_{2-}$]**) approximately 500 m from the patient examination site.	Six-day moving averages of all 4-particle metrics were associated with decreased vascular reactivity among patients with diabetes but not those at risk. Increases in SO_4 and black carbon associated with reduced FMD in the brachial artery.	(36)
Briet 2007 (Paris, France)	40 healthy non-smoker white males	**Ambient nitrogen, sulfur and carbon oxides, and $PM_{2.5}$** averaged 5 days preceding measurement of FMD	FMD independently and negatively correlated with the average levels of SO_2 ($P<0.001$) and NO ($P<0.01$) but positively correlated with PM_{10} and $PM_{2.5.}$	(37)
Delfino 2008 (California, USA)	29 nonsmoking elderly subjects with a history of coronary artery disease (several measurements were averaged)	**Combustion aerosols** (solid and gaseous constituents)	Organic carbon and ultrafine particles from combustion aerosols associated with increased systemic inflammation (CRP, IL-6, sTNF-RII significant) and platelet activation (sP-selectin) and decreased antioxidant enzyme activity (erythrocyte superoxide dismutase significant; glutathione peroxidase-1 by trend).	(38)
Liu 2009 (Ontario, Canada)	28 non-smoking seniors	Daily ambient indoor and outdoor **black carbon, $PM_{2.5}$** and personal $PM_{2.5}$	Increases in black carbon and $PM_{2.5}$ were associated with increases in blood pressure, heart rate, endothelin-1, vascular endothelial growth factor, and oxidative stress marker thiobarbituric acid reactive substances, and a decrease in brachial artery diameter.	(39)
Madrigano 2010	809 from ageing study	Ambient **$PM_{2.5}$ and black carbon**	Impact of carbon black on systemic inflammation (sVCAM-1) was more pronounced in individuals with glutathione S-transferase M1 polymorphism or obesity.	(40)
Delfino 2009 Los Angeles, CA	60 elderly subjects with coronary artery disease (several measurements were averaged)	**Combustion aerosols** (solid and gaseous constituents)	Mainly carbon black, organic carbon, CO and NO_x were positively correlated with inflammatory and platelet activation biomarkers (IL-6, sTNF-RII, sP-selectin) and inversely associated with erythrocyte antioxidant enzymes (erythrocyte superoxide dismutase and glutathione	(41)

			peroxidase-1). Statin and clopidogrel therapy decreased markers of inflammation and platelet activation in response to combustion aerosols exposure.	
Brook RD 2011 (Michigan, USA)	51 healthy subjects with repeated measurements of blood pressure, brachial artery diameter, FMD over 5 days.	24-hr personal **$PM_{2.5}$** monitoring during summer and/or winter periods.	The association between total personal $PM_{2.5}$ exposure and FMD or BAD did not show a clear temporal pattern. A positive association was observed between $PM_{2.5}$ exposure and brachial artery diameter just before measurement (0-2 hr). The strongest associations between heart trate and total personal $PM_{2.5}$ exposure recorded 1-10 hr before cardiovascular measurements	(42)
Pope CA 3rd 2011 (Utah, USA)	26 healthy subjects exposed to $PM_{2.5}$ generated from coal or wood combusition. Baseline, postexposure, and post-clean room reactive hyperemia-peripheral arterial tonometry was conducted.	Exposed to 150-200 μg/m^3 of **fine particles** generated from coal or wood combustion and 3 hr in a clean room, with exposure and nonexposure periods alternated between visits.	Declines in vascular response were associated with elevated ambient exposures for the previous 2 days, especially for female subjects but not immediately after.	(43)
Krishnan RM et al 2012. (various locations, USA)	Initial examination of the Multi-Ethnic Study of Atherosclerosis (n = 3,040) and FMD, brachial artery diameter measured at initial visit	Long-term **$PM_{2.5}$** estimated for the year 2000 at each participant's residence using a spatio-temporal model.	An interquartile increase long-term $PM_{2.5}$ 3 μg/m^3 but not short term levels associated with a 0.3% (95% CI: -0.6 -to -0.03, P=0.03) decrease in FMD.	(44)
DeJarnett 2015 (Kentucky, USA)	A cross-sectional study measuring circulating angiogenic cells in 316 participants with moderate-to-high cardiovascular risk and roadway distance	Road way distance	CD31(+)/AC133(+), AC133(+), CD34(+)/AC133(+) cell numbers after adjustment of co-variates, negatively associated with roadway distance suggesting a relationship between vascular repair and traffic exposure.	(45)
Zhang 2016 (California, USA)	93 elderly non-smoking adults living in the Los Angeles metropolitan	Ambient **$PM_{2.5}$** and **black carbon**	RHI was inversely associated with traffic-related pollutants such as ambient $PM_{2.5}$, black carbon, NOx, and carbon monoxide. An interquartile range change increase (1.06 μg/m(3)) in 5-day average black carbon was	(46)

	area, during July 2012-February 2014. Microvascular function, represented by reactive hyperemia index (RHI), was measured weekly for up to 12 weeks		associated with decreased RHI, -0.093 (95 % CI: -0.151 to -0.035)	
Pope CA 3rd et al 2016 (Utah, USA)	24 persons recruited for each of 3 consecutive winter/spring study periods in Utah	Circulating markers of **endothelial apoptosis** and inflammation in relation to **ambient $PM_{2.5}$** during winter inversion periods in Utah	Elevated levels of endothelial microparticles (annexin $V^+/CD41^-/CD31^+$). Decreased VEGF, PDGF, RANTES,GROα and VEGF and an increase in TNFα, IP-10, MCP-1, MIP-1α/β, IL-6, and IL-1β), and markers of endothelial adhesion sICAM-1 and sVCAM-1.	(47)
Mirowsky et al, 2017 (Durham, NC, USA)	15 individuals with established from a prospective cohort with CAD presenting to the cardiac catheterization lab at Duke University (CATHGEN cohort)	Daily measurements of **O_3 and $PM_{2.5}$** obtained from central monitoring stations. Circulating markers of **endothelial function (PAI-1, tPA), brachial endothelial function, diameter** and inflammation (IL-6) with various lag structures	Per 0.014 ppm (interquartile) increase in ambient ozone and various lag structures (0-5), tissue plasminogen factor and PAI-1 increased (6.6%, 41% respectively); neutrophil, monocytes and IL-6 also positively correlated. The large-artery elasticity index (−19.5%, 95% CI = −34.0, −1.7), and the baseline diameter of the brachial artery (−2.5%, 95% CI = −5.0, 0.1) were negatively correlated with ozone levels.	(48)
CONTROLLED EXPOSURE STUDIES				
Brook 2002	Randomized, double-blind, crossover study in 25 healthy volunteers exposed to concentrated ambient fine particles with or without ozone (120 ppb) versus inhalation of filtered air.	2-hour inhalation of 150 $\mu g/m^3$ of **concentrated ambient fine particles** plus ozone (120 ppb) vs filtered air. Primary end-point brachial artery endothelial function	Significant brachial artery vasoconstriction with concentrated ambient fine particles compared with filtered air inhalation. No significant differences in flow-mediated dilatation or nitroglycerin-mediated dilatation.	(49)
Mills 2005	30 healthy volunteers (crossover)	**Diesel exhaust** (300 $\mu g/m^3$ for 1 h with intermittent exercise)	Acute exposure to diesel exhaust impaired endogenous fibrinolysis as well as endothelium-dependent and nitric oxide-dependent vasodilation but not the beneficial effect of a calcium antagonist (measured by forearm blood	(50)

			flow using plethysmography).	
Tornquist 2007	Double-blinded, randomized, crossover study of 15 healthy men to diesel exhaust or filtered air for 1 hour. Forearm blood flow 24 hours following exposure in response to agonists including acetylcholine, bradykinin, nitroprusside.	**Diesel exhaust** concentration, 300 $\mu g/m^3$ or filtered air	Diesel exhaust reduced acetylcholine, and bradykinin induced forearm vasodilatation at 24 hours. No differences in endothelium-independent vasodilatation or bradykinin-induced tissue plasminogen activator release.	(51)
Mills 2007	20 men with prior myocardial infarction (cross-over)	**Diesel exhaust** (300 $\mu g/m^3$ for 1 h with moderate exercise)	Exercise-induced ST-segment depression was present in all patients, but there was a more pronounced ischemic burden (measured by electrocardiography) and also suppression of fibrinolytic activity of plasminogen during exposure to diesel exhaust.	(52)
Peretz 2008	Randomized, double-blinded, crossover study involving 27 adult volunteers with metabolic syndrome exposed to filtered air and two levels of diluted diesel exhaust	2 doses of diluted **diesel exhaust** (100 or 200 $\mu g/m^3$ of fine particulate matter or filtered air in 2-hr sessions. End-point: brachial artery diameter	DE at 200 $\mu g/m^3$ elicited a decrease in brachial artery diameter in a dose-related manner. Plasma levels of ET-1 increased after 200 $\mu g/m^3$ DE but not after filtered air.	(53)
Brook RD et al 2009	2 randomized, double-blinded, crossover studies in Ann Arbor and Toronto with cross over (n=50 and 31) involving exposure to $PM_{2.5}$ + ozone or $PM_{2.5}$ with various pre-treatments). End-points included blood pressure and flow mediated dilation	Protocols included exposure to **$PM_{2.5}$** (150 $\mu g/m^3$) plus **ozone** (120 ppb) for 2 hours on 3 occasions with pretreatment Bosentan, 250 mg (Endothelin-A antagonist), Vitamin C (2g), or placebo in Ann Arbor. In Toronto, subjects exposed to $PM_{2.5}$ plus ozone, $PM_{2.5}$, ozone or filtered air.	Acute increase in diastolic blood pressure at both locations in response to exposure to $PM_{2.5}$ and $PM_{2.5}$+ozone. No change in FMD in Ann Arbor but FMD decreased 24 hours following exposure in Toronto. None of the interventions prevented changes in blood pressure or altered FMD.	(54)
Stewart et al. 2010	19 subjects with type 2 diabetes exposed to markers of vascular activation, coagulation,	Controlled exposure to filtered air or 50 $\mu g/m^3$ elemental carbon **ultrafine particles** (count	Increased platelet expression of CD40 ligand (CD40L), platelet-leukocyte conjugates 3.5 hr after exposure. Plasma von Willebrand factor increased immediately after exposure	(55)

	and systemic inflammation before and after exposure sampled as part of a randomized trial.	median diameter, 32 nm) by mouthpiece for 2 hr.		
Lundbäck 2009	12 healthy volunteers	**Diesel exhaust** (350 $\mu g/m^3$ for 1 h with moderate exercise)	Acute exposure to diesel exhaust is associated with an immediate and transient increase in arterial stiffness (measured by applanation tonometry at the radial artery, femoral and carotid arteries) explaining the increased risk for cardiovascular disease associated with air pollution exposure.	(56)
O'Toole 2010	16 young non-smoking healthy adults	Episodic exposure to **ambient air pollution** ($PM_{2.5}$ 10, 20-40, >40 $\mu g/m^3$)	Episodic exposure to $PM_{2.5}$ induces reversible vascular injury, reflected in part by depletion of circulating endothelial progenitor cell levels (Flk-1^+/Sca-1^+), and increases in platelet activation (platelet (CD41a+)-monocyte (CD45+) aggregates) and the plasma level of HDL.	(57)
Devlin 2012	Randomized cross over study of 23 healthy individuals exposed to ozone or filtered air for 2 hours	Exposure to 0.3 ppm of **ozone** or filtered air for 2 hours during stationary exercise	A 100% increase in interleukin-8, a 21% decrease in PAI-1, a 51% decrease in the high-frequency component of heart rate variability, and a 1.2% increase in QT duration.	(58)
Wauters 2013	Randomized, controlled, crossover study in healthy male volunteers exposed to ambient and diesel exhaust (n=12).	**Diesel exhaust** ($PM_{2.5}$ concentration of 300 $\mu g/m^3$ or filtered air exposure for 12 minutes. Microvascular function using laser Doppler fluxmetry in skin with iontophoresis with acetylcholine, nitroprusside and L-N-arginine-methyl-ester	Diesel exhaust exposure reduced acetylcholine-induced vasodilation, decreased NO-mediated skin thermal vasodilatation, and increased ROS production.	(59)
Barath 2013	Randomized, controlled, crossover study of ozone exposure vs filtered air. Microvascular flow using forearm blood flow before and during intra-arterial infusions of vasodilators 2-4 and 6-8h after each exposure	Exposure to **ozone** (300 ppb) or filtered air for 75 min on two occasions. Heart rhythm and heart rate variability were monitored during and 24h after exposure.	Ozone exposure did not impair vasomotor or fibrinolytic function at 6-8h but increased vasodilatation to acetylcholine ($p = .015$) and sodium nitroprusside. Ozone did not affect measures of heart rate variability during or after the exposure.	(60)

Hunter et al 2014	Double-blind randomized cross-over study of fire fighters exposed to wood smoke particulate matter.	**Wood smoke** (~1 mg/m³ particulate matter) or filtered air for 1 h. Arterial pressure, stiffness were measured before and immediately after and forearm blood flow 4-6 hours after exposure. Thrombus formation assessed using ex vivo Badimon chamber at 2 hours.	Wood smoke exposure did not impair vascular vasomotor or fibrinolytic function, or increase thrombus formation in fire fighters. Following exposure to wood smoke, there was an increase in bradykinin-induced vasodilatation.	(61)
Liu 2015	50 healthy young non-smoking volunteers	Ambient **coarse** (2.5–10 μm; mean, 213 μg/m^3), **fine** (0.15–2.5 μm; mean, 238 μg/m^3) and **ultrafine particles** (< 0.3 μm; mean, 136 μg/m^3) for 130 min	Coarse particles increased circulating VEGF, fine particles elevated urinary malondialdehyde and ultrafine particles augmented urinary 8-hydroxydeoxyguanosine.	(62)
Byrd 2016	29 healthy young adults underwent a randomized double-blind crossover study involving 2-hour exposures to concentrated ambient coarse PM	**Course ambient coarse PM exposure** versus filtered air over 2 hours (164.2 ± 80.4 μg/m^3)	Both systolic (1.9 mm Hg) and diastolic (1.9 mm Hg) blood pressure levels were higher throughout coarse PM compared with filtered air exposure. Heart rate variability, endothelial function, and arterial compliance not significantly affected.	(63)

Supplemental Table 4. Interventional Studies reporting endothelial function or equivalent surrogates

Author(s)	Experimental Design and Population	Details on Intervention	Changes in Endothelial Function or Surrogates such as Blood Pressure	
HOME AIR FILTERS				
Brauner et al. (Copenhagen, Denmark)	21 nonsmoking couples in a randomized, crossover study with two consecutive 48-hour exposures to either particle-filtered or non-filtered air. Microvascular flow measured by digital tonometry	Two 48-hour exposures to particle-filtered or non-filtered air (2,533–4,058 and 7,718–12,988 particles/cm^3, respectively) in their homes	Improvement in microvascular flow with air-filtration of indoor air	(64)
Allen et al. (British Columbia, Canada)	Randomized crossover study of 45 healthy adults exposed to consecutive 7-day periods of filtered and non-filtered woodsmoke air	Indoor air filters reduced indoor fine particle concentrations by 60% (from 11.2 mg/m^3 with HEPA off to 4.6 mg/m^3 with HEPA on)	Endothelial function improved with air-filtration. CRP levels tended towards improvement	(65)
Weichenthal et al. (Manitoba, Canada)	A randomized crossover study on a First Nations reserve in Manitoba, Canada, including 37 residents in 20 homes.	Each home received an electrostatic air filter and a placebo filter for 1 week in random order. Mean difference = 37 µg/m(3) , 95% CI: 10, 64)	7.9-mm Hg (95% CI: -17, 0.82) decrease in SBP and a 4.5 mm Hg (95% CI: -11, 2.4) decrease in DBP.	(66)
Chen et al (Shanghai, China)	Double-blind, randomized, cross-over study of an air filter intervention >48 h, among 35 healthy young university students in Shanghai, China	Air filtration reduced indoor $PM_{2.5}$ concentration by more than one-half, from 96.2 to 41.3 $µg/m^3$.	After 48 h of “cleaner air” exposure, systolic and diastolic blood pressure MCP-1, interleukin-1β, myeloperoxidase and platelet activation (sCD40L) were significantly reduced	(67)
Shao et al. 2017 (Beijing, China)	Randomized crossover trial in 35 non-smoker senior participants	Portable air filtration units randomly allocated to active filtration (filter in) vs sham (filter out) for 2 weeks.	No changes in blood pressure, but had reduction in IL-8 by 59% compared with control	(68)
Kajbafzadeh et al 2015 (Vancouver, Canada)	Randomized single-blind, crossover study of 83 healthy adults in traffic- or woodsmoke-affected areas	HEPA filtration device with active (filter on) and placebo (filter off)	There was no difference in endothelial function as measured by RHI (2.1+0.6 vs 2.1+0.6), P=0.71. There was also no difference in CRP (2.2 ± 3.7 vs 2.4 ± 3.3 mg/L, P=0.85), IL-6 (3.1 ± 5.3 vs 2.9 ± 5.2 pg/mL, P=0.88), BCC (0.8 ± 0.9 vs 0.8 ±0.9, P=1.00).	(69)

Karottki et al. (Copenhagen, Denmark)	randomized, double-blind, crossover intervention study in 48 healthy non-smoking volunteers > 51 years	consecutive two-week periods with or without filter in living room/bedroom	No change in microvascular function as measured by peripheral artery tonometry; however, microvascular function was associated with $PM_{2.5}$ decrease in the bedroom	(70)
CLOSING CAR WINDOWS AND CAR AIR CONDITIONING				
Pui et al. (Minnesota, USA)	Open label intervention of car-ventilation system in the recirculation mode in 2 car models with and without an inexpensive cabin filter.	Particle of all sizes including ultrafine particles removed by filtration system.	Recirculation alone without air filter lowered concentration over time due to collection of particles in the ventilation and recirculation system. With air recirculation on and the filter in place, in-cabin aerosol concentration in was reduced to below typical office air concentrations in approximately 3 min.	(71)
Lin et al. (Taipei, Taiwan)	Open label intervention to closing windows versus keeping open in 300 healthy subjects from Taipei, aged 20 and over	Levels of PM_{10}, $PM_{2.5}$ and total volatile organic compounds decreased by 28, 3 and 11%, respectively with windows closed. There was 50, 44 and 32% decrease in PM_{10}, $PM_{2.5}$ and total volatile organic compounds respectively, when air conditioners was turned on. Air conditioners reduced all parameters more effectively compared to closing windows.	Measures of heart rate variability (deviation of normal to normal R-R intervals, and root mean square of successive heartbeat interval differences) improved by 29 and 41% with windows closed, and by 32% and 44% when AC was turned on. hs-CRP, 8-OhdG and fibrinogen decreased by 24%, 71% and 7%, respectively, when the air conditioners were turned on. No additional effect modification by air conditioning on parameters compared to windows closed	(72)
Chuang et al. Taipei, Taiwan	60 healthy subjects to commute for 2 h by a car equipped with AC system during the morning rush hour in Taipei with 3 different modes (off , AC on with inside air (IA) and AC on with outside air (OA)	There was 54% and 63% decrease in $PM_{2.5}$ when using AC system with IA- and OA-mode, respectively. No significant difference in car temperature, humidity and noise levels between off mode, IA and OA modes (temperature of 10-20C)	HRV indices associated with in-car PM2.5 with greatest decrease occurring with off mode. SDNN and r-MSSD increased 20% and 17% with IA-mode as well as 22% and 32% with OA-mode. No interaction seen between in-car $PM_{2.5}$ levels and IA/OA modes with HRV indices.	(73)
PERSONAL MASKS				
Langrish et al. (Beijing, China)	Open-label cross-over randomised controlled trial, 15 healthy volunteers. Mask efficiency of a range of masks	Mask penetrance was highly dependent on mask type. PM2.5 levels lower with mask (86 vs.140 mg/m3). No change in particle numbers.	During the 2-hour city walk, systolic blood pressure was lower (114 ± 10 vs 121 ± 11 mmHg, $P < 0.01$) when subjects wore a facemask. Over the 24-hour period heart	(74)

	tested prior to human intervention study.		rate variability increased (SDNN 65.6 ± 11.5 vs 61.2 ± 11.4 ms, P < 0.05; LF-power 919 ± 352 vs 816 ± 340 ms2, P < 0.05) when subjects wore the facemask.	
Langrish et al. (Beijing, China)	Open randomized crossover trial of face mask (Dust Respirator) in 98 patients with coronary heart disease.	Estimated exposure with mask (assuming 97% efficiency) reduced from 89 $\mu g/m^3$ and 43,900 particles/cm^3 to 2 $\mu g/m^3$ and 1,200 particles/cm^3 respectively.	Mask reduced maximal ST segment depression over 24-hr period. Mean arterial pressure lower (93±10 vs. 96±10 mmHg, p = 0.03) and heart rate (75) variability increased (HF power: 54 vs. 40 $msec^2$, p = 0.005; root mean square successive differences: 16.7 vs. 14.8 msec, p = 0.007)	(75)
Laumbach et al. (New Jersey, USA)	Randomized, cross-over trial in which 21 young adults took two 1.5-hr rides in a vehicle in morning rush-hour traffic and wore a powered air purifying respirator (PAPR) blinded to HEPA filtration.	Particle number reduced by 99.99% compared to unfiltered rides The reduction in $PM_{2.5}$ with HEPA filtration was of a smaller magnitude (9.1±4.8 vs. 1.4±0.6 $\mu g/m^3$).	Mean exhaled breath nitrites and sum of nit+nitrite lower with respirator compared to unfiltered rides. Trend towards lower exhaled breath malondialdehyde.	(76)
Vieira 2016 (São Paulo, Brazil)	26 patients with NYHA Class 1-III heart failure and 15 control volunteers. Double-blind, randomized controlled, 3-way crossover, trial of exposure to clean air, unfiltered diesel exhaust exposure (DE), or filtered DE.	Filtration reduced the particulate concentration (325 ± 31 $\mu g/m^3$ vs. 25 ± 6 $\mu g/m^3$; p < 0.001). Primary end point was reactive hyperemia index (RHi) while secondary endpoints included arterial stiffness, 6-minute walk test and heart rate variability	Diesel exhaust reduced endothelial function and increased BNP from 47 pg/ml to 66.5 pg/ml (p = 0.004). in the group with HF, Filtration improved RHI from 1.72 to 2.06 (p = 0.019) and decreased BNP. In both groups, DE decreased the 6-min walking distance and arterial stiffness, although filter did not change these responses	(77)
INTERVENTIONAL STUDIES				
Tong et al.	Normal volunteers (n=42, 58 ± 1 years of age) received 3 g/day of Olive Oil or Fish Oil, or no supplement for 4 weeks prior to undergoing 2-hr exposures to filtered air and concentrated ambient particulate matter (CAP; mean, 253 ± 16 µg/m3).	Flow-mediated dilation (FMD) of the brachial artery pre, immediately post and 20 hr postexposure.	FMD was significantly lower after CAP exposure in the naive (-19.4%; 95% CI: -36.4, -2.3 per 100 µg/m3 CAP relative to baseline; p = 0.03) and FO groups (-13.7%; 95% CI: -24.5, -2.9; p = 0.01), but not in the OO group (-7.6%; 95% CI: -21.5, 6.3; p = 0.27)	(78)

Abbreviations: Ach: Acetylcholine;BAT=Brown adipose tissue. DCF-DA: Dichlorofluorescein diacetate; FMD=Flow mediated dilation; CAP=Concentrated ambient particles; HEPA=High Efficiency Particulate Air; HRV=Heart rate variability; PM=Particulate Matter; FMD=Flow-mediated dilatation; RHI=Reactive-hyperemia index; ICAM=Intercellular adhesion molecule-1; VCAM-Vascular cell adhesion molecule-1; ROS=Reactive oxygen species; SDNN=Standard deviation of NN intervals. VEGF=Vascular endothelial grown factor-1

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