APPENDICES AVAILABLE ON THE HEI WEBSITE

Special Report 23

Systematic Review and Meta-analysis of Selected Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

HEI Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution

Chapter 3: Mechanistic Evidence Underlying the Health Effects of Traffic-Related Air Pollution

These Appendices were reviewed solely for spelling, grammar, and cross-references to the main text. They have not been formatted or fully edited by HEI. This document was part of the HEI Panel's review process.

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Appendices Chapter 3: Descriptive Tables
Mechanistic Evidence Underlying the Health Effects of Traffic-Related Air Pollution

Descriptive tables of studies describing the relationship between exposure to TRAP and selected adverse outcomes:

Table 3A. Studies investigating the relationship between exposure to TRAP and asthma.

Inflammatory effects on airway epithelium and immune cells: Epidemiological studies with a mechanistic component			
Reference	**Population/location**	**Exposure**	**Main findings**
Brandt et al. 2013	235 children with allergic asthma (5-18 y) enrolled in Greater Cincinnati Pediatric Clinic Repository N=46 with IL-17A serum data also enrolled in Pediatric Environmental Exposures Study Cincinnati, USA	DEP, calculated by estimating exposure to ECAT over the past 12 months Range of estimates: 0.25 $\mu g/m^3$ to 0.85 $\mu g/m^3$ across the entire study population	High DEP (> 0.464 $\mu g/m^3$) exposed children: • 32.2% had > frequent asthma symptoms over a 12 month period, compared to 14.2% in low DEP-exposed group • Associated with high IL-17A levels (OR=5.9, CI=1.5–24.0) • No other cytokine evaluated (IL-4, IL-5, IL-13) was associated with DEP exposure
Brandt et al. 2015	578 children enrolled in the Cincinnati Childhood Allergy and Air Pollution Study birth cohort Cincinnati, USA	DEP, calculated by estimating exposure to ECAT Average daily exposure to ECAT of ≥ & <0.41 $\mu g/m^3$ used to define high & low exposure	Among children sensitized to HDM by age 4, co-exposure to high ECAT at birth (defined as the top 25%) doubled the risk of asthma development by age 7 compared to those exposed to low ECAT (defined as the lower 75%) (36% vs 18%, p=0.045) HDM sensitization did not significantly increase the risk of asthma in children exposed to low levels of DEP (14% vs 18%, p=0.277) For sensitization to any aeroallergen at ages 1 – 4: significant increase in asthma prevalence at age 7 (16% vs 29%, p=0.02) in children co-exposed to high levels of ECAT at birth compared to children co-exposed to low ECAT
Weng et al. 2018a	24 female patients with severe asthma: • 12 living within 1000 m of a main road (53.3 ± 3.3 y) • 12 living > 1000 m of a main road (60.1 ± 2.1 y) Taoyuan City, Taiwan	Residential distance to a main road*: within versus > 1000 m *Highway or freeway where there was heavy traffic of trucks	Bronchial tissue of patients from high road traffic pollution areas had up-regulated expression of IL-17A mRNA & protein

Inflammatory effects on airway epithelium and immune cells: Real-world panel studies

Reference	Population/location	Exposure	Main findings
Brugge et al. 2013	40 participants: • 20 urban residents (living >1000 meters from the highway & >50 meters from major roadways; mean age 54.7 y) • 20 near highway residents (<100 m; mean age: 53.7 y) Somerville, USA	Proximity to major road	Near highway participants: • More likely to be more exposed to occupational vehicle exhaust exposure ($p<0.01$) • Blood biomarkers: elevated IL-1β, borderline higher IL-6 & no association with CRP or total cholesterol
McCreanor et al. 2007	60 participants with mild or moderate asthma (mean age 32 y) Central London, UK	Randomized crossover study Walking for 2h (a) down a busy street (Oxford Street) & (b) in a traffic-free area (Hyde Park) with lower pollution Median pollutant concentrations (µg/m^3): Oxford St Hyde Pk $PM_{2.5}$ 28.3 11.9 PM_{10} 125 72 UFP* 63.7 18.3 EC 7.5 1.3 NO_2 142 21.7 *thousands/cm^3	Walking for 2 hours on Oxford Street: • Larger asymptomatic but consistent reductions in FEV_1 & FVC • Effects greater in participants with moderate asthma than in those with mild asthma • Greater increases in sputum myeloperoxidase & airway acidification • Changes associated most consistently with exposures to UFPs & EC

Reference	Population/location	Exposure	Main findings
Mirowsky et al. 2015	23 healthy adults (mean age: 25 y) Northern New Jersey & Southern New York area, USA	Randomized crossover study: walking 2 hours along three diverse roadways (SF, GSP, GWB) with unique emission characteristics Mean pollutant concentrations (µg/m^3): SF GSP GWB $PM_{2.5}$ 13 21 31 PM_{10} 16 26 28 $PM_{2.5}$ EC 0.6 1.7 5.3 PM_{10} EC 0.9 2.3 6.6 BC 1.5 2.8 7.2 $PM_{2.5}$ OC 10 13 21 SF: Sterling Forest; GSP: Garden State Parkway; GWB: George Washington Bridge	24 hours after intermittent walking: • Minimal associations between pollutants & lung function measurements • Increases in IL-1β with increasing concentrations of $PM_{2.5}$ & EC

Inflammatory effects on airway epithelium and immune cells: Human controlled exposure studies

Reference	Population/location	Exposure	Main findings
Behndig 2006	15 healthy volunteers (mean age: 24 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM: 100 µg/m^3; 764 µg/m^3 NO_2); 2 h during intermittent exercise	18h post exposure: • Bronchial mucosa: increase in neutrophils & mast cells • Bronchial lavage: increased neutrophils IL-8 & MPO concentrations • BALF: no inflammatory responses; increased GSH & UA concentrations
Behndig et al. 2011	23 healthy volunteers 32 participants with mild asthma (18-45 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM: 100 µg/m^3; 764 µg/m^3 NO_2); 2 h during intermittent exercise	Healthy participants (18h post exposure) • Bronchial tissue: Increased neutrophils • BW: increases in neutrophils & IL-6 & MPO concentrations Asthmatic participants (18h post exposure) • No evidence of enhanced airway inflammation
Blomberg et al. 1997	30 healthy participants (mean age: 25 y)	Randomized crossover study of FA & NO_2 (3820 µg/m^3); 4 h during intermittent exercise	• BW: increased IL-8 & neutrophils • BALF: small increases in CD45RO$^+$ lymphocytes, B-cells, NK cells • Bronchial tissue: no signs of upregulation of adhesion molecules, no changes in inflammatory cells
Carlsten et al. 2016	18 atopic participants (19-24 y)	Randomized crossover study of FA & DE exposures DE (6.0 kW generator with Yanmar diesel engine; 300 µg PM/m^3); 2 h Allergen (or saline) challenge 1 h post-exposure	DE augmented allergen-induced increase in airway (BALF) of: • Eosinophils, IL-5, ECP GSTT1 null genotype significantly associated with augmented IL-5 response
Diaz-Sanchez et al. 1997	13 atopic participants (21-49 y)	Intranasal challenge with ragweed allergen alone or plus DEP (light duty diesel passenger car; 300 µg)	Ragweed alone (nasal lavage fluid) • Higher ragweed-specific IgE but not total IgE levels • Total IgA, IgG & IgG4 levels unchanged • Induced inconsistent & low levels of mucosal cytokine mRNAs DEP+ragweed (nasal lavage fluid) • Higher ragweed-specific IgE but not total IgE levels • Higher total & specific IgG4 levels • Total IgA & IgG levels unchanged • Decreased expression of mRNA for IFN-γ & IL-2

			• Elevated expression of mRNA for IL-4, -5, IL-6, IL-10, IL-13
Reference	**Population/location**	**Exposure**	**Main findings**
Diaz-Sanchez et al. 1999	25 atopic participants (21-55 y)	Intranasal challenge with allergen (KLH) alone or plus DEP (300 µg)	KLH alone • Anti-KLH IgG & IgA humoral response in nasal lavage fluid DEPs+KLH (nasal lavage fluid) • Anti-KLH IgG & IgA humoral response • 9 of 15 participants produced anti-KLH–specific IgE • Increased IL-4 (not IFN-γ)
Mohsenin 1991	19 healthy participants (21-33 y)	NO_2 7640 µg/m^3; 3h	BALF: increase in lipid peroxidation products & decrease in elastase inhibitory capacity
Mookherjee et al. 2018	14 atopic participants (22-26 y)	Randomized crossover study of FA & DE exposures DE (6.0 kW generator with Yanmar diesel engine; 300 µg PM/m^3); 2 h Allergen (or saline) challenge 1 h post-exposure	BALF: • Protein changes unique to co-exposure (DE+allergen) were undetected with mono-exposures (DE or allergen alone) • Specific proteins (e.g., antimicrobial peptide cystatin-SA) significantly enhanced with DE+allergen compared to either mono-exposure
Mudway et al. 2004	25 healthy volunteers (mean age: 24 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM: 100 µg/m^3; 1146 µg/m^3 NO_2); 1 h during intermittent exercise	Immediately post exposure: • Increase in subjective symptoms & mild bronchoconstriction 6h post exposure: • No reduction in airway inflammation or AA, UA & GSH • Increased flux of GSH into the bronchial & nasal airways
Nordenhäll et al. 2001	14 healthy participants (mean age: 26 y)	Single-blind crossover design of FA & DE (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM_{10}: 300 µg/m^3; 2292 µg/m^3 NO_2); 1 h during intermittent exercise	Increased hyperresponsiveness ($p<0.001$), airway resistance ($p=0.004$) & in sputum IL-6 ($p=0.048$) No changes were sputum methylhistamine, ECP, MPO & IL-8
Pathmanathan et al. 2003	12 healthy participants	NO_2 (3820 µg/m^3) or FA 4h/day for 4 successive days	Bronchial biopsy: • Increased expression of IL-5, IL-10, IL-13
Pourazar et al. 2004	15 healthy volunteers (mean age: 24 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM: 300	6h post exposure: • Increased flux of GSH into bronchial & nasal airways • Increase expression of IL-13 in bronchial epithelium cells

		µg/m^3; 3056 µg/m^3 NO_2); 1 h during intermittent exercise	• No significant changes in IL-10 & IL-18 expression

Reference	Population/location	Exposure	Main findings
Pourazar et al. 2005	15 healthy volunteers (mean age: 24 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM: 300 µg/m^3; 3056 µg/m^3 NO_2); 1 h during intermittent exercise	6h post exposure: • Increase in the nuclear translocation of NF-κB, AP-1, phosphorylated JNK, phosphorylated p38 • Increased total (cytoplasmic + nuclear) immunostaining of phosphorylated p38 • Increased nuclear phosphorylated tyrosine
Salvi et al. 1999	15 healthy volunteers (mean age: 24 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM: 300 µg/m^3; 3056 µg/m^3 NO_2); 1 h during intermittent exercise	6h post exposure: • No change in standard lung function measures • BALF: Increased neutrophils, B lymphocytes, histamine & fibronection • Bronchial tissue: increase in neutrophils, mast cells, $CD4^+$ & $CD8^+$ T lymphocytes, LFA-1+ cells • Blood: Increases in neutrophils & platelets • Bronchial tissue & BW: enhanced gene transcription of IL-8 • No significant changes in the gene transcript levels of IL-1β, TNFα, IFNγ, GM-CSF
Stenfors et al. 2004	25 healthy volunteers (mean age: 24 y) 15 participants with mild asthma (mean age: 30 y)	Randomized crossover study of FA & DE exposures (Volvo TD45, 4.5 L, four cylinders, 680 rpm, model 1991; PM_{10}: 108 µg/m^3; 1337 µg/m^3 NO_2); 2 h during intermittent exercise	Healthy participants (6h post exposure) • Airway inflammation (neutrophilia, lymphocytosis) • Increased IL-8 protein in BALF • Increased IL-8 mRNA expression in bronchial mucosa Asthmatic participants (6h post exposure) • No neutrophilic response, exacerbation of preexisting eosinophilic airway inflammation. • Increased IL-10 in bronchial epithelium
Wooding et al. 2019	14 allergen-sensitized participants (31 ± 9 y)	Randomized, double-blind crossover study FA, DE (6.0 kW generator with Yanmar diesel engine) or PDDE for 2h followed by inhaled allergen challenge DE: $PM_{2.5}$: 290 µg/m^3; NO_2: 101 µg/m^3 PDDE: $PM_{2.5}$: 20 µg/m^3; NO_2: 287 µg/m^3	PDDE + allergen impaired lung function > DE + allergen DE + allergen & PDDE + allergen increased airway responsiveness in normally responsive participants DE + allergen increased blood neutrophils & was associated with persistent eosinophilia at 48 hours DE & PDDE each increased total peripheral leukocyte counts in a manner affected by participant genotypes; changes in peripheral leukocytes correlated with lung function decline

Inflammatory effects on airway epithelium and immune cells: Animal models

Reference	Animal model	Exposure	Main findings
Alvarez-Simón et al. 2017	BALB/c mice	Soybean hull extract (SHE) or SHE + DEP (SRM 2975; 150 µg; intranasal admin)	5 mg SHE • AHR (p = 0.0033), increased eosinophilic inflammation (p = 0.0003), increased IL-4, IL-5, IL-13, IL-17A, IL-17F, CCL20 & reduced IFN-γ Compared to 5 mg SHE, 5 mg SHE + DEP • Slightly different cytokine profile with higher levels of Th17-related cytokines 3 mg SHE • Did not induce asthma Compared to 3 mg protein/ml SHE alone, DEP + SHE • Enhanced AHR & eosinophilic inflammation • Increased IL-5, IL-17F & CCL20 • Decreased levels IFN-γ
Brandt et al. 2013	BALB/c mice	DEP (Deutz engine; 150 µg IT) or saline &/or HDM 3x/week for 3 weeks	DEP alone • No inducement of asthma DEP + HDM • Enhanced AHR compared to HDM alone & a mixed Th2 & Th17 response including IL-13+IL-17A+ double producing T-cells • IL-17A neutralization prevented DEP induced exacerbation of AHR
Brandt et al. 2015	BALB/c mice	DEP (Deutz engine; 150 µg IT) or saline &/or HDM 3x/week for 3 weeks	DEP + HDM • Persistent Th2/Th17 CD127$^+$ effector/memory cells in lungs, spleen & lymph nodes • After 7 weeks of rest, a single exposure to HDM resulted in AHR & increased Th2 cytokines in only mice that had been previously exposed to both HDM & DEP versus HDM alone
De Grove et al. 2017	C57BL/6 mice	HDM or HDM + DEP (SRM 2975; 25µg intranasal admin) or saline on days 1, 8 & 15	DEPs + HDM: • Increased IL-25 & IL-33 protein lung levels compared to saline, sole DEP or HDM
Kobayashi and Miura 1995	Guinea pigs	NO_2 115-7640 µg/m^3; 24 h/day; 6-12 weeks	Enhanced AHR after 6 weeks @ 7640 µg/m^3, but not 115 or 955 & 7640 µg/m^3 for 6 weeks, 3820 µg/m^3 for 6 & 12 weeks & 1910 for 12 weeks

			Increased specific airway resistance in absence of a challenge agent after 3820 & 7640 µg/m^3 for 12 weeks

Reference	Animal model	Exposure	Main findings
Manners et al. 2014	Pregnant C57BL/6 mice	Pregnant mice: DEP (SRM 2975; 50 µg intranasal admin) or PBS on gestational days 3, 6, 9, 12, 15, 18 Offspring: OVA challenge or PBS	Offspring of mice exposed to DEP hypersensitive to OVA: • AHR, increased serum levels of OVA-specific IgE, increased pulmonary & systemic Th2 & Th17 cytokines. Asthma susceptibility was associated with increased transcription of genes known to be specifically regulated by AhR & oxidative stress
Ohta et al. 1999	A/J & C57BL/6 mice	DEP (light duty, Isuzu Automobile Company 2740 cc 4 cylinder engine; 250 µg, intranasal admin) every other day for 2 weeks	Increased GM-CSF mRNA total lung tissue Role for GM-CSF in AHR, BALF cell recruitment & mucus metaplasia
Provoost et al. 2010	BALB/c mice	DEP (10 or 100 µg; OA) on day 1, 4, 7	10 µg DEPs: • Increased DC numbers in BALF & lungs 100 µg DEPs: • Increased maturation status of DCs • Enhanced DC migration to the MLN in a CCR7- & DC-dependent manner • Enhanced T cell recruitment & effector differentiation in the MLN
Provoost et al. 2011	C57BL/6 mice	DEP (SRM 2075; 100 µg; IT) on day 1, 4, 7	Increased BALF IL-1β Role of IL-1 signalling in DEP-induced inflammation
Provoost et al. 2012	CCR2 knockout, CCR5 knockout, CCR6 knockout & C57BL/6 wild-type mice	DEP (SRM 2975; 100 µg DEPs IT) on day 1, 4, 7	DEP-induced monocyte & monocyte-derived DC recruitment: • Completely abolished in CCR2 knockout mice • Impaired in CCR6 knockout mice • Comparable between DEP-exposed wild-type & CCR5 knockout mice Impaired monocyte-derived DC recruitment in DEP-exposed CCR2 knockout mice (not CCR6 knockout) resulted in an abolished TH2 response in MLN
Sadakane et al. 2002	C57BL/6N & CBA/JN mice	HDM or HDM + DEP (50 µg DEPs IT) 4 times at 2 weeks intervals	HDM + DEPs: • Increased GM-CSF in lung homogenate compared to HDM • Not detected in CBA/JN mice
Sevanian et al. 1982	Sprague-Dawley rats	NO_2 5730 µg/m^3; 7 days	Induced AHR to histamine
Stoeger et al. 2006	BALB/c mice	DEP (SRM; 5-50 µg DEPs; IT)	No increased in BALF IL-1β

Reference	Animal model	Exposure	Main findings
Takano et al. 1998	ICR mice	DE (light duty, Isuzu Automobile Company 2740 cc 4 cylinder engine; 300, 1000 or 3000 µg/m^3) 12h/day, 7 days/week for 40 weeks OVA challenge at 3 week intervals during the last 24 weeks	DEP + OVA • Dose-dependent increase in lung GM-CSF
Wang et al. 2019	C57BL/6 mice	Der f 1 or Der f 1 + BaP (1 or 20 pmol) once a week for 6 weeks	Compared with Der f 1, BaP + Der f 1: • AHR, increased lung inflammation, increased expression of TSLP, IL-33 & IL-25 in the airways BaP + Der f 1: • Activated AhR signaling with increased expression of of AhR & CYP1A1 • Promoted airway epithelial ROS generation & TSLP & IL-33 (not IL-25) expression AhR antagonist CH223191 & NAC abrogated/suppressed BaP co-exposure-induced expression of ROS, TSLP, IL-33 & lung inflammation

Inflammatory effects on airway epithelium and immune cells: In vitro experiments

Reference	Cells/tissue	Exposure	Main findings
Bach et al. 2014	BEAS-2B cell line	DEP: Deutz 4 cylinder engine; 100 µg/ml; 2,4 or 6 h	Increased IL-6 & IL-8 mRNA expression
Blanchet et al. 2004	16HBE cells	$PM_{2.5}$ & DEPs: SRM 1650a; 10 µg/cm^2; 24 h	Causal relationship between amphiregulin & GM-CSF production in response to DEPs & PM
Bleck et al. 2006	DC from blood / HBEC from bronchial brushing normal volunteers	DEP: 1.6-liter Volkswagen diesel engine 40 kW; 10µg/ml; 48 h	Increased GM-CSF release GM-CSF-induced DC maturation
Bleck et al. 2008	DC from blood / HBEC from bronchial brushing normal volunteers	DEP: 1.6-liter Volkswagen diesel engine 40 kW; 3 µg/cm^2; 4 – 18 h	Increased TSLP mRNA & protein expression TSLP induced maturation & T cell proliferation of DC
Boland et al. 1999	16HBE14o- cells	DEPs (SRM 1650) & CB: 10 µg/cm^2; 6 - 48h	Time-dependent DEPs-induced increase in IL-8 & GM-CSF secretion CB ineffective
Boland et al. 2000	16HBE14o- cells	DEP: SRM 1960; 2.5-20 µg/cm^2; 6 – 48 h	Time & dose dependent increase in GM-CSF release in the presence of DEPs Importance organic compounds (lower effect of extracted DEPs & CB ineffective), ROS, tyrosine kinases & *de novo* protein synthesis
Bonvallot et al. 2001	16HBE14o- cells	DEP (SRM 1650), organic extracts of DEPs, stripped DEPs or CB: 10 µg/cm^2; 24 h	Increased GM-CSF secretion by DEPs & organic extracts of DEPs Importance organic compounds (lower effect of stripped DEP & no effect of CB), involvement of ROS & MAPK pathways
Ovrevik et al. 2011	BEAS-2B cell line	DEP: 5-80 µg/cm^2; 24h coarse & fine PM: 1.25-20 µg/cm^2; 24 h Details of generation of DEP not given	Dose-dependent increase in IL-8 release following coarse PM & DEP No response towards fine PM
Takizawa et al. 1999	BEAS-2B cell line	DEP: light duty, Isuzu Automobile Company 2740 cc 4-cylinder engine; 0.1-100 µg/ml; 24 h	Time- & dose-dependent increase in IL-8 mRNA expression Involvement ROS & NF-κB
Totlandsdal et al. 2012	BEAS-2B cell line	DEP: Deutz 4-cylinder engine; 100 µg/ml; 4 h	Increased IL-1β, IL-6 & IL-8 mRNA & protein levels

Reference	Cells/tissue	Exposure	Main findings
Totlandsdal et al. 2015	BEAS-2B cell line	DEP1 (Deutz 4-cylinder engine; low PAH & high metal content) or DEP2 (Cummins engine; high PAH & low metal content) 100 µg/ml; for 4 h	DEP2 more potent with respect to cytotoxicity, expression & release of proinflammatory mediators, CYP1A1 & HO-1 expression & MAPK activation
Wang et al. 2017	HBEC	Urban PM: 100-500 µg/cm^3; 24 h	Dose-dependent increase in IL-1β, IL-6 & IL-8 at both mRNA & protein level Involvement of ROS, MAPK pathway & NF-κB
Weng et al. 2018a	HBEC from bronchial brushing of 6 mild asthmatic patients with normal pulmonary function	DEP: light duty, Isuzu Automobile Company 2740 cc 4-cylinder engine; 0.1-10 µg/ml; 1-24 h	Concentration-dependent increase in IL-17A synthesis & release Increased ROS production Increased p65 & RelB subunits expression Increased NF-κB subunit RelB recruitment to IL-17A promoter Pretreatment with NAC inhibited DEP-induced IL-17A mRNA expression & IκBα degradation Pretreatment with NF-κB inhibitor inhibited DEP-induced IL- 17A expression
Weng et al. 2018b	HBEC from bronchial brushing of 6 mild asthmatic patients with normal pulmonary function	DEP: light duty, Isuzu Automobile Company 2740 cc 4-cylinder engine; 0.1-10 µg/ml; 1-24 h	Upregulation of IL-33, IL-25 & TSLP Effects abolished by knockdown of AhR Increased AhR/ARNT binding to promoters of IL-33, IL-25 & TSLP
Wu W et al. 2012	HBEC by brush biopsy	DEP: Deutz 4-cylinder engine; 25-100 µg/ml; 24 h	Increased IL-1β & IL-8 protein expression Involvement of GSTs through ROS-associated ERK & Akt activation

DNA methylation: Epidemiological studies with a mechanistic component

Reference	Population/location	Exposure	Main findings
Brunst et al. 2013	92 children (7 y) from the CCCEH longitudinal cohort Cincinnati, USA	Ambient DEP, calculated by estimating exposure to ECAT Mean DEP exposure in study sample: 0.38 µg/m^3	4.01% (95% CI: 1.83–6.18) increase in FOXP3 methylation per IQR increase in estimated DEP exposure Increased FOXP3 methylation associated with three times the risk of experiencing persistent wheezing during childhood (OR=3.05; 95% CI, 1.54–6.05), compared with children who had never wheezed Increased FOXP3 methylation associated with increased risk for early transient wheezing (OR=1.57; 95% CI, 1.01–2.41). Children with increased FOXP3 methylation were 2 times more likely to develop asthma than children with lower FOXP3 methylation (OR=2.12; 95% CI, 1.14–3.85)
Perera et al. 2009	56 children born to non-smoking Dominican & African-American women participating in the Columbia Center for Children's Environmental Health (CCCEH) longitudinal cohort Northern Manhattan & the South Bronx, USA	PAH Personal prenatal monitoring for 48 consecutive hours during third trimester Median PAH concentration of cohort: 2.3 ng/m^3	UCWBC DNA: Methylation of a CGI in *ACSL3* in UCWBCs positively associated with: • Level of maternal PAH exposure exceeding 2.41 ng/m^3 • Parental report of asthma symptoms prior to age 5
Prunicki et al. 2018	198 children (median age 14.7 y) Fresco, California, USA	NO_2, CO, $PM_{2.5}$ Average pollutant concentrations not reported as absolute values (but only graphically)	NO_2, CO, & $PM_{2.5}$ (90 days prior to the blood draw) positively associated with *FOXP3* methylation (p=0.001, p=0.001, p=0.012 respectively) In subset (N=33) retested 2 years later, association between exposure & methylation was retained Asthma associated with higher DMRs of *FOXP3* promoter region (p=0.030) & IL-10 intronic region (p=0.026) Negative correlation between average *FOXP3* methylation of the promoter region activated Treg levels (p=0.039) Positive correlation between average IL-10 methylation of region 3 of intron 4 & IL10 cytokine expression (p=0.030)

Reference	Population/location	Exposure	Main findings
Sofer et al. 2013	141 non-asthmatic males from NAS longitudinal study of aging (56-88 y) Boston, USA	BC 30 days averaged exposure: 0.85 µg/m^3	30-day average BC prior to blood draw associated with the methylation of 7 genes from the asthma pathway including those coding for: • Components in MHCII • IgE receptors • IL-9 • Eosinophil granule MBP
Zhang et al. 2018	29 sibling pairs discordant for asthma (5-18 y) from the Exposure Sibling Study Cincinnati, USA	ECAT *Median birth ECAT (µg/m^3)* Asthmatics: 0.42 Non-asthmatics: 0.45 *Median current ECAT (µg/m^3)* Asthmatics: 0.35 Non-asthmatics: 0.35	In nasal epithelial cells: • Methylation levels of cg14830002 & cg23602092 associated with current exposure to TRAP in non-asthmatics • Methylation levels of cg00112952, cg14830002 & cg23602092 associated with childhood asthma • Methylation levels of cg14830002 associated with allergic symptoms in non-asthmatic controls • Methylation levels of cg23602092 associated with asthma symptom frequency among asthmatics

DNA methylation: Human controlled exposure studies

Reference	Population	Exposure	Main findings
Clifford et al. 2017	17 participants (20-46 y)	Double-blind, randomized crossover study of FA & DE exposures DE (6.0 kW generator with Yanmar diesel engine; 300 µg PM/m^3); 2 h during intermittent exercise 1 h following each exposure to DE or FA, bronchoscopy to deliver a saline-controlled segmental allergen challenge	Exposure to allergen alone, DE alone, or allergen & DE together led to significant changes in 7 CpG sites at 48 h When same lung was exposed to allergen & DE but separated by ~ 4 weeks, significant changes in > than 500 sites were observed DMRs differed depending on which exposure was experienced first

Reference	Population	Exposure	Main findings
Jiang et al. 2014	16 non-smoking asthmatic participants (28.7 ± 6.7 y)	Double-blind, randomized crossover study of FA & DE exposures DE (6.0 kW generator with Yanmar diesel engine; 300 µg PM/m^3); 2 h during intermittent exercise	DNA methylation at 2827 CpG sites were affected by exposure to DE but not FA Sites enriched for genes involved in protein kinase & NFkB pathways CpG sites with significant changes in response to DE exposure primarily became < methylated DE-associated change found for CpG sites overlapping with Alu & LINE1 elements as well as for a site within miR-21

Sensory nerve activation

Reference	Animal/ in vitro models	Exposure	Main findings
Robinson et al. 2018	Anesthetized Dunkin-Hartley guinea pigs Human vagal tissue surplus to transplantation requirements Vagus nerves isolated from guinea pigs	IT DEP 10 µg/ml DEP 1 µg/ml DEP 1 µg/ml DEPs from a forklift truck (DEP SRM-2975) & its commercial organic extract (DEP-OE SRM-1975)	DEPs evoked action potential firing in chemosensitive C-fibers NOT in mechanosensitive Aδ-fibers Isolated guinea pig & human vagus • DEP-evoked concentration-dependent depolarization • DEP-OE (not cleaned particles) evoked depolarization • Inhibited by a TRPA1 antagonist & NAC

Abbreviations: AA: ascorbic acid; AhR: aryl hydrocarbon receptor; AHR: airway hyperresponsiveness; AP-1: activator protein-1; ARNT: aryl hydrocarbon receptor nuclear translocator; BALF: bronchoalveolar lavage fluid; BaP: benzo[a]pyrene; BW: bronchial wash; CCL20: chemokine (C-C motif) ligand 20; CGI: 5'-CpG island; CpG: cytosine-guanine dinucleotide; CRP: C-reactive protein; DC: dendritic cells; DE: diesel exhaust; DEP: diesel exhaust particles; DEP-OE: OE: organic extract of DEPs; Der f 1: dermatophagoides group 1 allergen; DMR: differentially methylated regions; ECAT: elemental carbon attributable to traffic; ECP: eosinophil cationic protein; ERK: extracellular signal-regulated kinase; FA: filtered air; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FOXP3: forkhead box protein 3; GM-CSF: granulocyte macrophage colony stimulating factor; GSH: reduced glutathione; GST: glutathione S transferase; HBE(C): human bronchial endothelial (cells); HDM: house dust mite; HO-1: Heme oxygenase-1; IFN: interferon; Ig: immunoglobulin; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IL: interleukin; IT: intratracheal; JNK: Jun N-terminal Kinase; KLH: keyhole limpet hemocyanin; LINE: long interspersed nucleotide elements; MAPK: mitogen-activated protein

kinase; MBP: major basic protein; MHCII: major histocompatibility complex, class II; MLN: mediastinal lymph nodes; MPO: myeloperoxidase; NAC: N-acetyl cysteine; NFkB: nuclear factor kappa-light-chain-enhancer of activated B cells; NK: natural killer; NTDE: new technology diesel exhaust; OA: oropharyngeal aspiration; OVA: ovalbumin; PAH: polycyclic aromatic hydrocarbons PDDE: particle depleted diesel exhaust; ROS: reactive oxygen species; (s)ICAM: (soluble) intercellular adhesion molecule-1; TNFα: tumor necrosis factor α; TRPA1: transient receptor potential ankyrin-1; Treg: regulatory T cells; UA: uric acid; UCWBC: umbilical cord white blood cell; VCAM: vascular cell adhesion molecule-1.

Table 3B. Studies investigating the relationship between exposure to TRAP and chronic obstructive pulmonary disease.

Human controlled exposure studies

Reference	Population/location	Exposure	Main findings
Wooding et al. 2020	Never smokers (N=7) Ex-smokers (N=4) Mild-moderate COPD patients (N=7)	Double-blind, randomized, crossover study DE: 6.0 kW generator with Yanmar diesel engine; 300 µg PM/m^3 or FA; 2 h during intermittent exercise	Reduced proportion of circulating band cells; exaggerated in COPD patients Increased peripheral neutrophil activation (> CD16, CXCR2 & activated CD11b expression) in COPD patients Increased NETs in BALF across all participants

Animal studies

Reference	Animal model	Exposure	Main findings
Amara et al. 2007	C57BL6 mice	DEP: SRM 2975; 50 µg IT or saline	Increased MMP-1 & NOX4 expression in alveolar epithelial cells
Chang et al. 2011	C57BL/6 mice	ufCB: 300 µg IT (or PBS)	Increases in neutrophils, mononuclear cells, total proteins, desmosine, hydroxyproline in BALF Significant increase in neutrophil elastase & MMP-12 activities Pulmonary infiltrations of MMP-12 positive DCs & macrophages Anti-neutrophil antibody significantly reduced neutrophil elastase activity & prevented increases in BALF desmosine & hydroxyproline
Chan et al. 2019	BALB/c mice	Traffic-related PM_{10}: 1 µg or 5 µg/day for 3 weeks by intranasal instillation (or saline)	1 µg PM_{10}: no significant effect on BALF inflammatory & mitochondrial markers 5 µg PM_{10}: • Increased BALF lymphocytes & macrophages • Increased lung inflammation (IL-1β & NLRP3) • No effect on markers of matrix remodeling (fibronection, TGF-β1, collagen III) • Reduced mitochondrial MnSOD & Opa-1 • Increased mitochondrial Drp-1 • Reduced autophagy markers LC3-II & phosphorylated-AMPK

			• Increased caspase 3

Reference	Animal model	Exposure	Main findings
He et al. 2017	Sprague-Dawley rats	Gasoline exhaust: Wuyang 1-cyclinder motorcycle engine; PM_1: 1450 µg/m^3; $PM_{2.5}$: 1460 µg/m^3; PM_{10}: 1470 µg/m^3; CO: 78.52 µg/m^3; NO_x: 956.25 µg/m^3 2x2 h/day, 5 days/week; 1, 3, 5, or 7 months	Development of pronounced COPD characterized by: • Increased BALF leukocytes by 1 month, continuing after 7 months • Elevated cytokine (MCP-1, IL-6, IFN-γ, TNF-α IL-13, IL-17, IL-1α, IL-1β, RANTES, EPO, G-CSF, MIP-3α) levels in sera & at 1, 3, 5 & 7 months • Emphysematous lesions at 7 months • Small airway remodeling at 7 months • Increased expression of MMP9 & MM12 at 7 months • Airway mucus hypersecretion at 3mo, increasing after 5 months • Lung function reduction at 7 months • Systemic inflammatory response, peaking after 1 months
Jheng et al. 2021	Sprague-Dawley rats	Traffic-related PM_1 (16.3 ± 8.2 µg/m^3) & gaseous pollutants (NO_x: 62.8 µg/m^3; O_3: 29.7 ppb) in an urban region near a major highway & expressway in New Tapai City, Taiwan; 3 or 6 months OR High-efficiency particulate air-filtered gaseous pollutants in above described urban area (GAS)	Histology & lung function 3 month PM_1 • Lung damage (increased congestion & macrophage infiltration) 6 month PM_1 • Similar signs of lung injury as those seen at 3 months plus increased thickness of airway walls, disruption of alveolar & airway integrity, immune cell accumulation • Significant decline in lung function (decreases in $FEF_{25–75\%}$ & FEV_{20}/FVC) 3 month GAS No significant changes 6 month GAS • Significant decline in lung function (decreases in $FEF_{25–75\%}$) Functional analysis of differentially expressed proteins following PM_1 & GAS Dysregulation of proteins involved in oxidative stress, cellular metabolism, calcium signalling, inflammatory responses, & actin dynamics

In vitro experiments

Reference	Cells/tissue	Exposure	Main findings
Amara et al. 2007	Alveolar human epithelial cell line (A549 & NCI-H292)	DEPs: SRM 2975; 5–10 µg/cm^2; 6 or 24 h	Increased MMP-1 mRNA, protein expression & activity No effect on TIMP-1 & -2 Increased ERK 1/2 phosphorylation & upregulation of expression & activity of NADPH oxidase analog NOX4 Cell transfection with a NOX4 small interfering RNA prevented effects
Li et al. 2009	BEAS-2B bronchial epithelia Primary HBE cells at air liquid interface	DEP: Deutz 4-cylinder engine; 100 µg/ml; 2 - 24 h	Activation of MMP-1 gene via RAS Subsequent activation of RAF-MEK-ERK1/2 mitogen-activated protein kinase signaling Role for the 1607GG polymorphism as a susceptibility factor for an accentuated response
Li et al. 2011	Primary cultures of HRE cells	DEP: Deutz 4-cylinder engine; 100 µg/ml; 30 or 60 min Organic extract: 20 µg/ml; 30 or 60 min	Organic extract component of DEP: Protracted Ca^{2+} influx via TRPV4 leading to MMP-1 activation Effects enhanced by COPD-predisposing human genetic polymorphism TRPV4P19S

Abbreviations: AMPK: AMP-activated protein kinase; BALF: bronchoalveolar lavage fluid; DCs: dendritic cells; DE: diesel exhaust; DEP: diesel exhaust particles; Drp-1: dynamin-related protein-1; FA: filtered air; HBE: human bronchial epithelial; HRE: human respiratory epithelial; IL-1β: interleukin-1β; IT: intratracheal; LC3-II: light-chain 3 microtubule-associated protein-II; MMP: matrix metalloproteases; MnSOD: manganese superoxide dismutase; NADPH: nicotinamide adenine dinucleotide phosphate; NETs: neutrophil extracellular traps; NLRP3: nucleotide-binding domain and leucine-rich repeat protein 3; Opa-1: Optic atrophy-1; TGF- β1: transforming growth factor β1; TIMP: tissue inhibitors of matrix metalloproteases; TRPV4: Transient receptor potential cation channel subfamily V member 4; ufCB: ultrafine carbon black.

Table 3C. Studies investigating the relationship between exposure to TRAP and acute lower respiratory infection.

Human controlled exposure studies

Reference	Population	Exposure	Main findings
Noah et al. 2012	Healthy volunteers (N=8) & participants with allergic rhinitis (N=9) (18-40 y)	Double-blind, randomized, placebo-controlled study DEE: 100 µg/m^3; 2 h at rest (details of generation not given) Standard intranasal dose of LAIV post exposure	DE: • IL-1β, IL-6, IL-10, IL-12p70, GM-CSF: no effect & no significant interaction with allergy • Increased IFN-γ responses; no interaction with allergy • Increased eotaxin-1, eosinophil cationic protein, influenza RNA sequences in nasal cells, linked to allergy

Animal studies

Reference	Animal model	Exposure	Main findings
Castranova et al. 2001	(1) Sprague-Dawley rats (2) Fisher 344 rats (3) Sprague-Dawley rats (4) CD-1 mice	(1) DEP (SRM 1650) or CB: 5000 µg/kg intratracheal followed by LPS (2) DEP (4 cylinder Caterpillar engine; or coal dust: 2000 µg/m^3 by inhalation) 7 h/day, 5 days/week, for 2 years followed by AM harvesting & exposure ex vivo to zymosan (3) DEP (SRM 1650); 5000 µg/kg intratracheal followed by infection with *L. monocytogenes* (4) DEP (4 cylinder Caterpillar engine; or coal dust 2000 µg/m^3) 7 h/day, 5 days/week, for 6 months followed by infection with influenza virus	(1) DEP (not CB): decreased LPS-induced TNF-α & IL-1 production from AM (2) DEP decreased the ability of AMs to produce antimicrobial ROS in response to zymosan (a fungal component); exposure to coal dust increased zymosan stimulated oxidant production (3) DEP (not CB) decreased the ability of the lungs to clear bacteria (4) DEP (not coal dust) depressed the ability of the lung to produce IFN & increased viral multiplication in the lung
Chang et al. 1986	Fisher 344 rats	(1) NO_2: 955 µg/m^3 continuously with 2, daily 1-h spikes of ~2865 to µg/m^3, 5 days/week for 6 weeks (2) NO_2: 3820 µg/m^3 continuously for 7 days/week for 6 weeks with 2, daily 1-h spikes	Increased number of AMs in the alveoli & increase in their cellular volume

		of ~11,460 µg/m^3	

Reference	Animal model	Exposure	Main findings
Ciencewicki et al. 2007	BALB/c mice	DEE: 30 kW 4-cylinder Deutz engine; 500 or 2000 µg/m^3 by inhalation; 4h/day for 5 days Followed by infection with influenza A/Bangkok/1/79	Increased susceptibility to influenza infection with 500 µg/m^3 DE (not 2000 µg /m^3 dose): • Increase in HA mRNA levels & greater immunohistochemical staining for influenza virus protein in lung • Increase in the expression of IL-6 but not antiviral lung IFN levels • Decreased expression & production of SP-A, SP-D
Fujimaki and Nohara 1994	Wistar rats & Hartley guinea pigs	NO_2: 1910, 3820 or 7640 µg/m^3 continuously for 12 weeks	No difference in the number of lung mast cells from rats & guinea pigs exposed to NO_2 Histamine, released by mast cells, was reduced in rats at 3820 µg/m^3 NO_2 & increased in guinea pigs at 7640 µg/m^3.
Gowdy et al. 2008	BALB/c mice	DEE: 30 kW 4-cylinder Deutz engine; 500 or 2000 µg/m^3 4 h/day for 1 or 5 days	Higher neutrophil numbers & lesion scoring Increased ICAM-1 Upregulation of TNF-α, MIP-2, IL-6, IFN-γ, IL-13 Decreased CCSP, SP-A, SP-D
Gowdy et al. 2010	BALB/c mice	Infection with influenza A/HongKong/8/68 & immediately exposed to DEE: 134 kW 8-cylinder 6.5 liter displacement indirect injection Detroit Diesel engine; 500 µg/m^3; 4 h/day for 14 days	Increase in viral titers & increased neutrophils & protein in BALF Increased expression & production of IL-4 Decreased expression of Th1 cytokines, IFN-γ & IL-12p40 Treatment with NAC did not affect diesel-enhanced virus titers but blocked DE-induced changes in cytokine profiles & lung inflammation
Greene and Schneider 1978	Baboons	NO_2: 3820 µg/m^3 8h/day, 5 days/week for 6 months	Pulmonary AM from 2 of 3 antigen-sensitized NO_2-exposed animals failed to respond to MIF derived from antigen-stimulated autologous lymphocytes Pulmonary AM from 3 of 4 NO_2-exposed animals had diminished responsiveness to MIF obtained by phytohemagglutinin stimulation of their own lymphocytes.
Gregory et al. 1983	Fisher 344 rats	(1) NO_2: 1910 µg/m^3 (2) NO_2: 9550 µg/m^3 (3) NO_2: 1910 µg/m^3 with 2 daily 1.5 h spikes of 9550 µg/m^3	Mild concentration-related pulmonary injury: • Histopathological evaluation: focal areas of hyperinflation & AM accumulation in some 5-ppm- & 1-5-ppm-exposed-exposed animals • Biochemical changes in BALF: elevated LDH, ALKP & GPx

		7 h/day for 5 days/week for up to 15 weeks	• Lung tissue: elevated glutathione reductase & glucose-6-phosphate dehydrogenase

Reference	Animal model	Exposure	Main findings
Harrod et al. 2003	C57Bl/6 Mice	DEE: 2000 Cummins engine; 1000 µg/m^3 by whole body inhalation; 6h/day for one week Followed by RSV infection	BALF Inflammatory cells increased in dose-dependent manner Pronounced peribronchial & peribronchiolar inflammation Increased mucous cell metaplasia Airway & alveolar host defense & immunomodulatory proteins & increased lung RSV gene expression
Harrod et al. 2005	Mice	DEE: 2000 Cummins engine; 30-1000 µg/m^3 by inhalation; 6h/day for one week Followed by *P. aeruginosa* infection	18h post infection: prior DEE impaired bacterial clearance & increased airway cell death DEE exacerbated lung histopathology during infection (decrease in ciliated & non-ciliated airway epithelial cell numbers) in a concentration-dependent manner Decrease in lung transcription regulator, TTF-1
Henry et al. 1970	Squirrel monkeys	NO_2: 9550 µg/m^3 continuously for 2 months Followed by infection with *K. pneumoniae* or influenza	Increased markers of infection, white blood cell counts & ESR 3 Increased the susceptibility of squirrel monkeys to *K. pneumoniae* - increased mortality & reduced lung clearance of viable bacteria Exposure to 5 ppm after viral infection produced death in one of 3 monkeys
Jaspers et al. 2009	Ovalbumin-sensitized C57BL/6 mice	DEP: 30 kW 4-cylinder Deutz engine; 25 µg by followed by oropharyngeal aspiration infection with influenza A/PR/8	Increased levels of eosinophils in lung lavage & tissue
Lambert et al. 2003	BALB/c mice	ufCB: 4 µg intratracheal Followed by RSV infection	Lungs of RSV + CB mice: • TNF-α reduced in BALF on days 1 & 2 of infection • Reduction in BALF lymphocytes • IP-10 reduced in BALF on day 4 of infection Day 2-4 of infection: Viral titers in RSV + CB mice were lower than RSV alone Day 7 of infection: increased neutrophils, proinflammatory cytokine mRNA expression, TNF-α, IL-13

Manzo et al. 2012	BALB/c mice	DEP: generated in 1999 by a diesel-powered automobile; 2000 µg/m^3 nose only inhalation; 4 h/day for 2 days Cytokine mixture (cytomix: TNFα, IL-1β, IFNγ) to induce a generic inflammatory state	cytomix + DEP-exposure: greater ROS production in lung phagocytes Effects largely prevented by treatment with FeTMPyP (catalyses decomposition of peroxynitrite)

Reference	**Animal model**	**Exposure**	**Main findings**
McDonald et al. 2011	C57BL/6 mice	DEE: 5.5 kW single-cylinder Yanmat generator; 2500 µg/m^3 by whole body inhalation at partial or high-load; 6h/day for 7 days followed by infection with RSV	High-load DEE caused more lung inflammation & greater susceptibility to viral infection than partial load
Yang et al. 2001	Sprague-Dawley rats	DEP (SRM 1650) or CB: 5000 µg/m^3 intratracheal Followed by *L. monocytogenes* infection	DEP (not CB): • Decreased pulmonary clearance of *Listeria* • Decreased *Listeria*-induced generation of luminol-dependent chemiluminescence by pulmonary phagocytes • Negated *Listeria*-induced production of NO by alveolar macrophages DEP or CB: • Enlarged lung-draining lymph nodes • Increased no. & percentage of CD4$^+$ & CD8$^+$ T cells
Yin et al. 2002	Brown Norway rats	DEP: SRM 1650; 50,000 & 100,000 µg/m^3 using a nose-only inhalation system; 4 h Followed by *L. monocytogenes* infection Estimated lung deposits of DEPs: 194 & 384 µg/rat for 50,000 & 100,000 µg/m^3 dose groups respectively	DEP: dose-dependent suppression of lung clearance of *Listeria*, phagocytosis & secretion of IL-1β & IL-12 by AMs; reduced BALF IL-1β & IL-12 Decreased secretion of IL-1β, IL-12 & TNF-α by AMs in response to ex vivo LPS challenge
Yin et al. 2003	Brown Norway rats	DEP: SRM 1650; 50,000 & 100,000 µg/m^3 using a nose-only inhalation system; 4 h Followed by *L. monocytogenes* infection	DEPs (100 µg/m^3) + *Listeria*: 10-fold increase occurred in pulmonary bacterial count at 3 days post infection compared with the *Listeria*-only exposure group Isolated lymphocytes: • Increase in CD4+ & CD8+ cell counts & CD8+/CD4+ ratio • Increased IL-2 responsiveness • Increased capacity in secretion of IL-2, IL-6 & IFN-γ T-cell immune response sufficient to allow rats to clear the bacteria at 7 days post infection

Yin 2004b	Brown Norway rats	DEP: SRM 2975; 20,620±1310 µg/m^3 using a nose-only inhalation system; 4h/day for 5 days Followed by *L. monocytogenes* infection	DEP exposed rats: significant increase in lung bacterial load at 3 & 7 days Repeated DEP exposure: Inhibited AM production of IL-1β, TNF-α, IL-12 Enhanced *L. monocytogenes* -induced AM production of IL-10 Suppressed T lymphocytes & CD4$^+$ & CD8$^+$ subsets Inhibited *L. monocytogenes* -induced lymphocyte secretion of IL-2 at day 7, IL-10 at d 3 & 7 & IFN-γ at d 3- 10

In vitro experiments

Reference	**Cells/tissue or Test system**	**Exposure**	**Main findings**
Castranova et al. 2001	Rat AMs	DEP (SRM 1650) or wDEP: 50 µg/ml for 2 h	DEP (but not wDEP): decreased LPS-mediated production of IL-1 &TNF-α
Ciencewicki et al. 2006	Differentiated human bronchial nasal epithelial cells A549 cells	DE_{as}: Caterpillar engine; 22 or 44 µg/cm^3 for 2 h Followed by infection with influenza A or poly(I:C) - a synthetic form of double-stranded RNA	DE_{as} + influenza or poly(I:C): significant upregulation of TLR3 expression DE_{as} + poly(I:C): • Increased expression of IL-6 (reversed by dominant-negative mutant form of TNF receptor-associated factor 6) • Increased nuclear levels of interferon regulatory factor 3 & expression of IFN-β (abated with pretreatment with wortmannin, a specific inhibitor of phosphatidylinositol 3-kinase)
Jaspers et al. 2005	Differentiated human bronchial nasal epithelial cells A549 cells	DE_{as}: Caterpillar engine; 22 or 44 µg/cm^3 (for nasal & epithelial cells) for 2 h & 6.25-25 µg/m^3 for A549 cells for 2 h Infected with influenza A/Bangkok/1/79	Enhanced susceptibility to influenza virus infection in all cell models & increased number of influenza-infected cells within 24 h post-infection Increased influenza virus attachment to respiratory epithelial cells within 2 h post-infection Oxidative stress in respiratory epithelial & addition of the antioxidant GSH-ET reversed effects of DE influenza infections
Jaguin et al. 2015	Human blood monocytes-derived macrophages incubated with IFNγ+LPS or IL-4 to obtain M1 & M2 subtypes	DEP extract: SRM 1975; 10 µg/ml; 24 h	Impaired expression of macrophagic M1 & M2 markers No overall inhibition of M1 & M2 polarization processes Activation of Nrf2 & AhR pathways & induced expression of their reference target genes Nrf2 or AhR silencing prevented DEP-related down-regulation of IL-6

			AhR silencing inhibited the down-secretion of IL-12p40 & CCL18 in M1- & M2-DEP-exposed subtypes respectively

Reference	Cells/tissue or Test system	Exposure	Main findings
Manzo et al. 2012	Murine lung epithelial (LA-4) cells	DEP: generated in 1999 by a diesel powered automobile; 25 µg/cm^2; 2 h (for flurescent end points) & 24 h (for cytotoxicity endpoints) Cytokine mixture (cytomix: TNFα, IL-1β, IFNγ) to induce a generic inflammatory state	Cytomix treatment acutely increased NO production though activation of epithelial cell iNOS Cytomix +DEP-exposed cells: greatest intracellular ROS production, redox imbalance & cytotoxicity Saline + DEP-exposed cells: effective antioxidant responses DEP effects were mediated by increased ROS & increased peroxynitrite generation Effects partially reduced by SOD supplementation or by blocking iNOS induction & largely prevented by treatment with FeTMPyP (catalyzes decomposition of peroxynitrite)
Müller et al. 2013	NK cells isolated from peripheral blood of healthy volunteers	pI:C, DEP (30 kW 4-cylinder Deutz engine): 10 µg/ml or pI:C+DEP; 18 h	pI:C & pI:C+DEP (not DEP alone) increased release of IL-1β, IL-2, IL-4, IL-8, IL-10, IL-12p70, IFN-γ & TNF-α Addition of DEP further reduced CD16, granzyme B & perforin expression & cell mediated cytotoxicity in pI:C stimulated cells
Selley et al. 2020	U937 monocyte-derived macrophage cell line	BAD or DEP (SRM 2975): 4-25 µg/ml; 24 h followed by inoculation by *S. aureus*	Decreased phagocytosis of *S. aureus* at particle concentrations as low as 4 µg/ml Phagocytic deficit recovered when challenged cells were incubated for a further 24 h in particle-free media Responses were abrogated by metal chelation using desferroxamine
Yin 2004a	AMs from rats inoculated with *Listeria monocytogenes*	DEP (SRM 2975) eDEP wDEP CB 50 µg/ml; 24 h	DEP & eDEP (wDEP or CB): increased intracellular ROS & HO-1 expression in AM Induction of ROS & HO-1 by eDEP was partially reversed by α-naphthoflavone (cytochrome P450 1A1 inhibitor) & totally blocked by NAC eDEP (not wDEP) inhibited LPS-stimulated TNF-α & IL-12 secretion & augmented production of IL-10 by AM SOD attenuated eDEP-induced HO-1 expression/activity & effect on IL-10 PYR (superoxide donor) upregulated HO-1 & IL-10 & decreased IL-12

Reference	Cells/tissue or Test system	Exposure	Main findings
Yin et al. 2007	AMs from rats inoculated with *Listeria monocytogenes*	DEP: SRM 2975; 10, 50 or 100 µg/ml; 1, 4, 16, or 24 h eDEP, wDEP, CB: 50 µg/ml; 24 h Infected with *Listeria monocytogenes*	DEP & eDEP significantly decreased the AM phagocytosis & killing of *L. monocytogenes*: • Suppressed *L. monocytogenes*-induced secretion of TNFα, IL-1β & IL-12 by AM & IL-2 & IFN-γ by lymphocytes • Augmented the AM secretion of IL-10 wDEP decreased AM phagocytosis & bacterial killing to a lesser extent CB reduced AM phagocytosis but had no significant effect on AM bactericidal activity wDEP or CB exerted little/no effect on *L. monocytogenes*-induced cytokines
Zhou and Kobzik 2007	Murine primary AMs Murine macrophage cell line, J774 A.1	CAPs: 100 µg/ml; 1 h or TiO_2 or CB or Washington urban air particle sample (SRM 1648) – concentrations not given Infected with *Streptococcus pneumoniae*	CAPs & SRM 1648 (but not TiO_2 or CB): • Increased binding of bacteria by primary AMs & J774 cells • Decreased internalization in AMs & J774 • Decreased absolute number of bacteria killed by macrophages Soluble components of CAPs mediated enhanced binding & decreased internalization of *S. pneumonia* Chelation of iron in soluble CAPs substantially reversed, while addition of iron as ferric ammonium citrate restored inhibition of phagocytosis

Abbreviations: ALKP: alkaline phosphatase; AMs: alveolar macrophages; AhR: aryl hydrocarbon receptor; BAD: brake abrasion dust; BALF: bronchoalveolar lavage fluid; CAPs; concentrated ambient particles; CCL18: chemokine (C-C motif) ligand 18; CCSP: clara secretory protein; DEE: diesel engine exhaust; DEP: diesel exhaust particles; DE_{as}: aqueous-trapped solution of DE; eDEP: organic extract of DE; ESR: erythrocyte sedimentation rate; GM-CSF: granulocyte macrophage colony stimulating factor; GPx: glutathione peroxidase; GSH-ET: glutathione-ethylester; HO-1: hemeoxygenase-1; ICAM-1: intercellular adhesion molecule 1; IFN: interferon; IL: interleukin; iNOS: inducible nitric oxide synthase; IP-10: IFN-γ-inducible protein; live attenuated influenza vaccine (LAIV); LPS: lipopolysaccharide; LDH: lactate dehydrogenase; MIF: migration inhibitory factor; MIP: macrophage inflammatory protein; NAC: N-acetylcysteine; NK: natural killer; Nrf2: nuclear factor erythroid 2-related factor 2; pI:C: polyinosinic: polycytidylic acid; PYR: pyrogallol; RSV: respiratory syncytial virus; SP: surfactant protein; ROS: reactive oxygen species; SOD: superoxide dismutase; TiO_2: titanium oxide; TNF: tumor necrosis factor; TLR: toll-like receptor; TTF-1: thyroid transcription factor; ufCB: ultrafine carbon black; wDE: washed diesel exhaust.

Table 3D. Studies describing the relationship between exposure to TRAP and cardiovascular disease.

Endothelial function — Vascular tone: Epidemiological studies with a mechanistic component			
Reference	**Population/location**	**Exposure**	**Main findings**
Levinsson et al. 2014	The INTERGENE/ADONIX (INTERplay between GENEtic susceptibility and environmental factors for the risk of chronic diseases in West Sweden/ADult-Onset asthma and exhaled Nitric oXide) study Gothenburg area, Sweden 119 AMI cases & 1310 controls (mean age 60.7 y)	Traffic-related NO_2 Mean concentrations ($\mu g/m^3$): AMI cases: 14.9 Hypertensive controls: 14.9 Non-hypertensive controls: 16.1	Air pollution significantly associated with risk of AMI: OR 1.78 (95% CI 1.04–3.03) per 10 mg/m^3 of long-term NO_2 exposure AMI risk modified (not significantly) by genetic variants in the GST genes
Mordukhovich et al. 2009	457 male participants of longitudinal NAS Study (71.16 ± 6.46 y) Boston, USA Repeated measures analysis in participants evaluated 3-5 years	Traffic-related BC particles $PM_{2.5}$ Average concentrations: BC 1.1 $\mu g/m^3$ $PM_{2.5}$ 12 $\mu g/m^3$	BC concentration associated with 1.5 mmHg increase in systolic BP [95% CI, 0.1–2.8) & 0.9 mmHg increase in diastolic BP (95% CI, 0.2–1.6) Associations strongest using a 7-day moving average No association between BP & $PM_{2.5}$ No evidence of statistical interaction between BC & genetic variants related to oxidative stress defense (*GSTM1*, *GSTP1*, *GSTT1*, *NQO1*, catalase, *HMOX-1*)

Endothelial function — Vascular tone: Real-world panel studies

Reference	Population/location	Exposure	Main findings
Pettit et al. 2015	20 non-smoking adults (46-70 y) New Jersey, USA	1.5 h drive (with or without cabin filters) in a passenger vehicle in morning rush-hour traffic on a busy roadway Mean concentrations in filtered ride (FR) versus unfiltered ride (UR) (µg/m^3) *FR* *UR* NO_2 29.2 26.5 BC 6.3 5.8 CO (ppm) 1.06 1.06	Resting plasma nitrite concentrations: Lower following unfiltered rides than filtered rides (18.3%, p=0.058) Vascular nitrite response to ischemic challenge: Following the car rides, significant nitrite increase from ischemia seen prior to rides (15.9%, p=0.017) no longer elicited in the unfiltered nor filtered condition
Zhang et al. 2016	Cohort panel study Repeated measures analysis in 93 non-smoking adults (≥ 65 y) Los Angeles metropolitan area, USA	$PM_{2.5}$, BC, NO_x, CO, O_3 Size fractionated PM ($PM_{0.18}$, $PM_{0.18\text{-}2.5}$, $PM_{2.5\text{-}10}$), PAH, hopanes, OA, OC, EC Personal exposures NO_x 53.6 µg/m^3 Ambient exposures (µg/m^3) BC 1.28 $PM_{2.5}$ 17.6 NO_x 67.7 CO 0.54 ppm	Impaired microvascular function (RHI) associated with short-term markers of primary fossil fuel combustion sources: EC, BC, CO, NO_x, PAHs & hopanes IQR increase (1.06 µg/m^3) in 5-day average BC associated with decreased RHI, −0.093 (95 % CI: −0.151 to −0.035) Degree of impairment inversely associated with OP of accumulation & ultrafine PM & transition metals

Endothelial function — Vascular tone: Human controlled exposure studies

Reference	Population	Exposure	Measurement	Main findings
Barath et al. 2010	18 healthy men (21-30 y)	Double-blind, randomized crossover study of FA & DE exposures DE (1991 Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; ≈ 250 µg PM/m^3); 1 h during intermittent exercise	6 h post exposure: bilateral forearm blood flow during unilateral intrabrachial bradykinin ACh, SNP & verapamil infusions	Dose-dependent increase in blood flow with each vasodilator DE attenuated vasodilatation to ACh (P<0.001), bradykinin (P<0.05), SNP (P<0.05) & verapamil (P<0.001)
Langrish et al. 2009	13 healthy men (21-28 y)	Double-blind, randomized crossover study of FA & DE exposures DE (1991 Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 300 µg PM/m^3); 1 h during intermittent exercise	24 h study period: Plasma ET-1, big-ET-1, BP, HR 2 h post exposure: forearm blood flow during infusion of ET-1 or ET_A receptor antagonist (BQ-123) alone or plus ET_B receptor antagonist (BQ-788)	No effect on plasma ET-1 & big-ET-1 concentrations, BP or HR ET-1 infusion increased plasma ET-1 concentrations by 58% (P< 0.01) but caused vasoconstriction only after DE (P< 0.001) DE reduced vasodilatation to isolated BQ-123 infusion (P< 0.001) but had no effect on vasodilatation to combined BQ-123 & BQ-788 administration (P>0.05)
Langrish et al. 2010	10 healthy men (25 ± 3 y)	Double-blind, randomized crossover study of FA & NO_2 exposures NO_2 (4 ppm) or FA; 1 h during intermittent exercise	4 h post exposure: bilateral forearm blood flow during unilateral intrabrachial bradykinin ACh, SNP & verapamil infusions	No differences in resting forearm blood flow after either exposure Increase in forearm blood flow with all vasodilators was similar after either exposure for all vasodilators
Lucking et al. 2011	19 healthy men (25 ± 3 y)	Randomized, double-blind, 3-way crossover design of FA, DE & DE that had passed through a particle trap DE (1991 Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 300 µg PM/m^3); 1 h during	6-8 h post exposure: bilateral forearm blood flow during unilateral intrabrachial bradykinin ACh, SNP & verapamil infusions	DE reduced vasodilatation Particle trap: Reduced DEP number (from 150 000-300 000/cm^3 to 30-300/cm^3; P<0.001) & mass (320±10 to 7.2±2.0 µg/m^3; P< 0.001) Increased vasodilatation

		intermittent exercise		
Reference	**Population**	**Exposure**	**Measurement**	**Main findings**
Mills et al. 2005	30 healthy men (20-38 y)	Double-blind, randomized crossover study of FA & DE exposures DE (1991 Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 300 µg PM/m^3); 1 h during intermittent exercise	2 & 6 h post exposure: forearm blood flow & inflammatory factors pre & during unilateral intrabrachial bradykinin, ACh, SNP, verapamil infusions	No differences in resting forearm blood flow or inflammatory markers post exposure to DE Dose-dependent increase in blood flow with each vasodilator (P<0.0001 for all) DE attenuated vasodilation to bradykinin (P<0.05), ACh (P<0.05) & SNP (P<0.001) infusions (but not with verapamil) 2 h post DE exposure, persisting at 6 h Bradykinin caused a dose-dependent increase in plasma tissue plasminogen activator (P<0.0001) that was suppressed 6 h post exposure to DE (P<0.001)
Mills et al. 2011b	16 healthy men (18-32 y)	Double-blind, randomized crossover study of FA, carbon nanoparticulate & DE exposures DE (Deutz, 4 cylinder, 2.2 L, 500 rpm; ≈300 µg PM/m^3), pure carbon nanoparticulate (4000 x10^3 particles/cm^3); 2 h during intermittent exercise	6-8 h post exposure: forearm blood flow & BP during intra-brachial bradykinin, ACh, SNP & verapamil infusions	DE increased systolic BP (145 ±4 vs. 133 ±3 mmHg, P < 0.05) & attenuated vasodilatation to bradykinin (P =0.005), ACh (P = 0.008) & (P <0.001) Pure carbon nanoparticulate or filtered DE had no effect on endothelium-dependent or -independent vasodilatation
Peretz et al. 2007	5 healthy men (20-31 y)	Double-blind, randomized, cross-over study of FA & DE DE (2002 Cummins B-series engine 5.9 L; 50 µg, 100 µg or 200 µg $PM_{2.5}$/m^3); 2 h	6 & 22 h post exposure: PBMC gene transcription	Gene expression analysis identified 1290 probe sets that were > 1.5-fold up- or down-regulated (p<0.05) following DE exposure (200 µg/m^3) Differential gene expression indicates effect on oxidative stress, inflammation & vascular homeostasis

Reference	Population	Exposure	Measurement	Main findings
Sack et al. 2016	21 healthy participants (19-47 y)	Double-blind, randomized, cross-over study of DE (2002 Cummins B-series engine 5.9 L; 200 µg/m^3 $PM_{2.5}$) or ambient air; 2 h Pretreatment with antioxidants (NAC & ascorbate)	BAd	DE resulted in a significant reduction in BAd (P=0.03) Pretreatment with antioxidants augmented DE-related vasoconstriction (P=0.001)
Törnqvist et al. 2007	15 healthy men (18-38 y)	Double-blind, randomized crossover study of FA & DE exposures DE (1991 Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 300 µg PM/m^3); 1 h during intermittent exercise	24 h post exposure: forearm blood flow, inflammatory & fibrinolytic markers pre & during unilateral intrabrachial bradykinin ACh, SNP & verapamil infusions	Resting forearm blood flow, BP & fibrinolytic markers similar 24 h post DE DE increased plasma cytokine concentrations (TNF_{α} & IL-6, $p < 0.05$ for both) & reduced ACh (p=0.01) & bradykinin (p=0.08) induced forearm vasodilatation No differences in endothelium-independent (SNP & verapamil) vasodilatation or bradykinin-induced acute plasma tissue plasminogen activator release
Wauters et al. 2013	12 healthy men (23.2 ± 0.5 y)	Double-blind, randomized crossover study of ambient air & DE exposures DE (PSA DW10 engine; 300 µg/m^3 $PM_{2.5}$); 2 h	Skin microvascular hyperemic provocative tests, including local heating & iontophoresis of Ach & SNP ROS (O_2^{*-}) production in HUVECs pre-incubated with serum from 5 of the participants	DE impaired NO-mediated endothelial vasomotor function & promoted O_2^{*-} generation in endothelial cells DE reduced Ach (but not SNP)-induced vasodilation (P<0.01) - decrease correlated to inhaled $PM_{2.5}$ (r =−0.55; P<0.01) ROS production was increased post DE (P<0.01) & correlated with total $PM_{2.5}$ inhaled

Endothelial function — Vascular tone: Animal studies

Reference	Animal model	Exposure	Main findings
Cherng et al. 2011	Sprague-Dawley rats	DE (Yanmar diesel generator; 300 µg/m^3 PM); 5 h	Impaired ACh-mediated relaxation & increased O_2^{*-} in coronary arteries of rats; signals blocked with O_2^{*-} scavenging, NOS inhibition or BH4 supplementation
Karoui et al. 2020	Wistar rats	NO_2 (9550 µg/m^3) 3 h/day, 5 days/week for 3 weeks)	Cardiac dysfunction, cardiac mitochondrial dysfunction (alteration of ATP synthesis, oxidative phosphorylation) & increase in mitochondrial ROS production, endothelial (reduced acetylcholine-induced vasodilatation)
Kodavanti et al. 2011	Wistar rats	DEP (30 kW Deutz engine; 2.1 mg/m^3); 5 h/day, 1 day/week; 16 weeks	Increased aortic (but not heart) HO−1, ET−1, ET_A, ET_B, eNOS, TF, PAI−1, tPA, vWF, MMP−2, MMP−3 & TIMP−2 Increase in *LOX-1* mRNA & LOX-1 protein not significant
Labranche et al. 2012	Normotensive Wistar or SH rats	IT DEP (SRM 2975; 0.8 mg) 3x/week; 4 weeks	Impaired ACh-induced relaxations & upregulation of p22phox in aortas of SH rats only
Li et al. 2011	Wistar rats	NO_2 (5000, 10,000 or 20,000 µg/m^3) 6 h/day; 7 days	Decreased Cu/Zn-SOD activity, increased Mn-SOD & GPx activity, increased MDA, PCO & upregulation of ET−1

Eendothelial function — Vascular tone: In vitro experiments

Reference	Cells/tissue	Exposure	Main findings
Miller et al. 2009	Isolated rat aortic rings	DEP (SRM 2975; 10–100 µg/ml)	Increased O_2^{*-} production, inhibition of endothelium dependent & NO-mediated vasodilation; effects reversed in the presence of SOD
Labranche et al. 2012	Isolated rat aortic rings	DEP (SRM 2975; 100 µg/ml)	Inhibited relaxations to ACh reversed in the presence of SOD
Lee et al. 2012	HUVEC	MEP (50-cm^3 Yamaha Cabin engine; 30 to 100 µg/ml)	MEP induced: • Adhesion between THP-1 & HUVEC in a time-& dose-dependent manner • mRNA & protein expression of VCAM-1 & ICAM-1 in HUVECs that was inhibited by NF-κB inhibitor • H_2O_2 & O_2^{*-} superoxide formation α-tocopherol inhibits MEP-induced generation of reactive oxygen intermediates & suppressed MEP-induced IκB degradation & adhesion molecules expression
Li et al. 2009	HAEC	UF DEPs (1998 Kenworth truck (11L engine; 50 µg/ml)	Dose-dependent induction of oxidative stress (increased cytosolic & mitochondrial O_2^{*-} production & expression of HO−1 via JNK activation)
Tseng et al. 2015a	HUVEC tube cells	DEP (light duty, Isuzu Automobile Company 2740 cc 4 cylinder engine; 10 &	H_2O_2 production & release of TNF-α & IL−6 suppressed by NAC through increased endogenous glutathione

		100 µg/ml)	
Reference	**Cells/tissue**	**Exposure**	**Main findings**
Tseng et al. 2015b	HUVEC tube cells	DEP (light duty, Isuzu Automobile Company 2740 cc 4 cylinder engine; 10 & 100 µg/ml)	ATP depletion, depolarization of actin cytoskeleton, inhibition of PI3K/Akt activity, induction of p53/Mdm2 feedback loop & endothelial apoptosis NAC provided substantial protection against cytotoxic effects

Abbreviations: ACh: acetylcholine; ATP: adenosine triphosphate; Akt: Protein kinase B; BH4: tetrahydrobiopterin; BAd: Brachial artery diameter; BP: blood pressure; DEP: diesel exhaust particles; eNOS: endothelial nitric oxide synthaseET-1: endothelin-1; ET_A: ET-1-endothelial receptor A; ET_B: ET-1-endothelial receptor B; FA: filtered air; GPx: glutathione peroxidase; H_2O_2: hydrogen peroxide; HAEC: human aortic endothelial cell; HR: heart rate; HO-1: hemeoxygenase-1; HUVEC: human umbilical vein endothelial cell; ICAM-1: intercellular adhesion molecule 1; IκB: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IL-6: interleukin-6; JNK: c-Jun NH2-terminal kinases; LOX-1: lectin-like oxidized low-density lipoprotein; MDA: malondialdehyde; Mdm2: Mouse double minute 2; MMP: matrix metalloprotease; MEP: motorcycle exhaust particles; NAC: N-acetylcysteine; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cell; NOS: nitric oxide synthase; OA: organic acids; OP: oxidative potential; $O_2{*}^-$:superoxide anion radical; PAH: polycylic aromatic hydrocarbon; PAI-1: plasminogen activator inhibitor-1; PBMC: peripheral blood mononuclear cells; PCO: protein carbonyl; PI13K: phosphoinositide 3-kinase; RHI: reactive hyperemia index; ROS: reactive oxygen species; SH: spontaneously hypertensive; SNP: sodium nitroprusside; SOD: superoxide dismutase; TF: tissue factor; TIMP-2: tissue inhibitor of matrix metalloprotease-2; TNF-α: tumor necrosis factor-α; tPA: tissue plasminogen activator; VCAM-1: vascular cell adhesion molecule; vWF: von Willebrand factor.

Atherosclerosis: Epidemiological studies with a mechanistic component

Reference	**Population/location**	**Exposure**	**Main findings**
Gan et al. 2014	509 healthy participants (30-65 y) of Multicultural Community Health Assessment Trial Vancouver, Canada	Living close versus living away from major roads (µg/m^3) Living close / Living away BC 3.3 / 1.2 $PM_{2.5}$ 4.27 / 4.03 NO_2 19.1 / 16.6 NO 39.0 / 24.1	No significant associations observed between total plaque area & long-term concentrations (5 year) BC, $PM_{2.5}$, NO_2, NO
Jiang et al. 2016	371 participants (45-75 y) Urban residential area, Shanghai, China	Participants divided into 4 categories: those living ≤50, 51–100, 101–200 & >200 m from major road	Participants living within 50 m to major road compared with those living more than 200 m away: • Higher HR, fasting insulin, HOMA-IR, LDL-C, IL-6, BP • Lower IL-10, NO, SOD, T-AOC
Johnson et al. 2020	2227 patients (62.9 ± 13.8 y) from Stroke Prevention and Atherosclerosis Research Centre London, Ontario, Canada	Long-term NO_2 Mean concentration: 10.31 µg/m^3	Low concentrations of NO_2 µg/m^3 associated with a significant increase in plaque (3.4 mm^2 total carotid plaque area per 1.91 µg/m^3 NO_2), exhibiting a linear dose-response NO_2 was positively associated with triglycerides, total cholesterol, ratio of low-to high-density lipoprotein cholesterol (P<0.05) Diabetes mellitus mediated the relationship between NO_2 & total carotid plaque area (P<0.05)
Madrigano et al. 2010	809 participants of longitudinal NAS cohort (21-80 y) Boston, USA	Ambient $PM_{2.5}$ & BC 24-hour average concentrations over all visits (µg/m^3) BC 0.84 $PM_{2.5}$ 10.67	BC 2 days prior to blood draw associated with increased & sVCAM-1 (4.5% increase per 1 µg/m^3, 95% CI 1.1, 8.0) Neither pollutant associated with sICAM-1 Larger effects of BC on sVCAM-1 in participants with obesity (p=0.007) & who were GSTM1 null (p=0.02)

Atherosclerosis: Occupational exposure studies

Reference	Population/location	Exposure	Main findings
Bagryantseva et al. 2010	50 bus drivers (33-63 y), 20 garage men (28-59 y) & 50 controls (24-66 y) Prague, Czech Republic	Median personal exposure for controls (C), bus drivers (BD), garage men (G) (μg/m^3): C BD G Benzene 5.1 7.9 6.8 Toluene 24 23 64 Ethylbenzene 4.1 3.8 5.8 m,p-Xylene 12 11 15.5 o-Xylene 3.4 3.4 6.2 Total PAHs* 3.91 5.35 5.70 Benzo[a]pyrene* 0.73 1.08 1.13 *in ng/m^3	8-oxodG in the urine & protein carbonyl groups in plasma significantly exceeded the control values in both exposed groups Incidence of oxidized lesions in lymphocyte DNA, correlated with exposure to benzene Oxidative damage to lipids & proteins was associated with exposure to cPAHs No striking relationship with blood LDL or HDL
Brucker et al. 2013	39 taxi drivers (44.72 ± 1.54 y) & 21 non-occupationally exposed persons (41.4 ± 3.54 y) Porto Alegre, Brazil	PAH evaluated by 1-OHP in urine & COHb in blood	Increased urinary 1-OHP levels positively correlated with pro-inflammatory cytokines but negatively correlated with CAT & GST Elevated pro-inflammatory cytokines IL-1β, IL-6, TNFα, IFNγ, biomarkers of oxidative damage & ox-LDL, ox-LDL-Ab & Hcy levels Decrease in anti-inflammatory IL-10

Atherosclerosis: Human controlled exposure studies

Reference	Population	Exposure	Main findings
Lund et al. 2011	10 healthy participants (18-40 y)	DE (Cummins engine; 100 µg PM/m^3) or clean air; 2 h on separate occasions	DE induced significant increases in plasma-soluble LOX-1 immediately after exposure, with further increases 24 h post exposure Effects correlated well with baseline circulating lipid concentrations
Channell et al. 2012	14 healthy participants (mean age 25 y)	NO_2 (955 µg/m^3) or DE (Cummins engine; 106 µg/m^3 particles, 1528 µg/m^3 NO_2; 2.8 ppm CO; 2.4 ppm hydrocarbons) for 2 h during intermittent exercise	Increased levels of sLOX-1 in plasma obtained from subjects 24 hours post-exposure with NO_2; no data for DE exposed group

Atherosclerosis: Animal studies

Reference	Animal model	Exposure	Main findings
Bai et al. 2011	ApoE-/- mice	DE (5.9-L Cummins engine; 200 µg/m^3); 6 h/day, 5 days/week for 7 weeks	Augmented plaque lipid content, cellularity, foam cell formation & smooth muscle; increased expression of plaque iNOS, CD36 & 3-NT, enhanced systemic lipid & DNA oxidation (15-F2t-IsoP & 8-oxodGuo)
Kodavanti et al. 2011	Wistar rats	DEP (30 kW Deutz engine; 2.1 mg/m^3); 5 h/day, 1 day/week; 16 weeks	Increased aortic (but not heart) HO−1, ET−1, ETA, ETB, eNOS, TF, PAI−1, tPA, vWF, MMP−2, MMP−3 & TIMP−2 Increase in *LOX-1* mRNA & LOX-1 protein not significant
Li et al. 2013	Fat fed LDLR$^{-/-}$ mice	FA or UFP collected from urban regions of LA, in close proximity to a network of major freeways: 360 µg/m^3; 5 h/day, 3days/week for 10 weeks +/- administering an apolipoprotein A-I mimetic peptide made of D-amino acids (D-4F)	Reduced plasma HDL level (P < 0.01), paraoxonase activity (P<0.01), HDL anti-oxidant capacity (P<0.05) Increased LDL oxidation, free oxidized fatty acids, triglycerides, serum amyloid A (P<0.05), TNF-α (P<0.05) 62% increase in the atherosclerotic lesion ratio of the en face aortic staining & 220% increase in the cross-sectional lesion area of the aortic sinus (P<0.001) D-4F administration significantly attenuated these changes

Reference	Animal model	Exposure	Main findings
Lund et al. 2009	ApoE-/- mice	GEE (2 1996 model 4.3L General Motors V-6 engines; 60 µg/m^3 PM); 6 h/day for 7 days	Increased production of aortic lipid peroxidation & O_2^{*-}; aortic upregulation of MMP-2, MMP-9, TIMP-2, ET-1 mediated in part through activation of ET_A
Lund et al. 2011	ApoE-/- mice	DEP (2000 Cummins 5.9L engine; 250 µg/m^3) & GEE (2 1996 model 4.3L General Motors V-6 engines; 50 µg/m^3) 6 h/day for 7 days	Mixed emissions exposure increased oxLDL, ROS, LOX-1, MMP-9, ET-1 mRNA expression, monocyte/macrophage infiltration All of above attenuated with LOX-1 antibody treatment
Miller et al. 2013	ApoE-/- mice	DEP (SRM 2975; IT 35 µg) 2x/week for 4 weeks	Increased plaque size, number, lipid rich area & frequency of buried fibrous caps; correlated with liver HO−1, NADPH-quinone oxidoreductase 1 & NFE2-related factor−2 gene expression
Soares et al. 2009	LDLR$^{-/-}$ mice	HFD plus inhalation exposure in open-top filtered (F) versus non-filtered (NF) chambers located 20 m away from the roadside, 150 m from a busy traffic intersection in downtown São Paulo; 4 months Pollutants inside the exposure chambers: F: BS: 2.18 µm/m^3; PM_{10} 2.68 µm/m^3; $PM_{2.5}$ 1.63 µm/m^3; NO_2 60.33 µm/m^3 NF: BS: 45.5 µm/m^3; PM_{10} 34.6 µm/m^3; $PM_{2.5}$ 20.4 µm/m^3; NO_2 70.5 µm/m^3	Increased susceptibility of LDL to oxidation & increased anti-oxLDL & anti-apo-B levels — even higher than in mice submitted to a HFD & non-polluted air Lipid content of atherosclerotic plaques in the aorta increased in groups with a high cholesterol diet independently of air quality but thickness of arterial wall was greater in mice fed a HFD with polluted air
Takano et al. 2004	Otsuka Long-Evans Tokushima Fatty (OLETF) rats as obese subjects Long-Evans Tokushima (LETO) rats as non obese controls.	NO_2 (306 or 1520 µg/m^3 for 32 weeks)	306 µg/m^3: elevated levels of triglycerides & decreased HDL & HDL/total cholesterol levels in OLETF rats 1520 µg/m$^{3:}$ HDL levels were also decreased after NO_2 in LETO rats, as well as the OLETF strain.
Yin et al. 2013	ApoE-/- mice	DE (Yanmar America Corp. single cylinder engine generator, 5.5 kW ; ≈ 250 µg/m^3) 2 weeks	Lipid peroxidation in plasma (8-isoprostanes, 12-hydroxyeicosatetraenoic acid, 13-hydroxyoctadecadienoic acid) & liver (MDA) associated with impaired HDL anti-oxidant capacity

Atherosclerosis: In vitro experiments

Reference	Cells/tissue	Exposure	Main findings
Cao et al. 2014	THP−1 derived human macrophages	CB (25 µg/m^3)	Increased cellular lipid load at concentrations lower than those required to trigger intracellular DCFH-DA oxidation; BSO increased CB-induced oxidants but showed no effect on particle-induced lipid accumulation
Cao et al. 2015	THP−1 derived human macrophages	DEP (SRM 2975; 10 µg/ml)	Induce lipid droplet formation at concentrations not associated with increased DCFH-DA oxidation
Channell et al. 2012	hCAECs	Plasma samples from human volunteers immediately or 24 h post exposure to: NO_2 (955 µg/m^3) or DE (Cummins engine; 106 µg/m^3 particles, 1528 µg/m^3 NO_2; 2.8 ppm CO; 2.4 ppm hydrocarbons) for 2 h 1:9 (10%) or 3:7 (30%) in media for 24 h	Plasma obtained immediately & 24 h post NO_2 exposure: increased ICAM-1 & VCAM-1 mRNA Plasma obtained immediately post NO_2 exposure elevated IL-8; no effect on MCP-1 Plasma obtained 24 h post DE exposure: increased VCAM-1 mRNA expression; no significant effects on ICAM-1, IL-8 or MCP-1

Abbreviations: 1-OHP: 1-hydroxypyrene; 3-NT: 3-nitrotyrosine; 8-oxodG: 8-oxo-7,8-dihydro-2'-deoxyguanosine; 15-F2t-IsoP: 15-F2t-isoprostane; BP: blood pressure; BSO: buthionine sulphoximine; CAT: catalase; CD36: oxoLDL receptor; COHb: carboxyhemoglobin; cPAHs: carcinogenic polycyclic aromatic hydrocarbons; DCFH-DA: dichlorodihydrofluorescein diacetate; DEP: diesel exhaust particles; eNOS: endothelial nitric oxide synthase; ET-1: endothelin-1; ET_A: ET-1-endothelial receptor A; ET_B: ET-1-endothelial receptor B; FA: filtered air; GEE: gasoline engine exhaust; GST: glutathione transferase; hCAECs: primary human coronary artery endothelial cells; Hcy: homocysteine; HDL: high density lipoprotein; HFD: high fat diet; HOMA: homeostasis model assessment of insulin resistance; HR: heart rate; IFNγ: interferon gamma; IL: interleukin; iNOS: inducible nitric oxide synthase; LDL: low density lipoprotein; LDL-C: low-density lipoprotein cholesterol; LOX-1: lectin-like oxidized low-density lipoprotein; MCP-1: monocyte chemotactic protein; MDA: malondialdehyde; MMP: matrix metalloprotease; NADPH: nicotinamide adenine dinucleotide phosphate, reduced; O_2^{*-}: superoxide anion radical; oxLDL: oxidized low-density lipoprotein; PAH: polycylic aromatic hydrocarbon; PAI-1: plasminogen activator inhibitor-1; ROS: reactive oxygen species; sVCAM-1: soluble vascular cell adhesion molecule; T-AOC: total antioxidant capacity; TF: tissue factor; TIMP-2: tissue inhibitor of matrix metalloprotease-2; TNF-α: tumor necrosis factor-α; tPA: tissue plasminogen activator; vWF: von Willebrand factor.

Thrombosis — Pro-coagulant changes: Real-world panel studies

Reference	Population/location	Exposure	Main findings
Delfino et al. 2009	Panel study of 60 participants (≥ 65 y) with coronary artery disease	Primary combustion markers (EC, BC, OC_{pri}, CO, NO_x, NO_2) 24-hour average concentrations (µg/m^3) EC 1.45 BC 1.59 OC_{pri} 4.36 CO 0.50 (ppm) NO_x 50.44 NO_2 70.99	Positive association with increased systemic inflammation & sP-selectin & decreased erythrocyte GPx1 & Cu,ZnSOD activity In many cases, associations strongest for longer-term averages out to the last 5 days & in some cases, 9 days
Strak et al. 2013	RAPTES Project – a semi-experimental design; exposing 31 volunteers (mean 22 y) for 5 h at 5 locations in the Netherlands including a continuous & stop-and-go traffic location	$PM_{2.5}$, PM_{10}, PNC, BC, OC, trace metals, sulfate, nitrate, PM OP Some average concentrations over 55 visits at urban background (UB), continuous traffic (CT) & stop-and-go traffic (SGT) sites UB CT SGT $PM_{2.5}$ 18 28 27 BC 0.63 0.88 0.65	18 h post exposure: OC, nitrate & sulfate most consistently associated with thrombotic biomarkers (fibrinogen, platelet count, tPA, vWF, PAI-1) Associations with $PM_{2.5}$, PM_{10} & OP less consistent PNC, EC, trace metals & NO_2 not associated with the biomarkers after adjusting for other pollutants
Wu S et al. 2012	Panel of 40 healthy college students relocating from suburban to urban campus in Beijing	32 $PM_{2.5}$ chemical constituents Median concentrations 24-hour average concentrations at suburban (S), Urban period 1 (U1) & Urban period 2 (U2) (µg/m^3): S U1 U2 $PM_{2.5}$ 52.8 35.9 56.6 EC 1.81 2.83 1.58 NO_x 75.82 111.35 96.26 NO_2 44.69 69.14 60.55 CO (ppm) 0.89 1.71 1.39	Positive associations between: PAI-1 & titanium, cobalt, manganese; t-PA & cadmium, selenium; vWF & aluminum. Inverse associations between: vWF & nitrate/chloride/sodium, sP-selectin & manganese. We only found weak air pollution effects on hs-CRP & tHcy.

Thrombosis — Pro-coagulant changes: Human controlled exposure studies

Reference	Population	Exposure	Measurement	Main findings
Lucking et al. 2008	20 healthy men (21-44 y)	Randomized, double-blind, 3-way crossover design DE (Deutz engine; 350 µg PM/m^3) or FA; 1 h during intermittent exercise	2 & 6 h post exposure: thrombus formation, coagulation, platelet activation & inflammatory markers	DE increased thrombus formation under low- & high-shear conditions by 24% % 19% respectively at 2 & 6 h DE increased platelet–neutrophil & platelet–monocyte aggregates by 52% & 30%, respectively, at 2 h
Lucking et al. 2011	19 healthy men (25 ± 3 y)	Randomized, double-blind, 3-way crossover design FA, DE & DE (Volvo TD40 GJE) that had passed through a particle trap; 1 h during intermittent exercise	6-8 h post exposure: bilateral forearm blood flow & fibrinolytic markers during unilateral intra-brachial agonist infusions	DE reduced vasodilatation & increased ex vivo thrombus formation Particle trap: Reduced DEP number (from 150 000-300 000/cm^3 to 30-300/cm^3; P<0.001) & mass (320±10 to 7.2±2.0 µg/m^3; P< 0.001) Increased vasodilatation, reduced thrombus formation & increased tissue-type plasminogen activator release
Mills et al. 2005	30 healthy men (20-38 y)	Double-blind, randomized, cross-over study DE (1991 Volvo TD45, 4.5 L, 4 cylinders, 680 rpm; 300 µg PM/m^3) or air; 1 h during intermittent exercise	2 & 6 h post exposure: forearm blood flow & inflammatory factors pre & during intra-brachial agonist infusions	Bradykinin caused dose-dependent increase in plasma tPA (P< 0.0001) that was suppressed 6 h after exposure to DEl (P< 0.001; area under the curve decreased by 34%)
Mills et al. 2007	20 male patients with prior myocardial infarction (mean 60 y)	Double-blind, randomized, cross-over study DE (Volvo TD45; 300 µg PM/m^3) or air; 1 h during intermittent exercise	During exposure: MI quantified by ST-segment analysis 6 h post exposure: vasomotor & fibrinolytic function assessed by intra-arterial agonist infusions	During exposure: ischemic burden detected during exercise in all participants, with greater maximum ST-segment depression during exposure to DE (P<0.05) 6 h post exposure: DE did not aggravate preexisting vasomotor dysfunction, but did reduce the acute release of endothelial t-PA (P = 0.009)

Reference	Population	Exposure	Measurement	Main findings
Pettit et al. 2012	14 healthy men (21-44 y)	DE (5.5 kW Yanmar electricity generator, with 406 cc displacement air-cooled engine; 300 µg/m^3) 60 min on 2 separate days	Prior to & 24 h post exposure: whole blood sampled & fractionated for PBMC isolation, RNA extraction & generation of cDNA followed by hybridization with Agilent Whole Human Genome (4X44K) arrays	Changes in gene expression connected with key OS & coagulation pathways

Thrombosis — Pro-coagulant changes: Animal studies

Reference	Animal model	Exposure	Main findings
Kodavanti et al. 2011	Wistar rats	DEP (SRM 2975; 2100 µg/m^3); 5 h/days, 1 d/week; 16 weeks	Increased aortic (but not heart) HO−1, ET−1, ETA, ETB, eNOS, TF, PAI−1, tPA, vWF, MMP−2, MMP−3 & TIMP−2 Increase in *LOX-1* mRN&LOX-1 protein not significant
McDonald et al. 2011	ApoE-/- mice	DEE generated from a single-cylinder diesel generator operated at partial or full load 3500 µg/m^3; 6 h/day for 3 days	At same PM mass concentration, partial load resulted in higher proportions of particle OC content & smaller particle size; vapor-phase hydrocarbon content greater at partial load Compared with high-load DEE, partial-load DEE caused greater responses in heart rate & T-wave morphology in terms of magnitude & rapidity of onset of effects
Tabor et al. 2015	Rats	DEP (SRM 2975), CB (control carbon nanoparticle), DQ12 quartz microparticles (to induce pulmonary inflammation) or saline (vehicle) by intratracheal (500 µg, except Quartz; 125 µg) or IV injection (500 µg/kg)	2, &24 h post exposure: DEP reduced the time to thrombotic occlusion, coinciding with peak of DEP-induced pulmonary inflammation (6 h) CB & DQ12 produced greater inflammation than DEP but did not alter time to thrombotic occlusion DEP produced an earlier (2 h) acceleration of thrombosis (as did CB) without pulmonary or systemic inflammation DEP reduced t-PA/PAI-1 ratio; similar effects seen with CB & DQ12 DEP but not CB or DQ12, increased platelet-monocyte aggregates
Upadhyay et al. 2014	Aged SH rats	Ultrafine carbon particle (180 µg/m^3); 24 h	Pulmonary & systemic inflammation associated with increased pulmonary expression of HO−1 & systemic changes in fibrinogen & TF

Thrombosis – Pro-coagulant changes: In vitro experiments			
Reference	**Cells/tissue**	**Exposure**	**Main findings**
Nemmar et al. 2015	Whole blood from Tuck Ordinary mice	DEP (NIST, Gaithersburg, MD, USA; 1 µg/ml) +/- emodin (1 µg/ml)	Emodin prevented platelet aggregation in vitro in whole blood (P<0.01) & shortening of activated partial thromboplastin time (P<0.001) & prothrombin time (P<0.01) caused by DEP
Tabor et al. 2015	HUVECs	DEP (SRM 2975; 10– 150 µg/ml)	DEP inhibited t-PA & PAI-1 release

Abbreviations: Ach: acetylcholine; BALF: bronchoalveolar lavage fluid; CRP: C-reactive protein; DEE: diesel engine exhaust; DEP: diesel exhaust particles; eNOS: endothelial nitric oxide synthase; ET-1: endothelin-1; ET_A: ET-1-endothelial receptor A; ET_B: ET-1-endothelial receptor B; FA: filtered air; GPx: glutathione peroxidase; HO-1: hemeoxygenase-1; HUVEC: human umbilical vein endothelial cell; IL-1β: interleukin-1β; LOX-1: lectin-like oxidized low-density lipoprotein; MMP: matrix metalloprotease; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cell; OC_{pri}: primary organic carbon; OS: oxidative stress; OTC: l-2-oxothiazolidine-4-carboxylic acid; PAI-1: plasminogen activator inhibitor-1; PBMC: peripheral blood mononuclear cell; SBP: systemic blood pressure; SH: spontaneously hypertensive; SNP: sodium nitroprusside; SOD: superoxide dismutase; TEAC: Trolox equivalent antioxidant capacity; TF: tissue factor; TNF: tumor necrosis factor; TIMP-2: tissue inhibitor of matrix metalloprotease-2; tPA: tissue plasminogen activator; vWF: von Willebrand factor.

Heart rate variability: Epidemiological studies with a mechanistic component

Reference	Population/location	Exposure	Main findings
Baja et al. 2010	580 participants of longitudinal NAS cohort (74±6.8 y)	Traffic-related air pollution Concentration (µg/m^3) during or 10 h before ECG monitoring: During / 10 h before BC 1.08 / 0.64 NO_2 40.11 / 36.29 CO (ppm) 0.436 / 0.332	Stronger association between QT & elevated short-term exposure to BC among participants with high number of unfavorable genotypes related to oxidative stress, as well as in nonsmokers, obese individuals or diabetics

Heart rate variability: Human controlled exposure studies

Reference	Population	Exposure	Measurement	Main findings
Mills et al. 2011a	32 healthy men (20-38 y) 20 patients with prior myocardial infarction (51-67 y)	Double-blind, randomized cross-over study DE (Volvo TD45, 4.5L, 4 cylinders, 680 rpm; 300 µg PM/m^3) or air; 1 h during intermittent exercise	Heart rhythm & HRV during & for 24 h after the exposure using continuous ambulatory electrocardiography	No significant arrhythmias occurred during or following exposures. Diesel exhaust did not affect HRV compared with filtered air

Heart rate variability: Real-world panel studies

Reference	Population	Exposure	Main findings
Hemmingsen et al. 2015	Controlled exposure; 60 overweight middle-aged, elderly adults (55-83 y)	Crossover study Chamber exposure to particle ($PM_{2.5}$ 24 µg/m^3) or filtered ($PM_{2.5}$ 3 µg/m^3) air from a busy street for 5 h	Reduced HRV & vasomotor dysfunction post sham filtered exposure; effects not associated with OS biomarkers (dihydrobiopterin, biopterin, uric acid, ascorbic acid, dehydroascorbate)
Langrish et al. 2012	98 patients with CHD (62 ± 7 y)	Open & randomized crossover study Prescribed walk in Central Beijing with & without a facemask Ambient $PM_{2.5}$: 74 µg/m^3, containing OC & PAH & highly oxidizing, generating large amounts of free radicals	Face mask use associated with reduced maximal ST segment depression (–142 vs. –156 µV, *p*=0.046) over a 24 h period, lower mean arterial pressure (93 ± 10 vs. 96 ± 10 mm Hg, *p*=0.025), increased HRV (high-frequency power: 54 vs. 40 msec^2, *p*=0.005; high-frequency normalized power: 23.5 vs. 20.5 msec, *p*=0.001) No effect on heart rate
Sarnat et al. 2014	21 asthmatic and 21 non-asthmatic participants (mean 32.4 y)	2 h highway commute during rush hour Mean in-vehicle concentrations (µg/m^3): $PM_{2.5}$ 19.2 BC 6.6 EC 2.8 OC 19.2 PNC (particles/cm^3) 26,067 Pb-PAH (ng/m^3) 118.8	In-vehicle concentrations of BC, PNC, $PM_{2.5}$ & pb-PAHs were generally elevated during the commuting periods, relative to corresponding ambient pollutant concentrations Slight and insignificant elevation of exhaled MDA levels in participants who experienced decreases in HRV
Wu et al. 2010	11 young, healthy, highly exposed taxi drivers (mean 35.5 y)	Traffic related $PM_{2.5}$ (personal exposure) before (B), during (D) and after (A) the Beijing 20008 Olympic Games (µg/m^3): B D A $PM_{2.5}$ real time 95.4 39.5 64.0 $PM_{2.5}$ mass 105.5 45.2 80.4 NO 69.5 57.9 70.9 NO_2 336.4 298 511.9 Average daily exposures inside taxicab	SDNN intervals decreased by 2.2% (95% CI, -3.8% to -0.6%) with IQR; 69.5 µg/m^3 increase in 30-min $PM_{2.5}$ moving average Low-frequency & high-frequency powers decreased by 4.2% (95% CI, -9.0 to 0.8) & 6.2% (95% CI, -10.7 to -1.5), respectively, in association with IQR increase in the 2 h $PM_{2.5}$ moving average

Heart rate variability: Animal studies

Reference	Animal model	Exposure	Main findings
Hazari et al. 2011	SH rats implanted with radiotelemeters	DE: Yanmar diesel generator; 500 µg/m^3 (high) or 150 µg/m^3 (low) or fDE, or FA; 4 h +/- TRPA1 antagonist or sympathetic blockade	DE or fDE: prolonged ventricular depolarization & shortened repolarization periods DE: development of arrhythmia at lower doses of aconitine; the dose was even lower in rats exposed to fDE Pretreatment of low DE–exposed rats with a TRPA1 antagonist or sympathetic blockade prevented heightened sensitivity to arrhythmia
Kim et al. 2012	Sprague–Dawley rats	DEP (SRM 1650b; intratracheal, 200 µg) for 30 min & perfused rat hearts (12.5 µg/ml for 20 min)	Action potential duration prolongation, early after depolarization & ventricular arrhythmia — all prevented by pretreatment with NAC as well as active $Ca^{2+/}$ calmodulin-dependent protein kinase II blockade
Robertson et al. 2014	Wistar rats	DEP (SRM 2975; intratracheal, 500 µg) 6 h post intratracheal, myocardial ischemia & reperfusion +/- antagonist of vanilloid receptor TRPV1 (AMG 9810) +/- systemic β1 adrenoreceptor antagonism with metoprolol	Oxidant stress of heart perfusate before I/R, increased vulnerability to ischemia-associated arrhythmia Rats instilled with DE more prone to likelihood of arrhythmia associated death Myocardial oxidant radical production, tissue apoptosis & necrosis increased prior to ischemia, in the absence of recruited inflammatory cells Area of infarction more than twice as large in DE exposed rats AMG 9810 prevented enhancement arrhythmia, basal & reperfusion-induced myocardial injury Systemic β1 adrenoreceptor antagonism blocked enhancement of myocardial oxidative stress & reperfusion injury

Abbreviations: DEP: diesel exhaust particles; fDE: filtered diesel exhaust; HRV: heart rate variability; I/R: ischemia and reperfusion; MDA: malondialdehyde; NAC: N-acetylcysteine; PAH: polycylic aromatic hydrocarbon; SDNN: standard deviation of normal-to-normal; SH: spontaneously hypertensive.

Table 3E. Studies investigating the relationship between exposure to TRAP and metabolic disorders.

Insulin resistance — Glucose homeostasis			
Reference	**Animal model**	**Exposure**	**Main findings**
Chen et al. 2017	Pregnant C57BL/6 mice plus offspring	DEP: SRM 2975; 20 µg IT (representing an average daily dose of 8.6 µg/mouse & ~ equating to inhalational exposure to 160 µg/m^3 $PM_{2.5}$) or saline 3 times/week from 5 weeks of age until offspring were weaned	Effects of prenatal exposure on offspring: • No effect on birth weight; reduced body weight from postnatal week 2 • Reduced food intake; no effect on BAT morphology; decreased hypothalamic expression of an orexigenic NPY • Increased mass of epididymal adipose tissue Effects of postnatal mothering by DEP-exposed dams on offspring: • Increased body weight & fat accumulation • Decreased UCP1 expression in BAT • No change in food intake
Chen et al. 2018	Pregnant C57BL/6 mice plus offspring	DEP: SRM 2975; 20 µg IT (representing an average daily dose of 8.6 µg/mouse & ~ equating to inhalational exposure to 160 µg/m^3 $PM_{2.5}$) or saline 3 times/week from 5 weeks of age until offspring were weaned	Effects of prenatal exposure on adult male offspring: • No effect on glucose homeostasis • No effect on function/morphology of pancreatic β cells Effects of postnatal mothering by DEP-exposed dams on adult male offspring: • Impaired glucose intolerance • No effect on IR • Decreased GIIS • Decreased pancreatic insulin content & β cell area
Miranda et al. 2018	Pregnant Wistar rats plus offspring	PM_{10} (50 µg PM/day by gavage; day 7 pregnancy until last day of lactation) PM collected from an urban area where traffic was dense during pregnancy & lactation	Male offspring at 21 & 90 days of age: • Unchanged blood glucose levels • 2.5 & 2-fold increase in insulin levels at 21 & 90 days of age respectively • Increased HOMA-IR & HOMA-β • Increase in number, islet area & insulin immunodensity of pancreatic islets

Reference	Animal model	Exposure	Main findings
Yan et al. 2011	Normal chow diet and high fat diet male Sprague-Dawley rats (to produce an obese model with IR)	250 µg $PM_{2.5}$ or saline (n=6 per group) IT once a week for 3 weeks PM collected from the centre of Taipei's metropolis — particulate properties represented typical urban, traffic-oriented ambient particles	High fat diet rats: significantly increased fasting insulin levels, significantly elevated HOMA-IR but no effect on blood glucose; no effect on normal chow diet rats All rats: • No significant PM effect on total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides. • Significant increase in blood fibrinogen levels • No significant PM effect on WBC, total NO production indicator or CRP

Inflammation

Reference	Population/animal model	Exposure	Main findings
Pan et al. 2019	C57BL/6 mice	Concentrated $PM_{2.5}$ (324.2±45.2 µg/m^3) or FA (17.3±3.7 µg/m^3) using Shanghai-METAS located (where ambient $PM_{2.5}$ mostly comes from traffic exhausts) for 12 weeks	Impairments of glucose tolerance, insulin resistance, lipid metabolism disorders & disturbances of energy metabolism Increased release of IL-6 & TNFα in lung, serum & VAT
Lucht et al. 2020	2451 participants of the Heinz Nixdorf Recall cohort study, Germany. (Mean age 58 y)	Median traffic-specific (TRAP) concentrations (µg/m^3): PM_{10}-TRAP: 3.4 $PM_{2.5}$-TRAP: 2.9 NO_2-TRAP: 23.8	PM_{10}-TRAP, $PM_{2.5}$-TRAP & NO_2-TRAP all associated with diabetes risk Potential mediation of the association observed for adiponectin but not for hsCRP & IL-1RA
Wei et al. 2016	Pregnant Sprague-Dawley rats plus offspring	Beijing air (2 km away from northwestern fourth Ring Road, Beijing — a major artery of the city carrying ~ 220,000 vehicles/day Unfiltered chamber: $PM_{2.5}$ 73.5±61.3 µg/m^3 Filtered chamber: $PM_{2.5}$ 19.8±9.3 µg/m^3 From gestational day 4 until offspring 3 or 8 weeks old	Offspring: • Increased body weight at 8 weeks • Perivascular & peribronchial inflammation in lungs • Decreased blood GSH • Increased MDA & 8-isoprostane in liver, lung, spleen brain • Dyslipidemia (increased LDL, TC, TG; decreased HDL) • Decreased GLP-1 (incretin hormone) • Increased CXCL5, CCL2, IL-6, & TNF-α in epididymal fat

Fatty acid and amino acid metabolism			
Reference	**Population/animal model**	**Exposure**	**Main findings**
Chen et al. 2019	173 young adults (ages 18-23 years) from 8 Children's Health Study Californian communities	Near roadway air pollution (NRAP) exposure (freeway & non-freeway) during one year before study visit Mean long-term concentration estimated from individual residential history for lagged 1-year exposure level prior to study visit (µg/m^3): Freeway NRAP 9.7 Non-freeway NRAP 2.9 Total NRAP 12.6	Higher lagged one-year averaged non-freeway NRAP exposure associated with higher concentrations of glycerol & metabolites related to NEFA oxidation
Mutlu et al. 2011	C57BL/6 mice In vitro studies using cultured Caco-2 cells (a human colon adenocarcinoma cell line)	Urban PM: 200 µg/mouse or saline via Gastric Gavage PM (0.5-50 µg/cm^2) or control vehicle	Mice: • Small bowel: decreased tight junction protein (ZO-1) • Small bowel & colon: higher levels of IL-6 mRNA & reduced levels of ZO-1 mRNA • Colon: apoptosis Caco-2 cells: • Cell death & mitochondrial ROS generation • Oxidant NF-κB activation • Disruption of tight junction proteins • Increased permeability of Caco-2 monolayers

Abbreviations: BAT: brown adipose tissue; CCL2: chemokine (C-C motif) ligand 2; C-reactive protein; CXCL5: C-X-C motif chemokine 5; DEP: diesel exhaust particles; FA: filtered air; GSH: glutathione; GIIS: glucose-induced insulin secretion; HDL: high-density lipoprotein; HOMA-β: homeostasis model assessment-β-cell function; HOMA-IR: homeostasis model assessment-insulin resistance; hsCRP: high sensitivity C-reactive protein; IGM: impaired glucose metabolism; IL-1RA: interleukin 1 receptor antagonist; IL-6: interleukin-6; IR: insulin resistance; LDL: low-density lipoprotein; MDA: malondialdehyde; NEFA: non-esterified fatty acid; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NPY: neuropeptide Y; ROS: reactive oxygen species; TC: total cholesterol; TG: triglyceride TNFα: tumor necrosis factor-α; VAT: visceral adipose tissue; WBC: white blood cells.

Table 3F. Studies describing the relationship between exposure to TRAP and birth outcomes.

Altered growth, development, and function of the placenta and umbilical cord circulation: Epidemiological studies with a mechanistic component				
Reference	**Population/location**	**Exposure**	**Placentation & hemodynamic measurements**	**Main findings**
Carvalho et al. 2016	São Paulo, Brazil N=366 PROCIAR cohort	NO_2 (personally monitored; 3 times in each trimester of pregnancy) Pregnancy mean (µg/m^3): T1: 42.9 T2: 39.2 T3: 37.2	T1, T2, T3: Umbilical artery PI Middle cerebral artery PI Uterine artery PI Fetal weight	No associations
Contreras et al. 2018	Los Angeles, USA N=566 Behaviour in Pregnancy Study	NO_2 mean LUR: 43.4 µg/m^3 NO_x mean CALINE (µg/m^3): T1: 119.8 T2: 111.0 T3: 108.9	Uterine vascular resistance: RI, PI, S/D ratio Visits: 1: 18–20 w gestation 2: 28–30 w gestation 3: 35–37 w gestation	LUR NO_2 increased uterine vascular resistance indices (OR = 4.16, 95% CI: 1.73-10.02) at 3rd visit CALINE NO_x increased uterine vascular resistance indices at 3rd visit (β = 0.30, 95% CI: 0.01-0.59)
van den Hooven et al. 2012b	Generation R Study in Rotterdam, The Netherlands N=7,801	NO_2 Mean: 39.9 µg/m^3	PlGF (cord blood) sFlt-1 (cord blood) Umbilical artery PI (T2&T3) Uterine artery PI (T2&T3) Uterine artery notching (T2&T3) Placenta weight	NO_2 averaged over whole pregnancy associated with higher sFlt-1 (8.9%; 95% CI: 0.6-17.3 per 10 µg/m^3 increase in NO_2) & lower PlGF– 14.6%; 95% CI: –19.3 to –10.0) levels in cord blood NO_2 exposures not consistently associated with T2 or T3 placental resistance NO_2 exposures associated with lower placenta weight (–10.7 g; 95% CI: –19.0 to –2.4, per 10 µg/m^3 increase) in the prior 2 months but not during the prior 2 weeks or over whole pregnancy NO_2 exposures during all three time periods associated with significant reductions in birth weight (differences: –39.3; 95% CI: –69.1 to –9.6

				per 10 µg/m^3 increase during total pregnancy) but not with placenta to birth weight ratio

Altered growth, development and function of the placenta and umbilical cord circulation: Animal studies

Reference	**Animal model**	**Exposure**	**Main findings**
Valentino et al. 2016	Rabbits	1000 µg/m^3 filtered DE (25KVA Loxam engine) for 2 h/day, 5 days/week for 20 days of a 31-day gestation or clean air	Reduced placental efficiency (fetal/placental weight), placental blood flow & fetal vessel volume Increased volume of maternal blood space Mid gestation: decreased head length & umbilical pulse Near term, reduced fetal head length & plasma insulin & IGF1 concentrations
Veras et al. 2008	BALB/c mice	Unfiltered São Paulo ambient air (mean $PM_{2.5}$ 27.5 µg/m^3) or filtered air (6.5 µg/m^3) throughout pregnancy until 18th day of gestation	Reduced volumes, calibers & surface areas of maternal blood spaces Greater fetal capillary surfaces & diffusive conductances Significant reduction in fetal weight
Veras et al. 2012	BALB/c mice	Unfiltered São Paulo ambient air (mean $PM_{2.5}$ 32.8 µg/m^3 or filtered air (6.4 µg/m^3) throughout mating & pregnancy	Umbilical cords of mice from non-filtered chambers 22% smaller in volume due to 28% loss of mucoid connective tissue & 60% decrease in volume of collagen
Weldy et al. 2014	C57BL/6 mice	DE (single cylinder Yanmar engine; ~300 µg/m^3 $PM_{2.5}$, 6 h/day, 5 days/week) or filtered air from embryonic day 0.5 to 17.5	Embryo resorption No effect on fetal weight Reduced placental weight Placental injury

Oxidative stress — Epidemiological studies with a mechanistic component

Reference	**Population/location**	**Exposure**	**Biomarker (sample)**	**Main findings**
Clemente et al. 2016	Belgium & Spain ENVIRONAGE: N=550 INMA: N=376	NO_2 ENVIR*ON*AGE: mean 21.1 µg/m^3 INMA: mean 25.5 µg/m^3 ENVIR*ON*AGE + INMA: mean 22.7 µg/m^3	mtDNA content (placenta)	10 µg/m^3 increment in average NO_2 exposure during pregnancy associated with a 4.9% decrease in placental mtDNA content & 48 g decrease in birth weight. Placental mtDNA content positively & significantly associated with birth weight
Janssen et al. 2012	ENVIRONAGE Genk, Belgium N=174	Residential distance to major road	mtDNA content (placenta & cord blood)	Each doubling in residential distance to major roads associated with 4% increase in placental mtDNA content (95% CI: 0.4-7.8, p=0.03) No association between cord blood mtDNA content & distance to major roads
Saenen et al. 2016	ENVIRONAGE Genk, Belgium N=330	NO_2 Mean: 20.5 µg/m^3 BC Mean: 0.97 µg/m^3	3-NTp (placenta)	No association between NO_2 exposure during pregnancy & placental 3-NTp Placental 3-NTp levels increased by 13.9% for each IQR increment in entire pregnancy BC exposure. Result mainly driven by the first-trimester exposure window No significant associations between placental 3-NT & birth weight or birth length

Oxidative stress – Animal studies

Reference	Animal model	Exposure conditions (concentration, time)	Biomarker (sample)	Main findings
Veras et al. 2012	BALB/c mice	Unfiltered São Paulo ambient air (mean $PM_{2.5}$ 32.8 µg/m^3 or filtered air (6.4 µg/m^3) throughout mating & pregnancy	15-F2t-IsoP ET_AR & ET_BR (umbilical vessels)	Greater volumes of regions immunostained for 15-F2t-IsoP, ET_AR & ET_BR.
Weldy et al. 2014	C57BL/6 mice	DE (single cylinder Yanmar engine; ~300 µg/m^3 $PM_{2.5}$, 6 h/day, 5 days/week) or filtered air from embryonic day 0.5 to 17.5	3-NT (placenta)	Elevated 3-NT protein modification, predominantly within perivascular regions in the foetal labyrinth layer

Inflammation – Epidemiological studies with a mechanistic component

Reference	Population/ location	Exposure	Sample & collection time	Biomarker	Main findings
Lee et al. 2011	Prenatal Exposures and Preeclampsia Prevention Study Allegheny County, PA, USA N=1,696	NO_2 0-7 days before blood collection: 35.91 µg/m^3	Maternal blood (before 11 weeks of pregnancy)	hs CRP	No association
van den Hooven et al. 2012a	Generation R Study in Rotterdam, the Netherlands N=6,508	NO_2 Mean: 39.9 µg/m^3	Maternal blood (median, 13.2 weeks of pregnancy) Cord blood (N=4,450)	hs CRP	NO_2 exposure not associated with elevated maternal CRP levels Higher total pregnancy NO_2 exposure levels associated with elevated fetal CRP levels at delivery

Inflammation – Animal studies			
Reference	**Animal model**	**Exposure**	**Main findings**
de Melo et al. 2015	Wistar rats	Filtered air or CAPs, 600 µg/m^3 $PM_{2.5}$; 5x/week during the 3 weeks before pregnancy &/or once per day (30-90 min), 7 days a week during pregnancy, starting on the 6th day of gestation CAPs collected from urban areas of São Paolo where vehicular emissions are the most relevant source $PM_{2.5}$	IL-4 content elevated in the fetal portion of the placenta (but not in serum) No differences observed for placental or serum IL-1β, IL-4, IL-6, IL-10, INF-γ, TNF-α, TLR4
Fujimoto et al. 2005	BALB/c mice	300-3000 µg/m^3 DEP (Isuzu Motor Co); from 2 until 13 days post coitum; 12 h/day, 7 days/week	Elevation in mRNA levels of IL-1β, IL-2α, IL-2β, IL-5, IL-6 & TNF-α & other inflammatory markers in placenta of mice at day 14 post coitum
Weldy et al. 2014	C57BL/6 mice	DE (single cylinder Yanmar engine; ~300 µg/m^3 $PM_{2.5}$, 6 h/day, 5 days/week) or filtered air from embryonic day 0.5 to 17.5	Increased CD45+ cells within the decidua layer in placentas

DNA methylation: Epidemiological studies with a mechanistic component

Reference	Population/location	Exposure	Sample	Main findings
Gruzieva et al. 2017	Meta-analysis of 4 North American & European studies N=1,508 MeDALL (pooled cohort from INMA Spain, EDEN France, BAMSE Sweden and PIAMA the Netherlands) Generation R Study (the Netherlands) CHS (USA) MoBa (Norway)	NO_2 Percentiles 25th, 50th, 75th (minimum-maximum) µg/m^3: MeDALL pooled: 19.0, 37.4, 47.1 (9.0-89.9) Generation R: 36.0, 38.7, 41.8 (28.6-55.9) CHS: 23.0, 32.1, 41.8 (7.5-51.0) MoBa: 7.5, 10.3, 12.9 (0.01-27.6)	Cord blood	Associations between NO_2 exposure & DNA for 3 CpG sites in genes involved in mitochondrial function (cg12283362 [LONP1], cg24172570 [3.8 kbp upstream of HIBADH], cg08973675 [SLC25A28]) & antioxidant defense pathways (CAT & TPO)
Herbstman et al. 2012	CCCEH cohort in NYC N=164	PAH Mean: 0.23 ng/m^3	Cord blood	PAH exposure associated with decreased global methylation Higher global methylation levels were positively associated with the presence of detectable BaP–DNA adducts in cord blood
Kingsley et al. 2016	RICHS cohort in USA N=471	Residential proximity to roadway Defined as living ≤ 150 m from a primary highway or primary road or ≤ 50 m from a secondary road	Placenta	Living close to major roadway associated with: • 175.9 g (95% CI:−319.4 to −32.5; p=0.016) lower birth weight • 0.82 percentage points (95% CI: −1.57 to −0.07; p=0.03) lower mean placental LINE-1 methylation levels • Differential methylation of 7 CpG sites (in N=215 sub-cohort) Additional adjustment for placental methylation did not attenuate the association between roadway proximity & birth weight

Reference	Population/location	Exposure	Sample	Main findings
Ladd-Acosta et al. 2019	EARLI (Early Autism Risk Longitudinal Investigation) in Philadelphia, Baltimore, San Francisco Bay Area, & Sacramento, USA N=175	NO_2 24-h average: 23.44 µg/m^3	Placenta Cord blood	Suggestive decrease in placental global DNA methylation in association with NO_2 exposure; no effect on global methylation in cord blood DMRs identified included those located at genes involved in immune & inflammatory responses
Maghbooli et al. 2018	A nested case-control of a birth cohort study in Tehran, Iran N=192	$PM_{2.5}$ Mean: 87.29 µg/m^3 PM_{10} Mean: 60.20 µg/m^3	Placenta	Positive correlations between PM_{10} & $PM_{2.5}$ & increased global methylation for T1 No significant association between birth outcomes & global methylation

Abbreviations: 3-NT: 3-nitrotyrosine; 15-F2t-IsoP: 15-F2t-isoprostane; BaP: BaP: benzo[a]pyrene; CAPs: concentrated ambient particles; CAT: catalase; DE: diesel exhaust; DMR: differentially methylated regions; ET_A: endothelin A receptor; ET_B: endothelin B receptor; hs CRP: high sensitivity C-reactive protein; IFN: interferon; IGE1: insulin-like growth factor 1; IL: interleukin; LINE: long interspersed nucleotide elements; mtDNA: mitochondrial DNA; PI: pulsatility index; PIGF: Placental growth factor; PAH: polycyclic aromatic hydrocarbons; RI: resistance index, S/D: systolic/diastolic; sFlt-1: soluble fms-like tyrosine kinase 1; T: trimester; TPO: thyroid peroxidase; TLR-4: toll-like receptor 4; TNF-α: tumor necrosis factor alpha.

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