cardiovascular effects of ozone evidence from clinical studies

HEALTH EFFECTS INSTITUTE ANNUAL CONFERENCE 2016

THE UNIVERSITY of EDINBURGH

PROFESSOR NICHOLAS L MILLS
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Disclosures

Funding:	British Heart Foundation Senior Clinical Research Fellowship (FS16/14/32023) and Special Project Grant (SP/12/10/29922) Health Effects Institute
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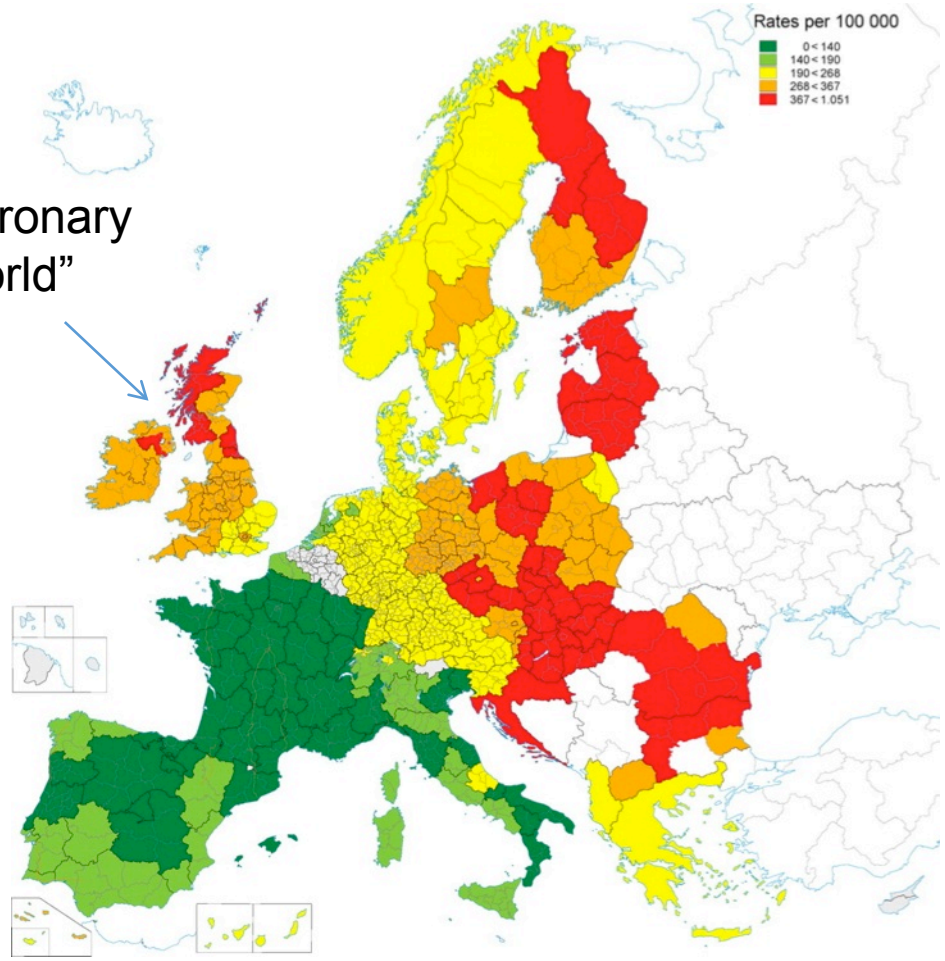
Interests:	Consultancy and speaker fees (Roche, Abbott Diagnostics, Beckman & Coulter, Singulex, GlaxoSmithKline, Sanofi-Aventis); Research grants (Abbott Diagnostics) NICE Diagnostics Advisory Committee, Scottish Inter-Collegiate Guideline Network (SIGN)

Coronary heart disease is the leading cause of death

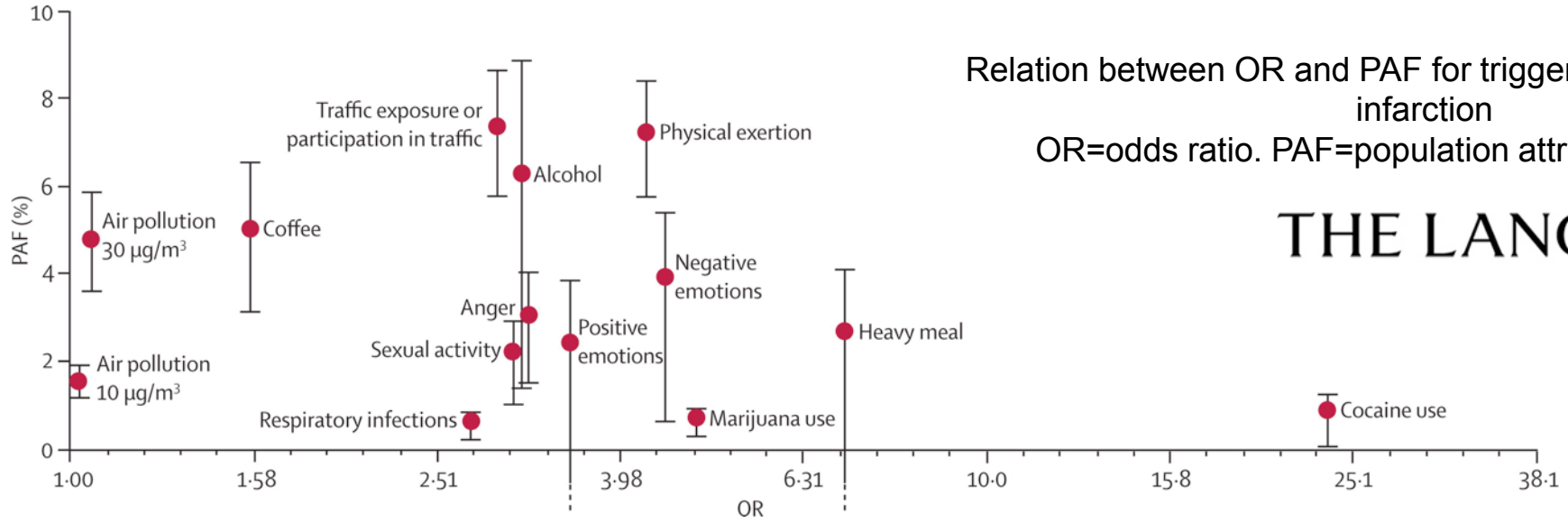
"Glasgow is the coronary capital of the world"



Age-standardized mortality from coronary heart disease in European regions

Tunsdall-Pedoe Circulation 1994;90

Triggers of acute cardiovascular events: comparative risk analysis



Relation between OR and PAF for triggers of acute myocardial infarction
OR=odds ratio. PAF=population attributable fraction.

THE LANCET

THE UNIVERSITY of EDINBURGH

The Lancet 2011;377:732–740

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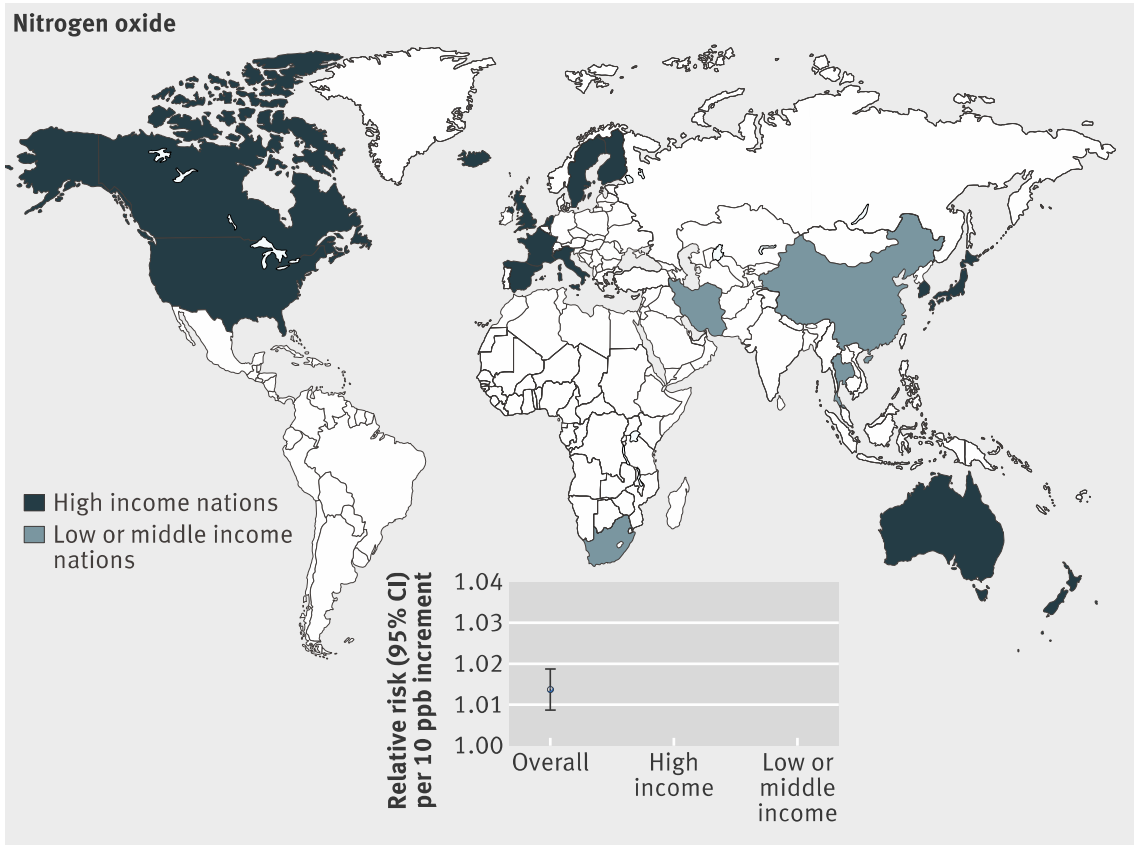
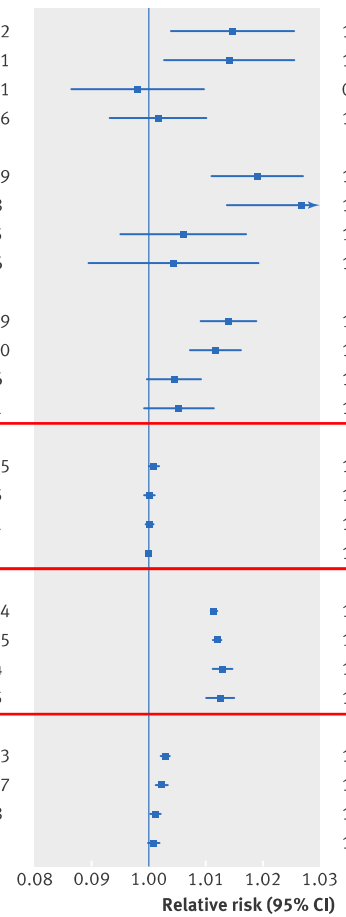
Short term exposure to air pollution and acute cardiovascular events

Systematic review and meta-analysis - stroke



	No of events	No of estimates	Relative risk (95% CI)	I^2
CO (per 1 ppm increment)				
Overall	2 010 272	2 010 272	1.015 (1.004 to 1.026)	68
Lag 0	1 719 291	1 719 291	1.014 (1.003 to 1.026)	61
Lag 1	1 488 861	1 488 861	0.998 (0.986 to 1.010)	74
Lag 2	1 515 116	1 515 116	1.002 (0.993 to 1.010)	46
SO_2 (per 10 ppb increment)				
Overall	1 791 159	1 791 159	1.019 (1.011 to 1.027)	32
Lag 0	800 628	800 628	1.027 (1.014 to 1.040)	30
Lag 1	711 955	711 955	1.006 (0.995 to 1.017)	30
Lag 2	654 676	654 676	1.004 (0.989 to 1.019)	34
NO_2 (per 10 ppb increment)				
Overall	2 012 159	2 012 159	1.014 (1.009 to 1.019)	52
Lag 0	1 175 010	1 175 010	1.012 (1.008 to 1.016)	17
Lag 1	783 556	783 556	1.004 (0.999 to 1.009)	13
Lag 2	700 551	700 551	1.005 (0.999 to 1.011)	18
O_3 (per 10 ppb increment)				
Overall	1 234 335	1 234 335	1.001 (1.000 to 1.002)	58
Lag 0	433 935	433 935	1.000 (0.999 to 1.001)	9
Lag 1	236 551	236 551	1.000 (1.000 to 1.001)	24
Lag 2	82 199	82 199	1.000 (1.000 to 1.000)	0
$PM_{2.5}$ (per 10 µg/m³ increment)				
Overall	2 476 524	2 476 524	1.011 (1.011 to 1.012)	86
Lag 0	1 963 515	1 963 515	1.012 (1.011 to 1.013)	86
Lag 1	803 394	803 394	1.013 (1.011 to 1.015)	66
Lag 2	697 365	697 365	1.013 (1.010 to 1.015)	70
PM_{10} (per 10 µg/m³ increment)				
Overall	2 607 993	2 607 993	1.011 (1.011 to 1.012)	24
Lag 0	1 405 957	1 405 957	1.012 (1.011 to 1.013)	17
Lag 1	864 448	864 448	1.013 (1.011 to 1.015)	19
Lag 2	694 772	694 772	1.013 (1.010 to 1.015)	11



ozone

$PM_{2.5}$

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Shah et al BMJ 2015

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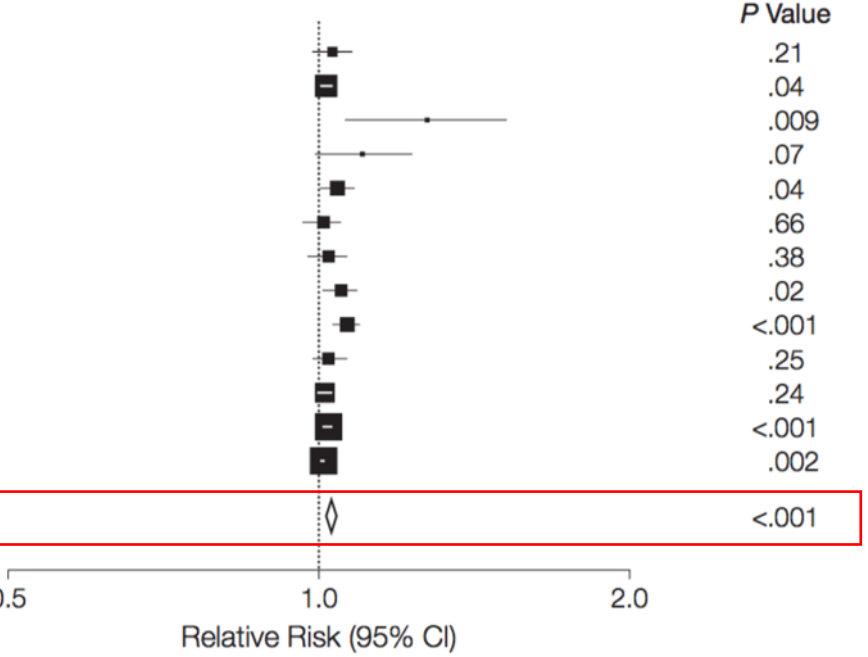
Short term exposure to air pollution and acute cardiovascular events

Systematic review and meta-analysis – myocardial infarction

$PM_{2.5}$ analysis

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Barnett et al,[9] 2006	Case-crossover	3.93	1.031 (0.983-1.082)	.21
Belleudi et al,[41] 2010	Case-crossover	13.82	1.018 (1.001-1.036)	.04
Peters et al,[20] 2001	Case-crossover	0.33	1.272 (1.061-1.525)	.009
Peters et al,[43] 2005	Case-crossover	0.89	1.105 (0.991-1.232)	.07
Pope et al,[35] 2006	Case-crossover	5.58	1.042 (1.003-1.083)	.04
Rich et al,[21] 2010	Case-crossover	4.43	1.010 (0.966-1.056)	.66
Sullivan et al,[22] 2005	Case-crossover	4.50	1.020 (0.976-1.066)	.38
Zanobetti and Schwartz,[45] 2006	Case-crossover	5.25	1.051 (1.010-1.094)	.02
Maté et al,[25] 2010	Time-series	7.26	1.066 (1.033-1.101)	<.001
Stieb et al,[28] 2009	Time-series	5.14	1.024 (0.983-1.066)	.25
Ueda et al,[38] 2009	Time-series	11.31	1.013 (0.991-1.035)	.24
Zanobetti et al,[30] 2009	Time-series	17.53	1.022 (1.011-1.034)	<.001
Zanobetti and Schwartz,[31] 2009	Time-series	20.03	1.011 (1.004-1.018)	.002
Combined (I^2 = 51%, Egger regression test, *P* = .004)			1.025 (1.015-1.036)	<.001



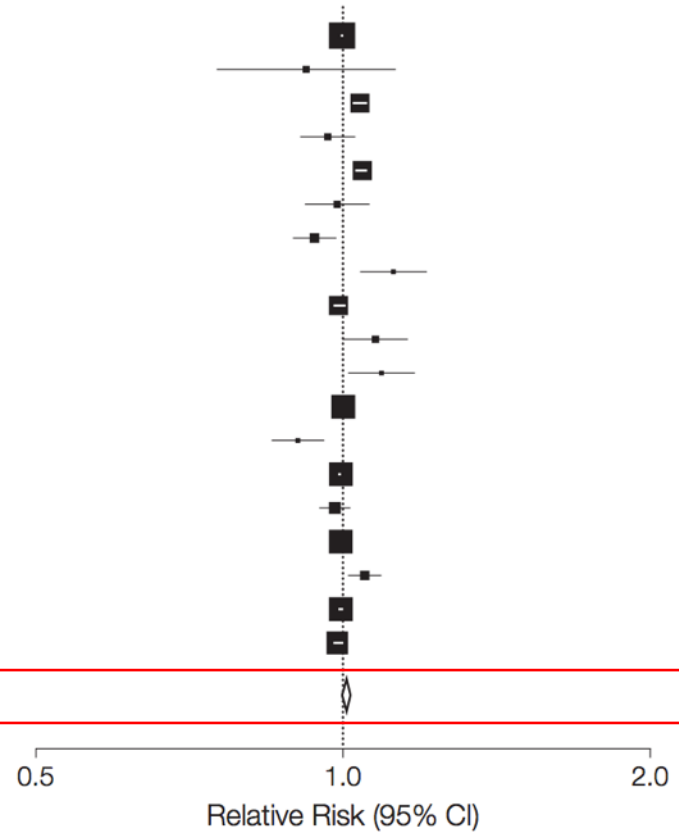
$PM_{2.5}$

Mustafic et al. JAMA. 2012

Short term exposure to air pollution and acute cardiovascular events

Systematic review and meta-analysis – myocardial infarction

Source	Study Design	Relative Study Weight, %	Relative Risk (95% CI)	*P* Value
Bhaskaran et al,[46] 2011	Case-crossover	11.44	0.999 (0.993-1.005)	.74
Berglind et al,[10] 2010	Case-crossover	0.10	0.920 (0.750-1.129)	.42
Cheng et al,[33] 2009	Case-crossover	6.84	1.042 (1.025-1.060)	<.001
Henrotin et al,[37] 2010	Case-crossover	0.97	0.967 (0.908-1.030)	.30
Hsieh et al,[34] 2010	Case-crossover	7.41	1.044 (1.028-1.060)	<.001
Peters et al,[20] 2001	Case-crossover	0.69	0.989 (0.917-1.067)	.78
Peters et al,[43] 2005	Case-crossover	1.54	0.940 (0.895-0.987)	.01
Ruidavets et al,[44] 2005	Case-crossover	0.66	1.123 (1.039-1.214)	.003
Zanobetti and Schwartz,[45] 2006	Case-crossover	7.50	0.993 (0.978-1.008)	.36
Eilstein et al,[23] 2001	Time-series	0.74	1.078 (1.002-1.159)	.04
Cendon et al,[11] 2006	Time-series	0.70	1.093 (1.014-1.178)	.02
Hoek et al,[32] 2000	Time-series	12.54	1.001 (0.999-1.003)	.33
Koken et al,[8] 2003	Time-series	1.06	0.904 (0.851-0.960)	.001
Lanki et al,[24] 2006	Time-series	10.61	0.994 (0.986-1.002)	.14
Linn et al,[12] 2000	Time-series	2.68	0.982 (0.948-1.017)	.31
Mann et al,[39] 2002	Time-series	12.35	0.996 (0.993-0.999)	.009
Medina et al,[26] 1997	Time-series	2.17	1.050 (1.009-1.093)	.02
Poloniecki et al,[27] 1997	Time-series	11.43	0.996 (0.990-1.002)	.19
Stieb et al,[28] 2009	Time-series	8.56	0.990 (0.978-1.003)	.12
Combined (I^2 = 83%, Egger regression test, *P* = .56)			1.003 (0.997-1.010)	.36



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Mustafic et al. JAMA. 2012

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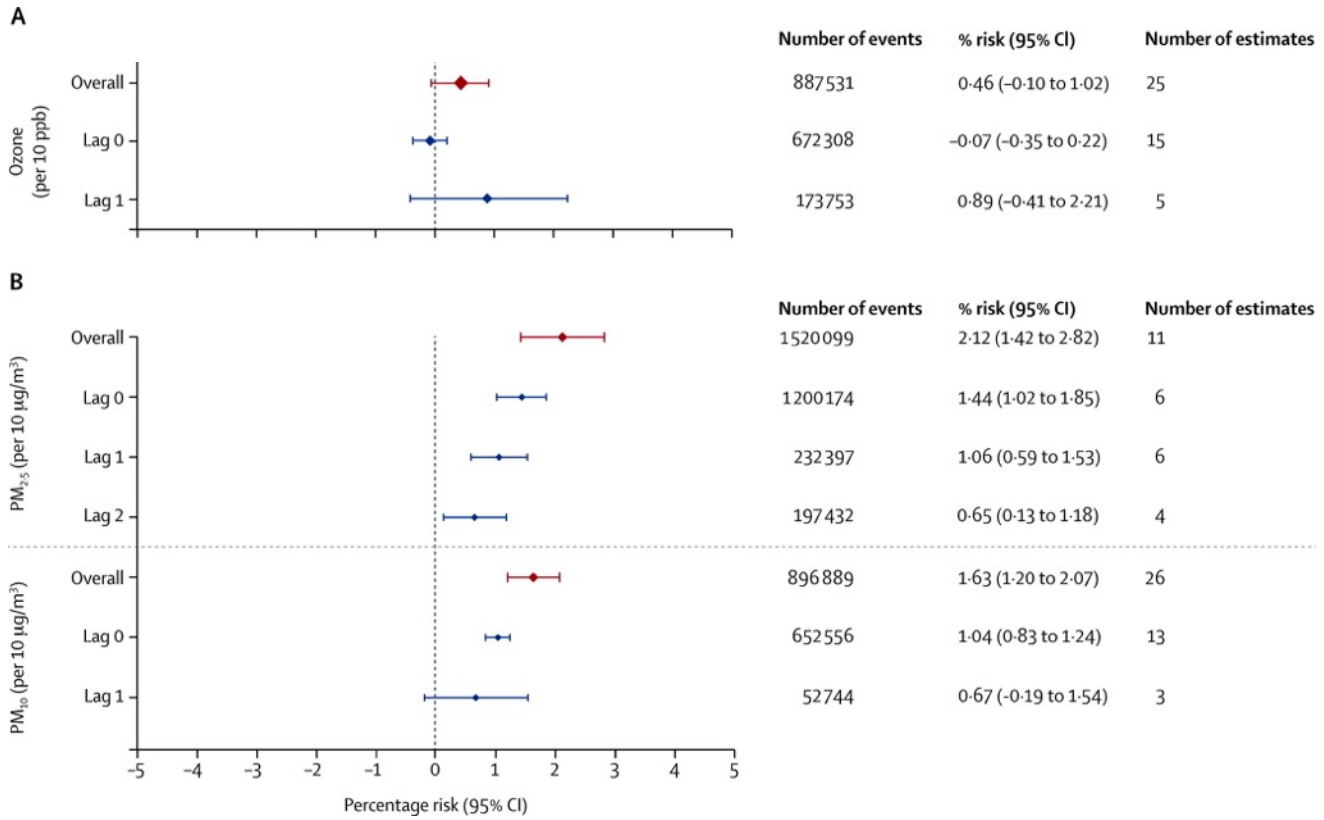
Short term exposure to air pollution and acute cardiovascular events

Systematic review and meta-analysis – heart failure

ozone

$PM_{2.5}$

PM_{10}



Particulate matter (PM) air pollution but not ozone has a close temporal association with heart failure hospitalisation and mortality

Royal College of Physicians of Edinburgh

Shah et al Lancet 2013

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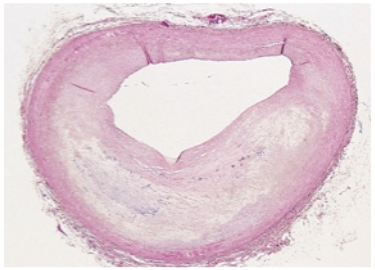
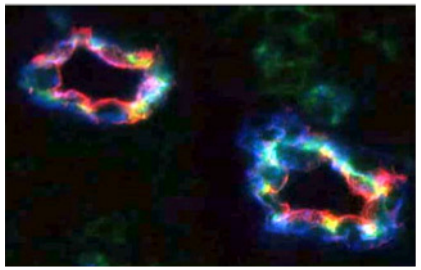
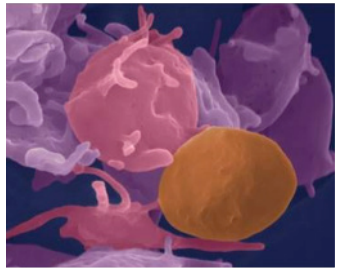
Pathophysiological mechanisms in acute cardiovascular events







Atheroma

Endothelium

Platelets

Heart rhythm

Plaque progression

Vasomotor dysfunction

Fibrinolytic imbalance

Activation and aggregation

Reduced Heart rate variability

Plaque rupture

Vasoconstriction

Thrombogenesis

Myocardial ischaemia and infarction

Arrhythmia

Cardiovascular morbidity and mortality

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Mills et al. Nat Clin Pract Cardiovasc Med 2008

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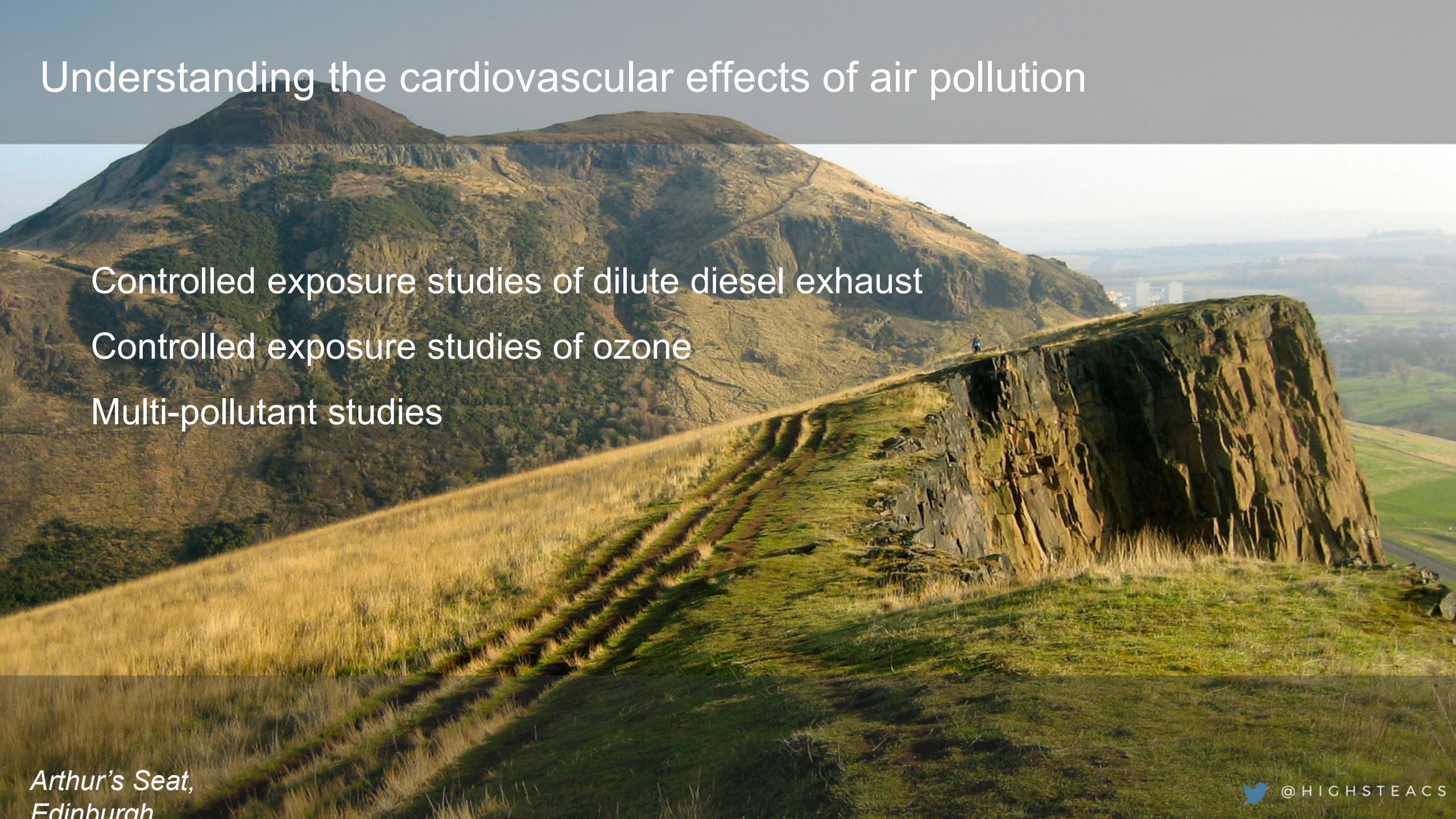
Understanding the cardiovascular effects of air pollution



Controlled exposure studies of dilute diesel exhaust

Controlled exposure studies of ozone

Multi-pollutant studies

Arthur's Seat, Edinburgh

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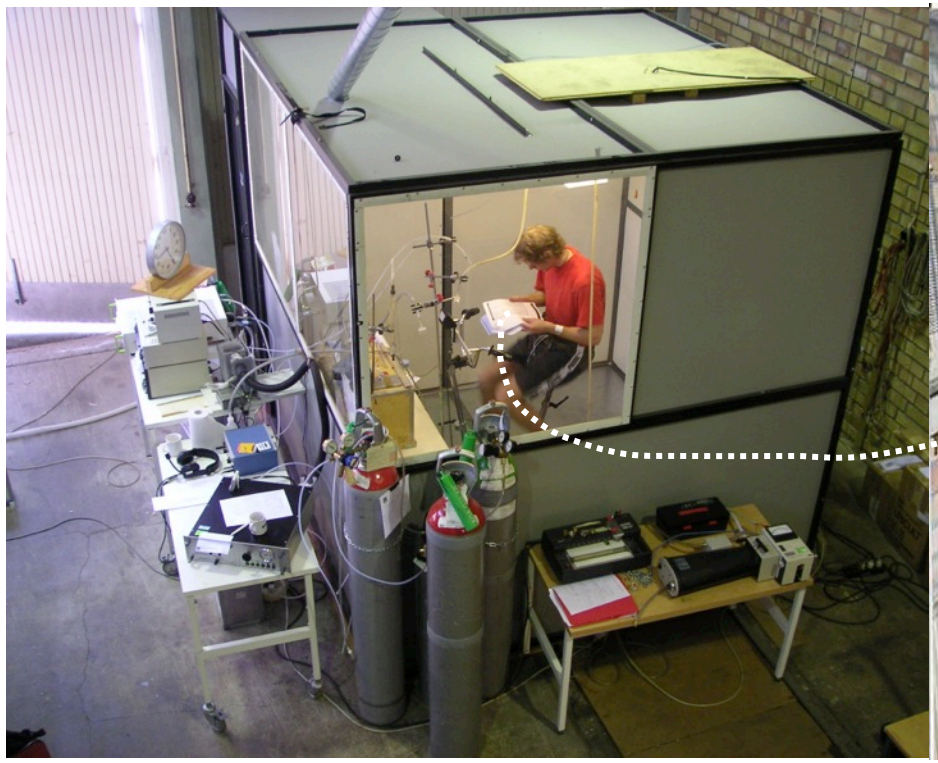
Controlled exposure studies to fresh and dilute diesel exhaust



PM concentration 300µg/m^3 (median diameter 54nm; range 20-120); particle number = 1.26±0.01x10^6 particles/cm^3; NO_x = 4.45±0.02ppm; NO_2 =1.01±0.01ppm; NO = 3.45±0.03ppm; CO = 2.9±0.1ppm; total hydrocarbon 2.8±0.1ppm

Umea University, Edinburgh University
and Washington University

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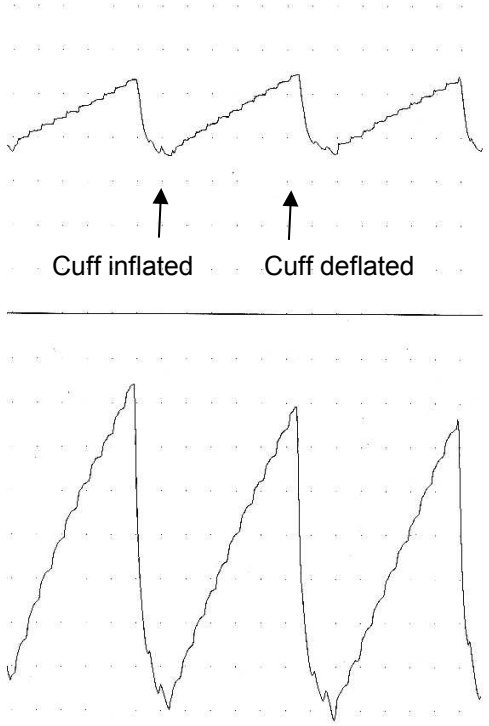
Diesel exhaust and forearm blood flow

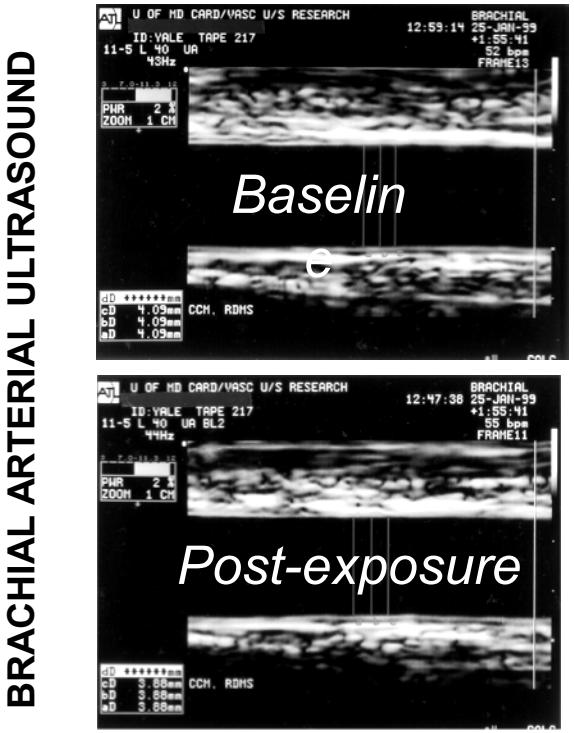
VENOUS OCCLUSION PLETHYSMOGRAPHY

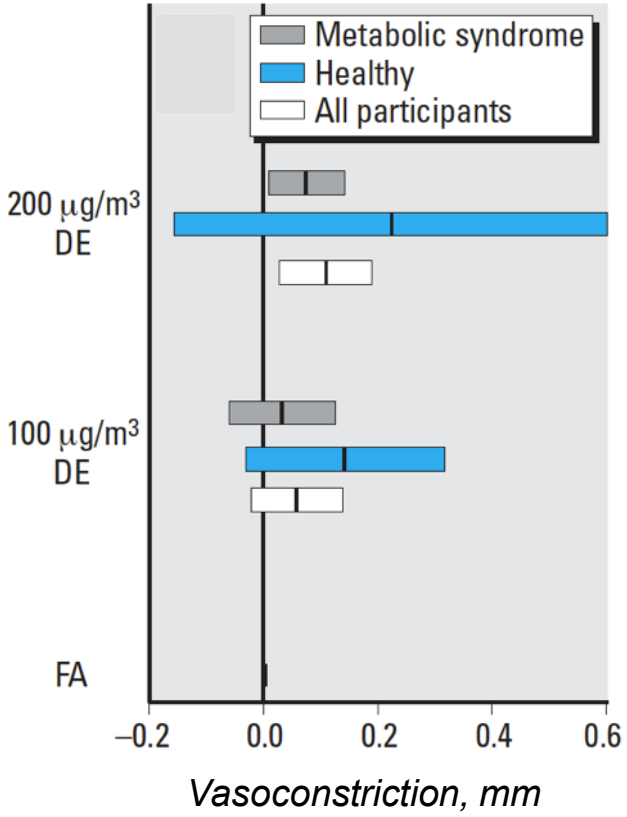


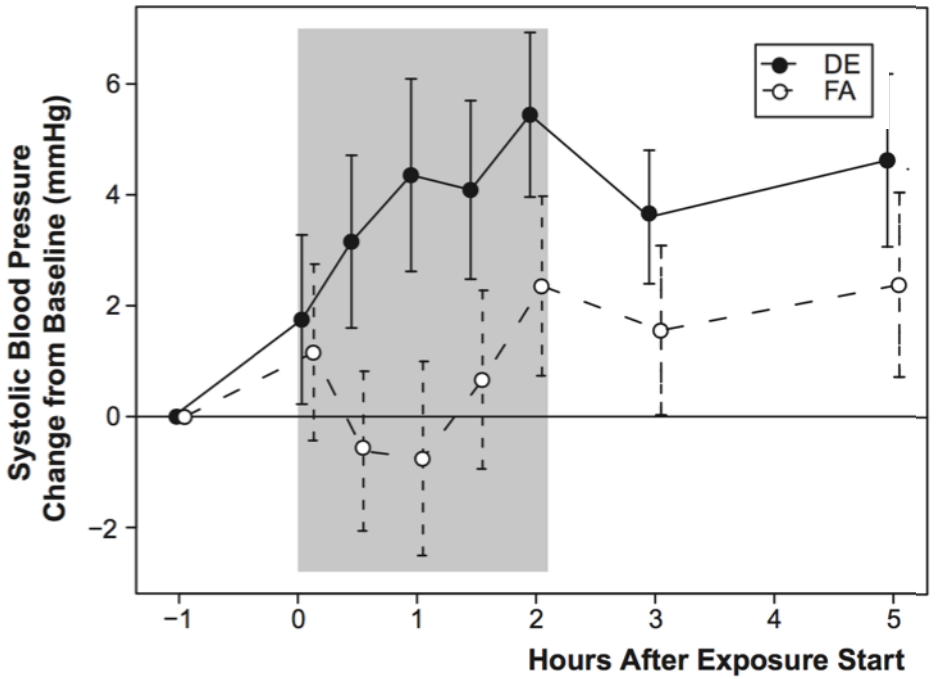
Dilatation of blood vessels in the forearm reduced following exposure to dilute diesel exhaust for one hour

Mills et al. Circulation 2005; Tornqvist et al. AJCCRM 2007

Diesel exhaust, arterial vasoconstriction and blood pressure



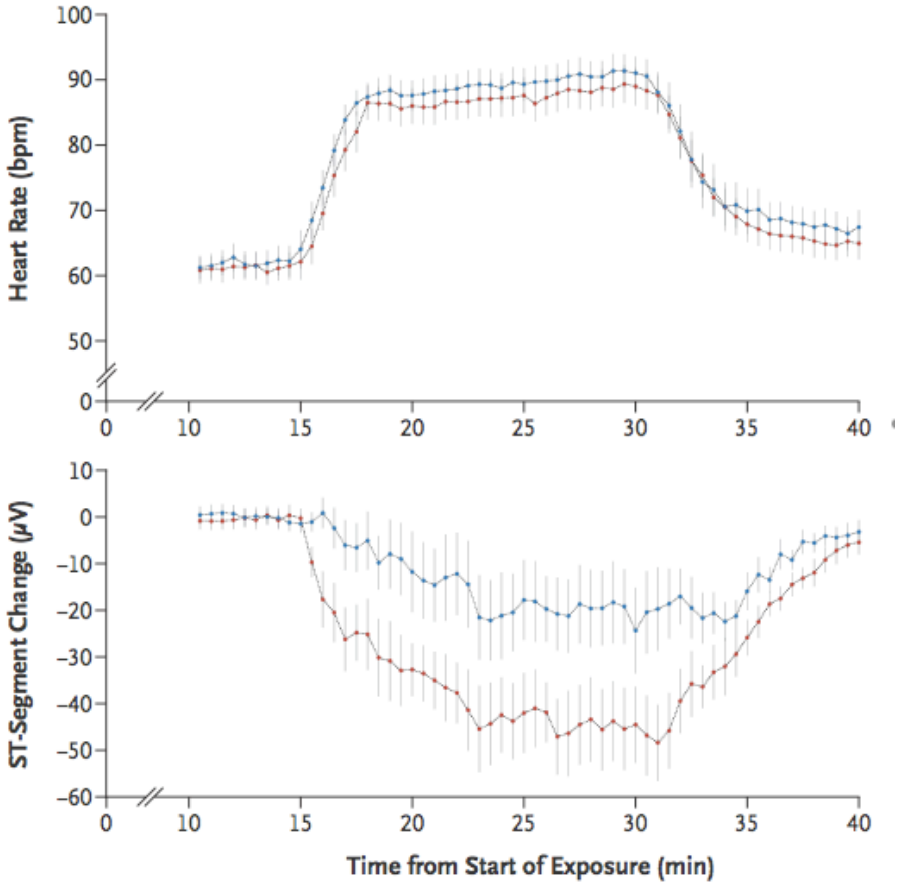


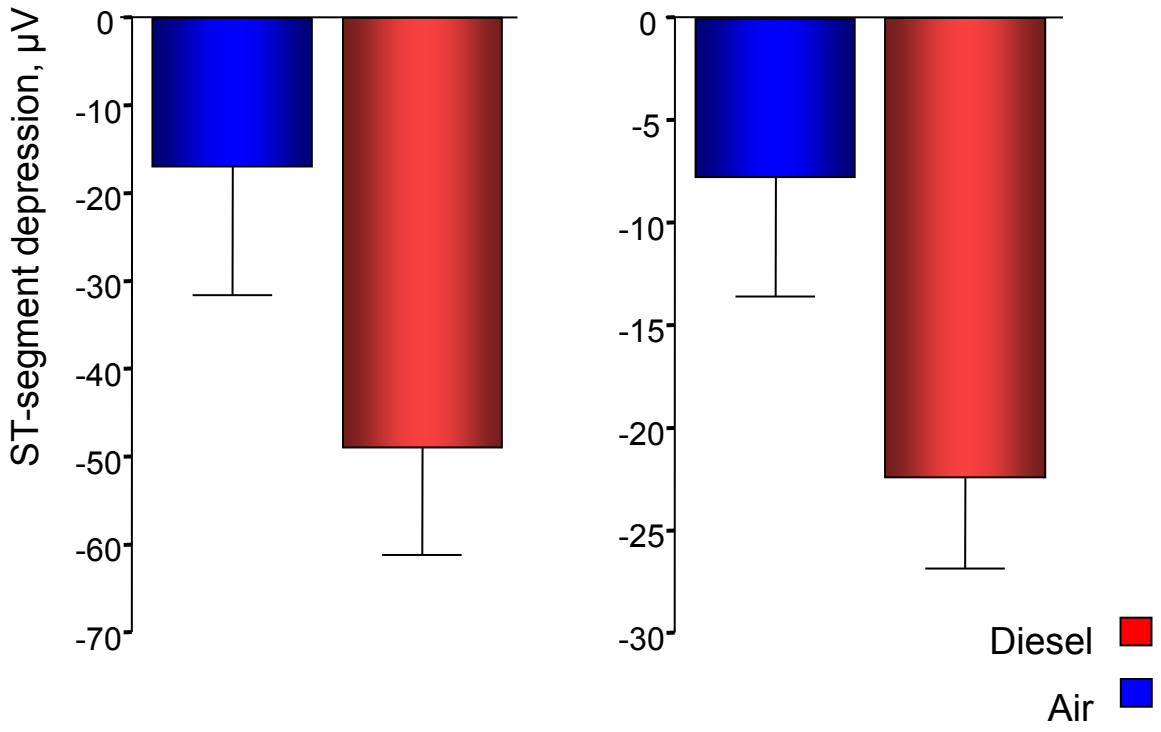


Exposure to dilute diesel exhaust is associated with acute arterial vasoconstriction and an increase in systolic blood pressure in a dose-dependent manner

Peretz A et al Environ Health Perspect. 2008;
Cosselman et al. Hypertension 2012

Diesel exhaust and exercise induced ischemia in coronary heart disease

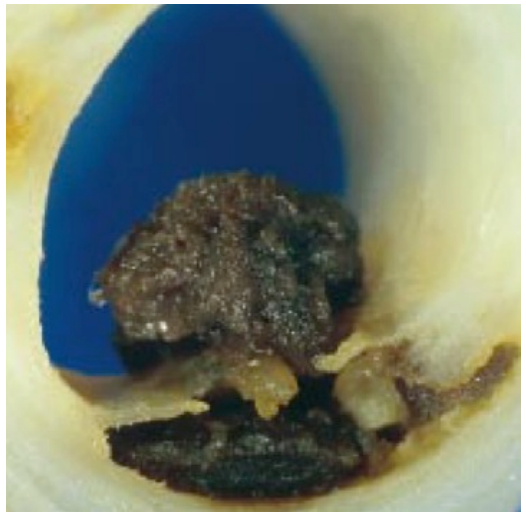


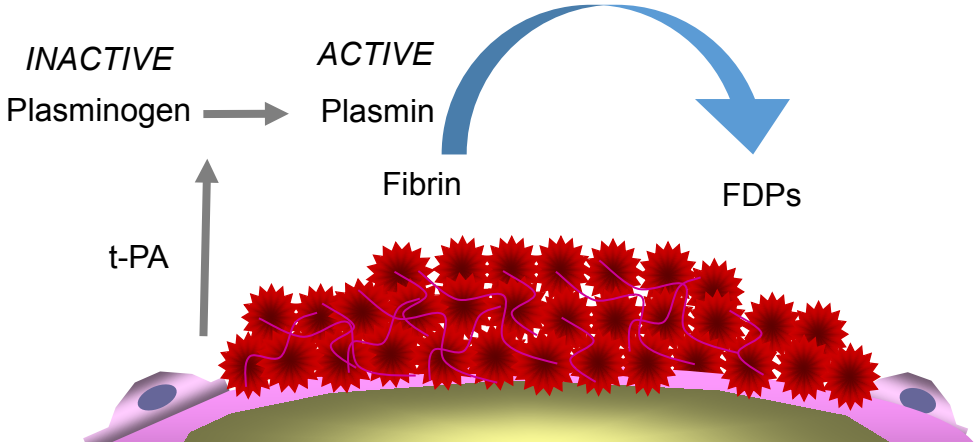


Silent myocardial ischemia is increased in patients with stable coronary heart disease exercising during exposure to dilute diesel exhaust

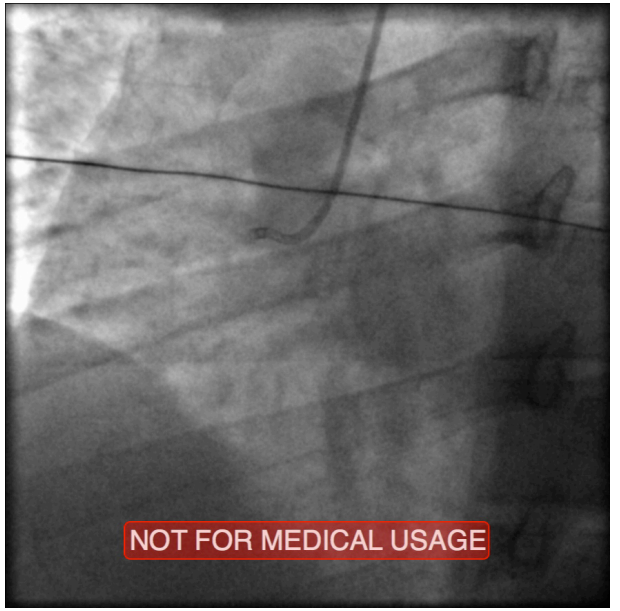
Mills et al N Eng J Med 2007

Plaque rupture, thrombus formation and lysis





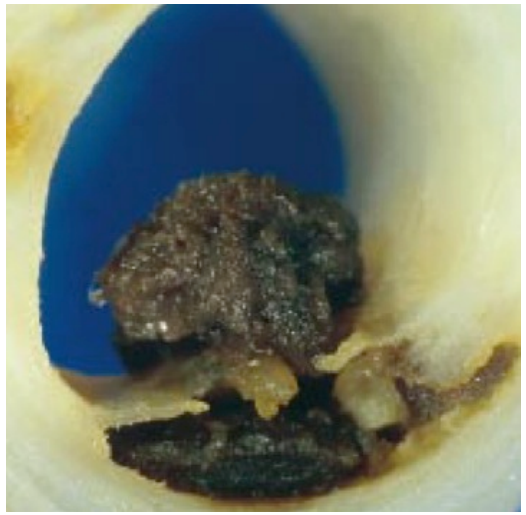
Fibrin-rich thrombus formed over area of endothelial denudation

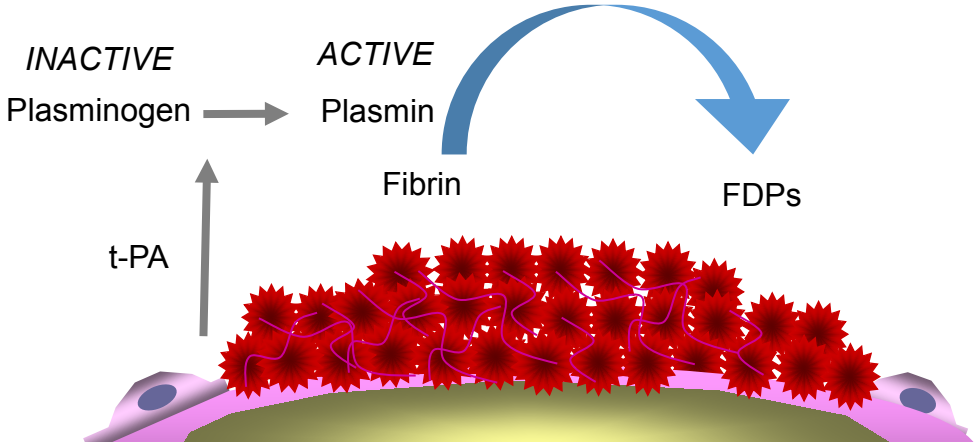


Platelet aggregation and activation occurs rapidly following plaque rupture with thrombus propagation which stimulates local tissue plasminogen activator (t-PA) release from the endothelium and initiates fibrinolysis and resolution of thrombus

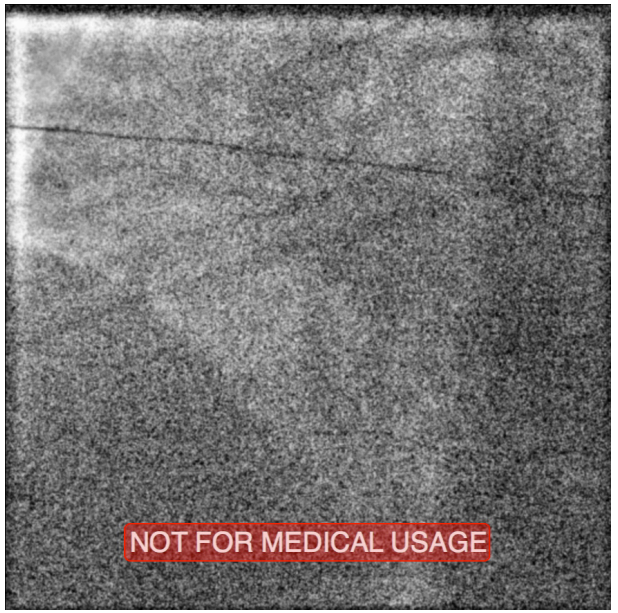
Mills et al N Eng J Med 2007

Plaque rupture, thrombus formation and lysis





Fibrin-rich thrombus formed over area of endothelial denudation



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Mills et al N Eng J Med 2007

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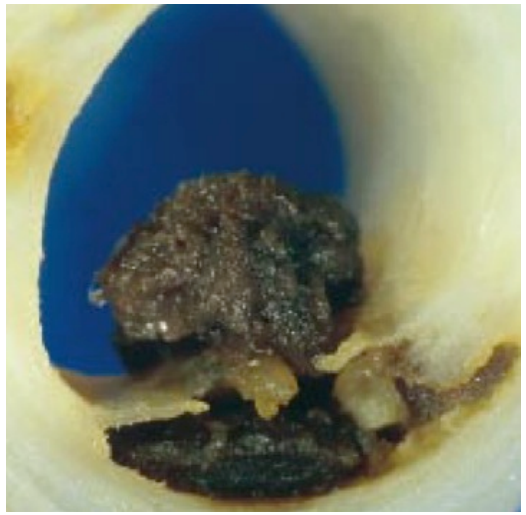

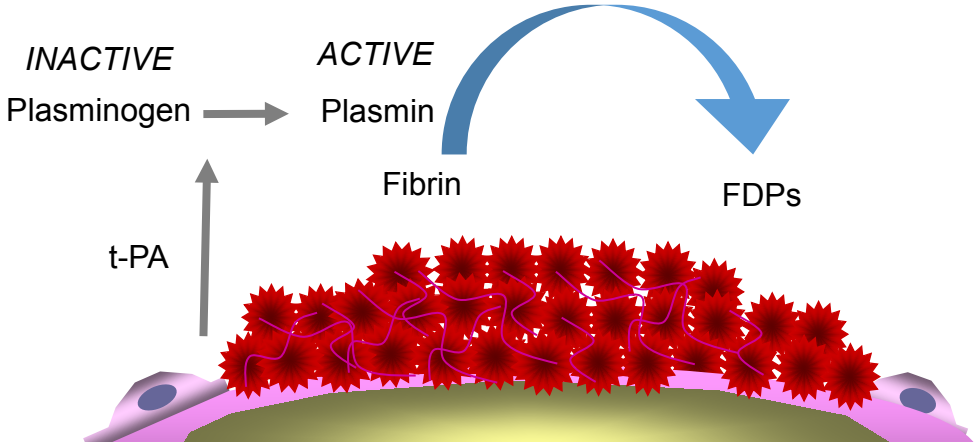

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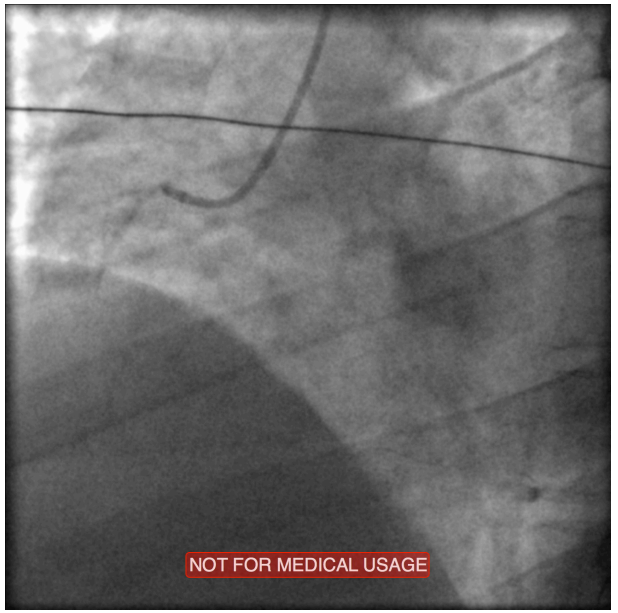
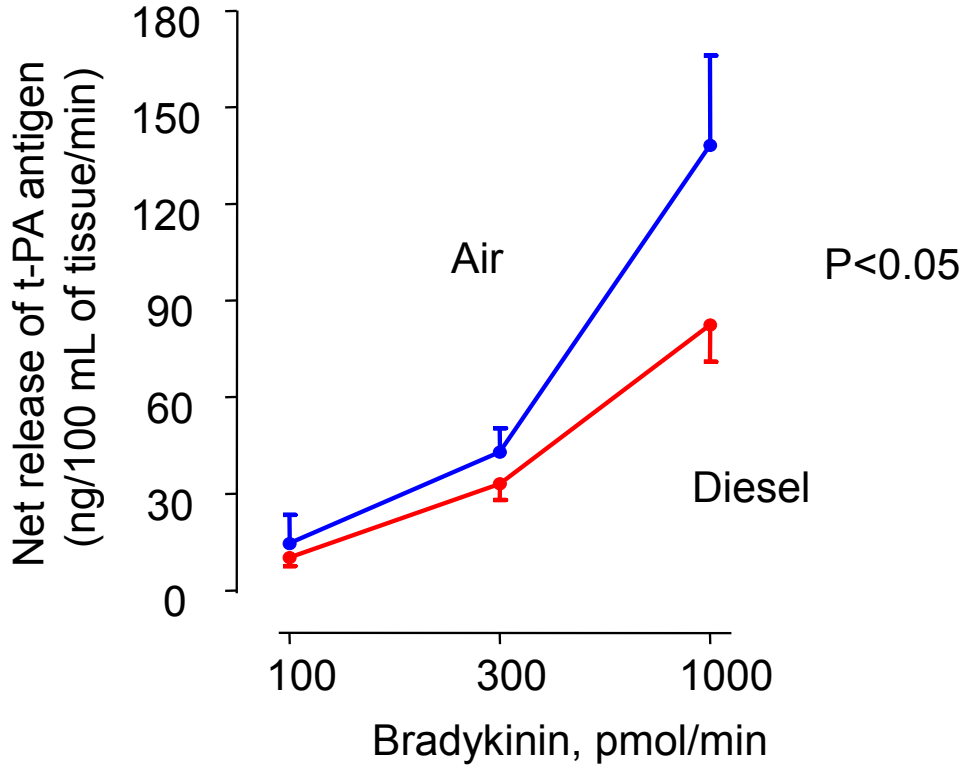


Platelet aggregation and activation occurs rapidly following plaque rupture with thrombus propagation which stimulates local tissue plasminogen activator (t-PA) release from the endothelium and initiates fibrinolysis and resolution of thrombus

Mills et al N Eng J Med 2007

Diesel exhaust and endogenous fibrinolysis

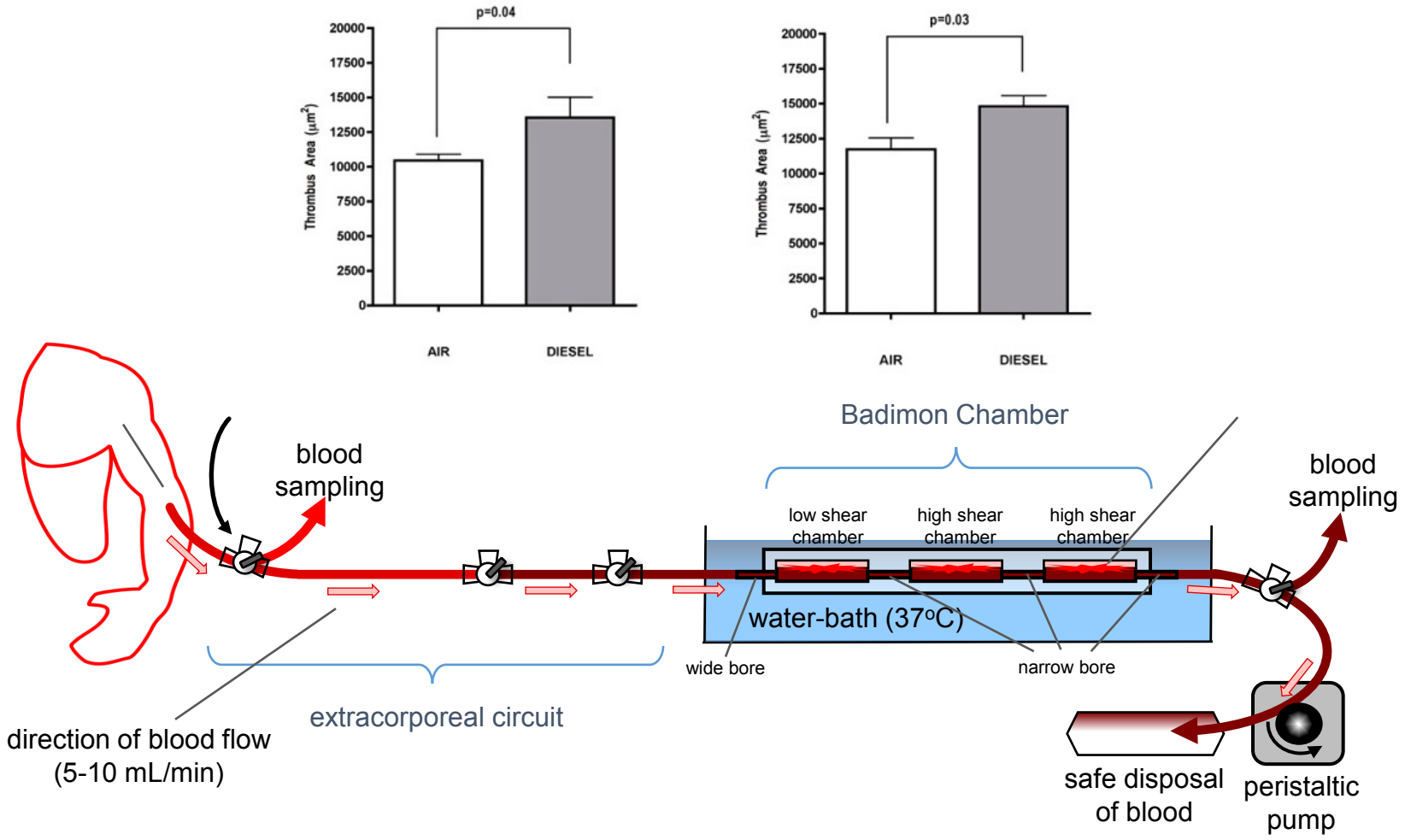
VENOUS OCCLUSION PLETHYSMOGRAPHY



Exposure to dilute diesel exhaust for one hour impairs tissue plasminogen activator release from the vascular endothelium

Mills et al. Circulation 2005; Mills et al. N Engl J Med 2007

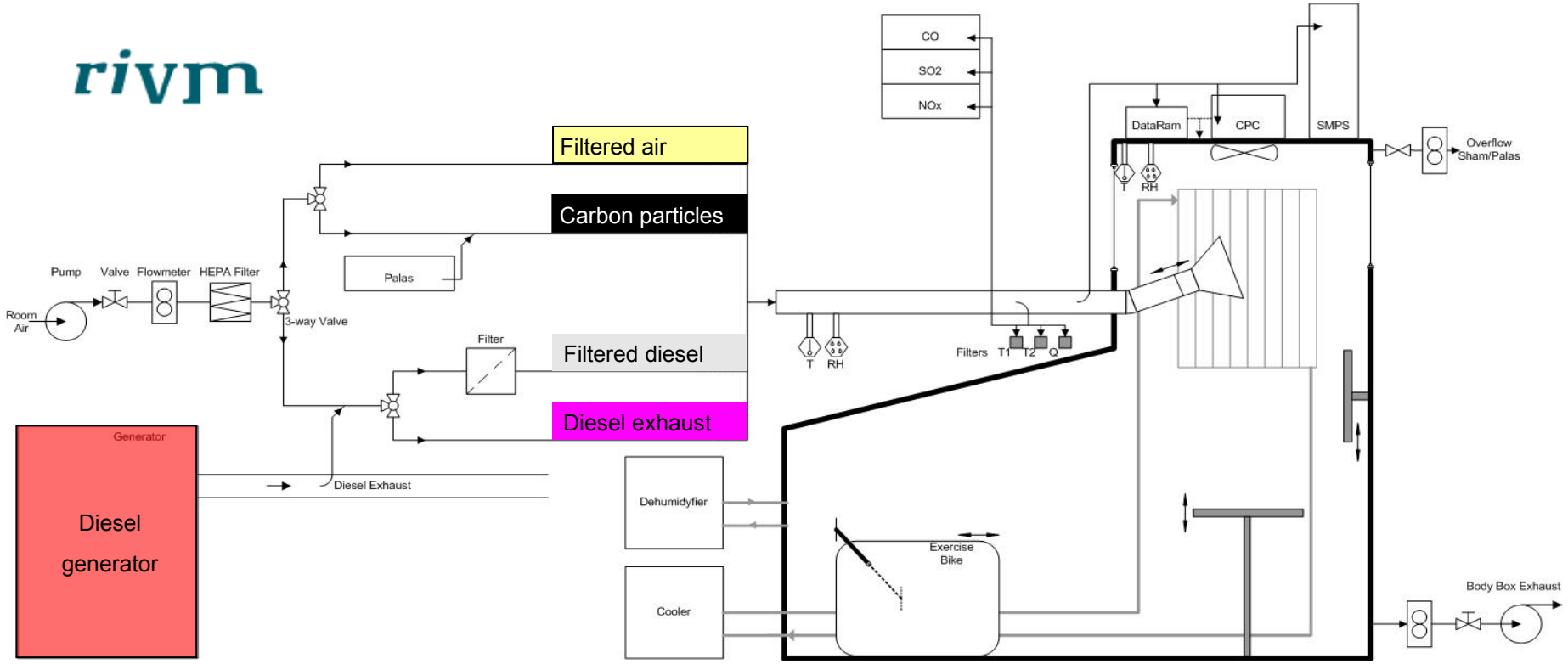
Diesel exhaust and thrombogenicity



Ex vivo thrombus formation is increased following exposure to dilute diesel exhaust for one hour

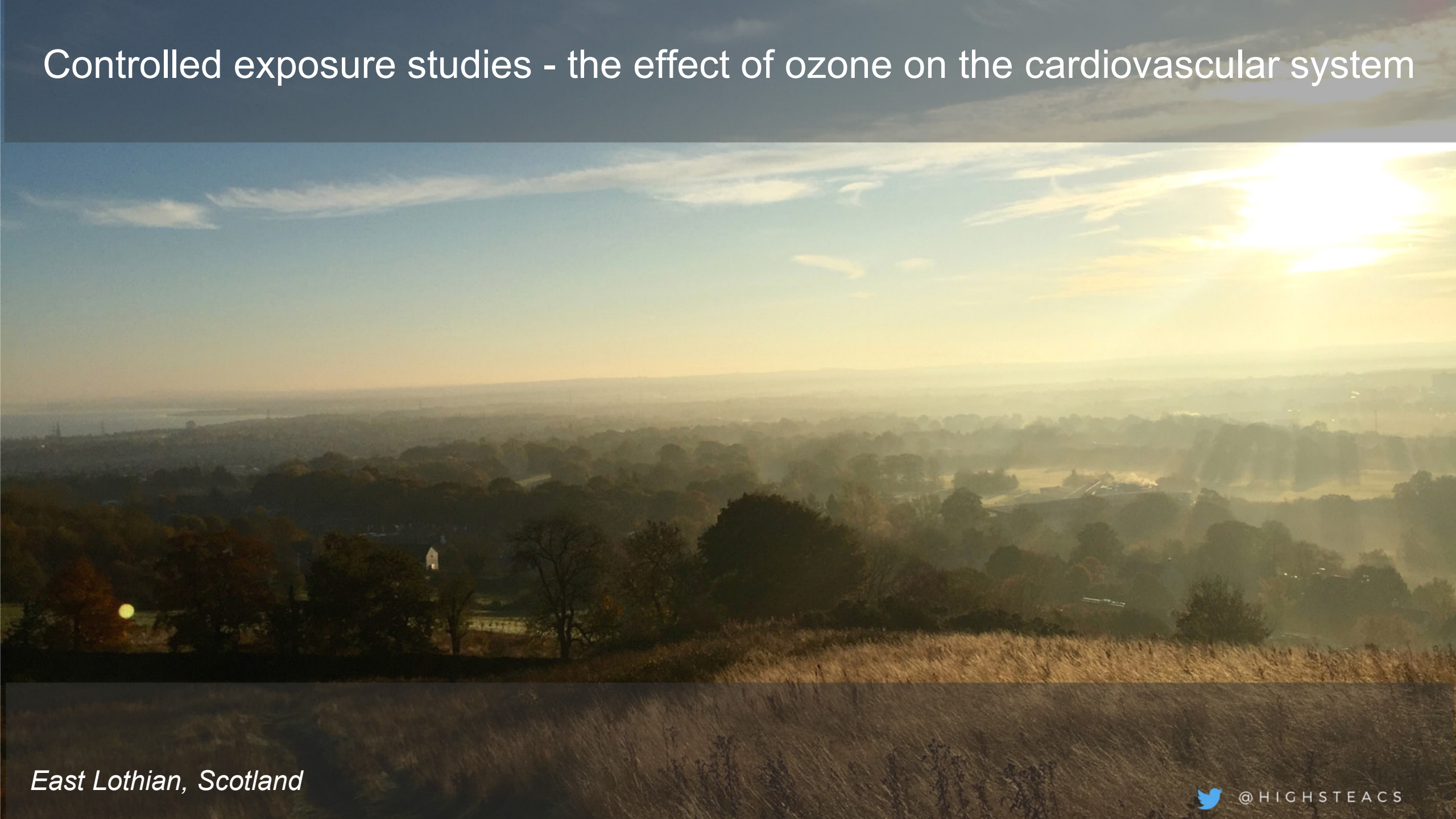
Lucking et al. Eur Heart J 2008; Lucking et al Circulation 2011

Diesel exhaust with ultrafine particle filtration



Mills NL et al. Eur Heart J. 2011

Controlled exposure studies - the effect of ozone on the cardiovascular system



East Lothian, Scotland

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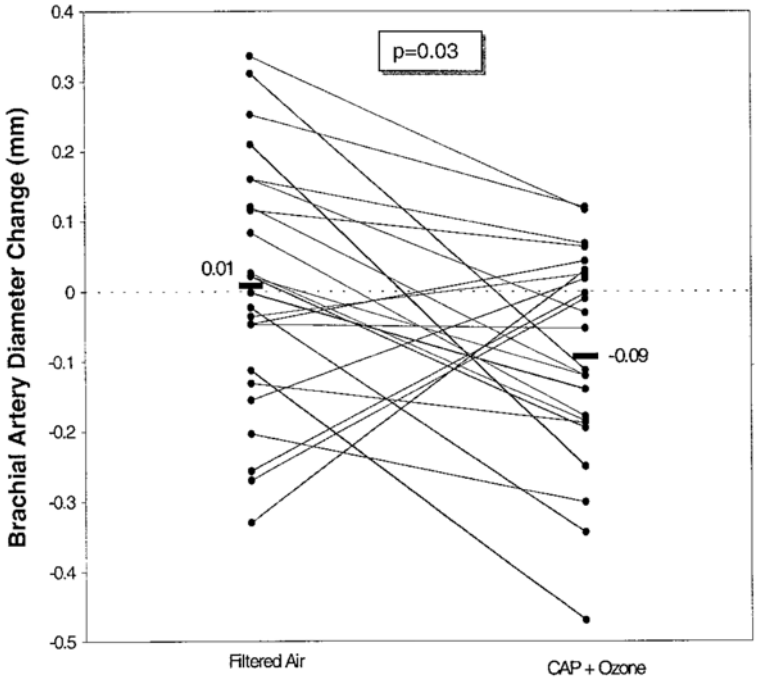
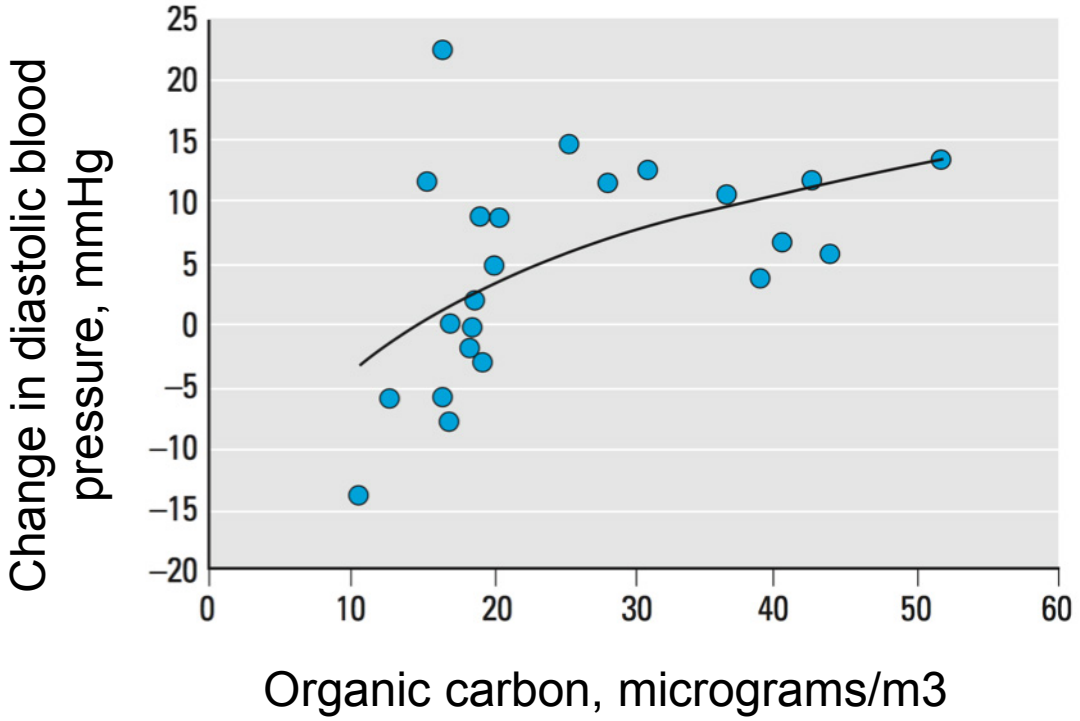
Ozone and ambient particles, vasoconstriction and blood pressure



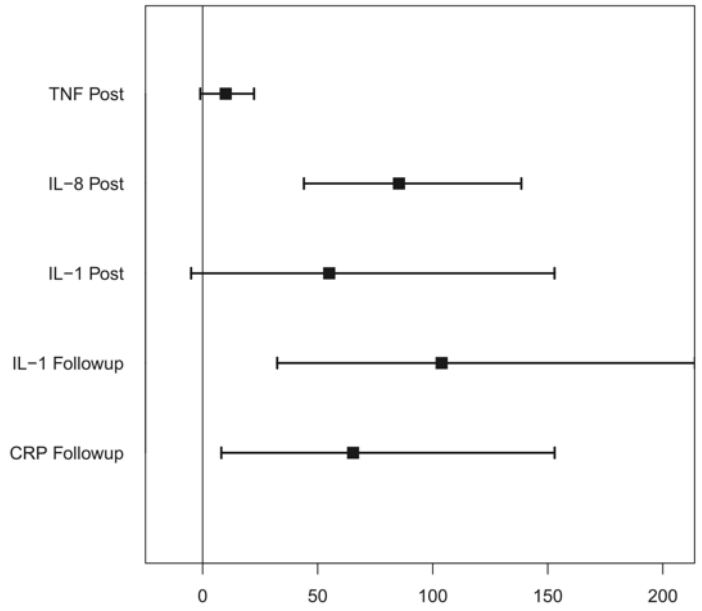


Two hour exposure to 150 micrograms/m3 of concentrated ambient fine particles (CAP) plus ozone (120 ppb) (n=25) was associated with acute arterial vasoconstriction and a 6 mmHg increase in diastolic blood pressure in healthy persons

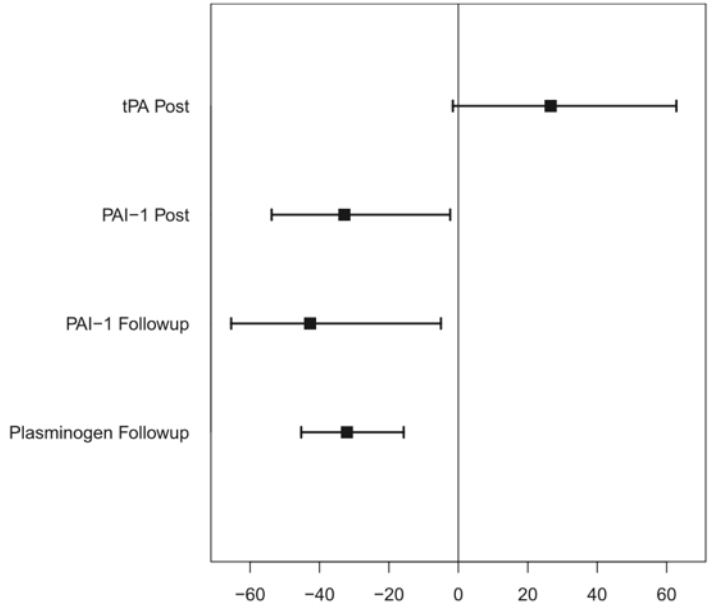
Brook et al. Circulation 2002; Urch et al. EHP 2005

Ozone and blood markers of cardiovascular risk

Inflammation

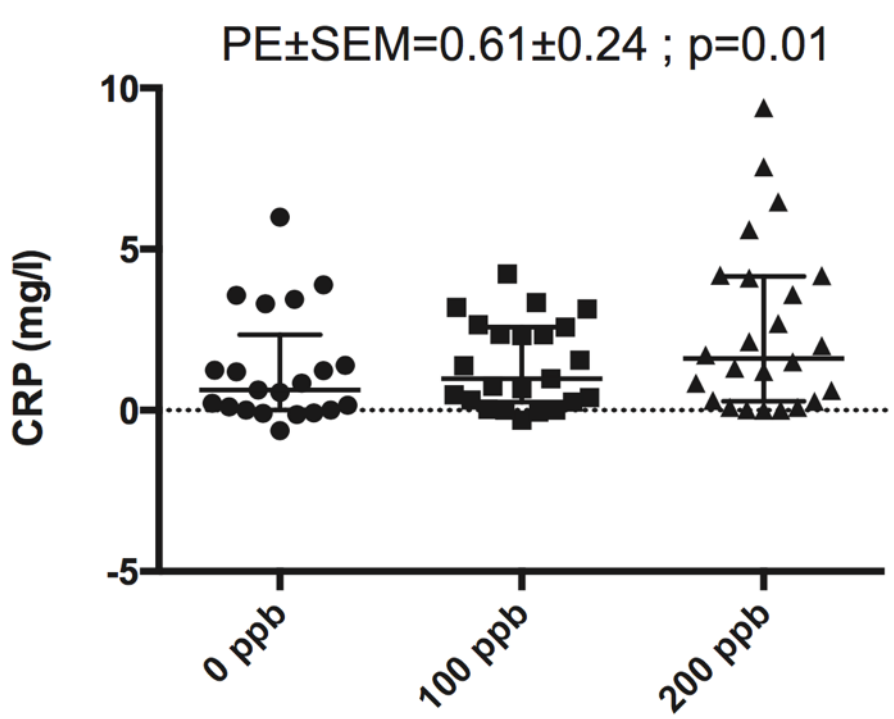


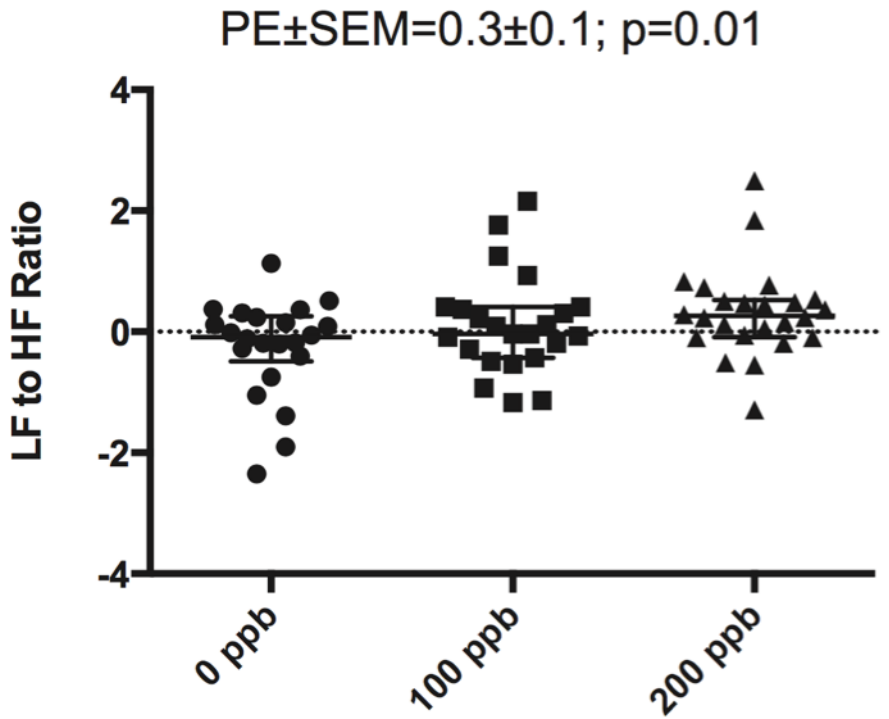
Fibrinolysis



Two hour exposure to ozone (300 ppb) or filtered air (n=25) increased IL-8, decreased plasminogen activator inhibitor-1(PAI-1), decreased HF component of HRV and increased QT-duration

Ozone and blood markers of cardiovascular risk



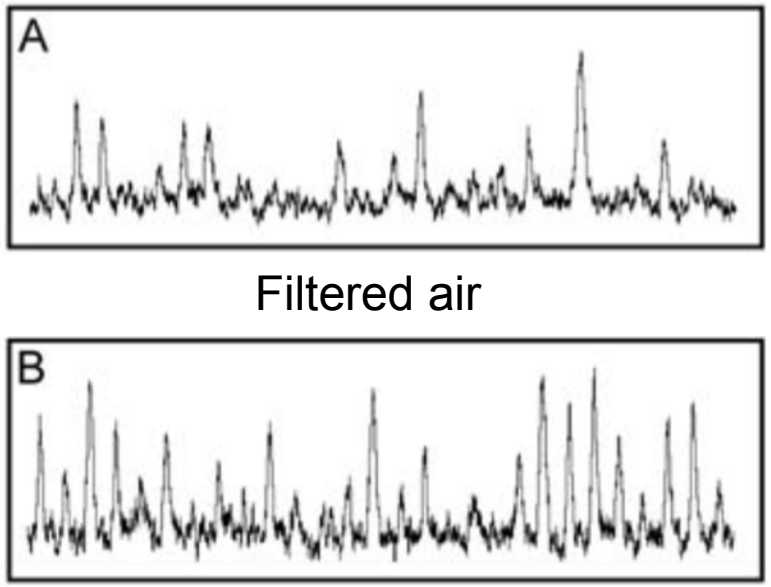


Four hour exposure to ozone (100 and 200 ppb) or filtered air (n=26) increased lung inflammation (BAL), LF/HF ratio (sympathetic activation) and high-sensitivity CRP in regression models

Arjomandi et al Am J Physiol Heart Circ Physiol 2015

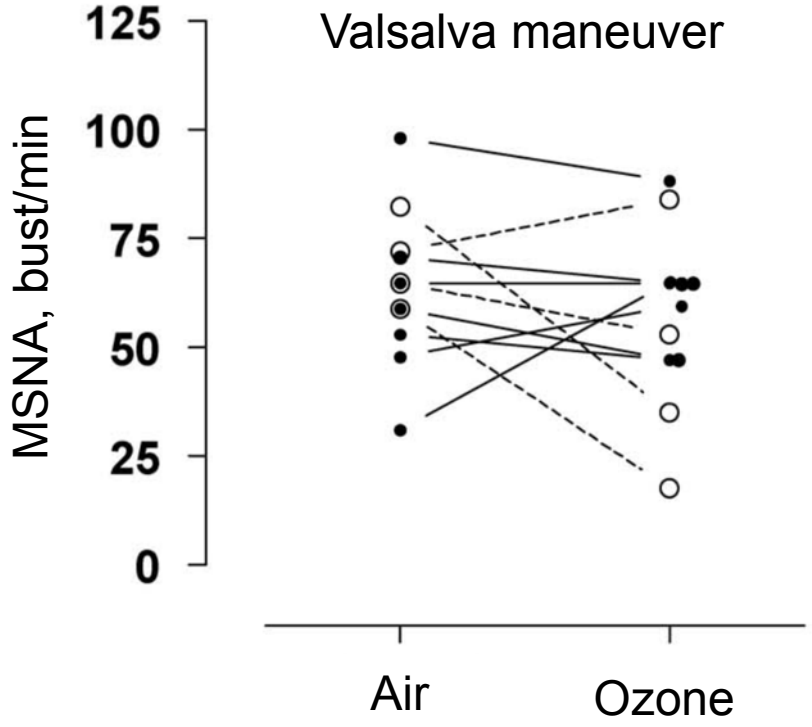
Ozone and sympathetic nerve activity

MICRONEUROGRAPHY



Filtered air

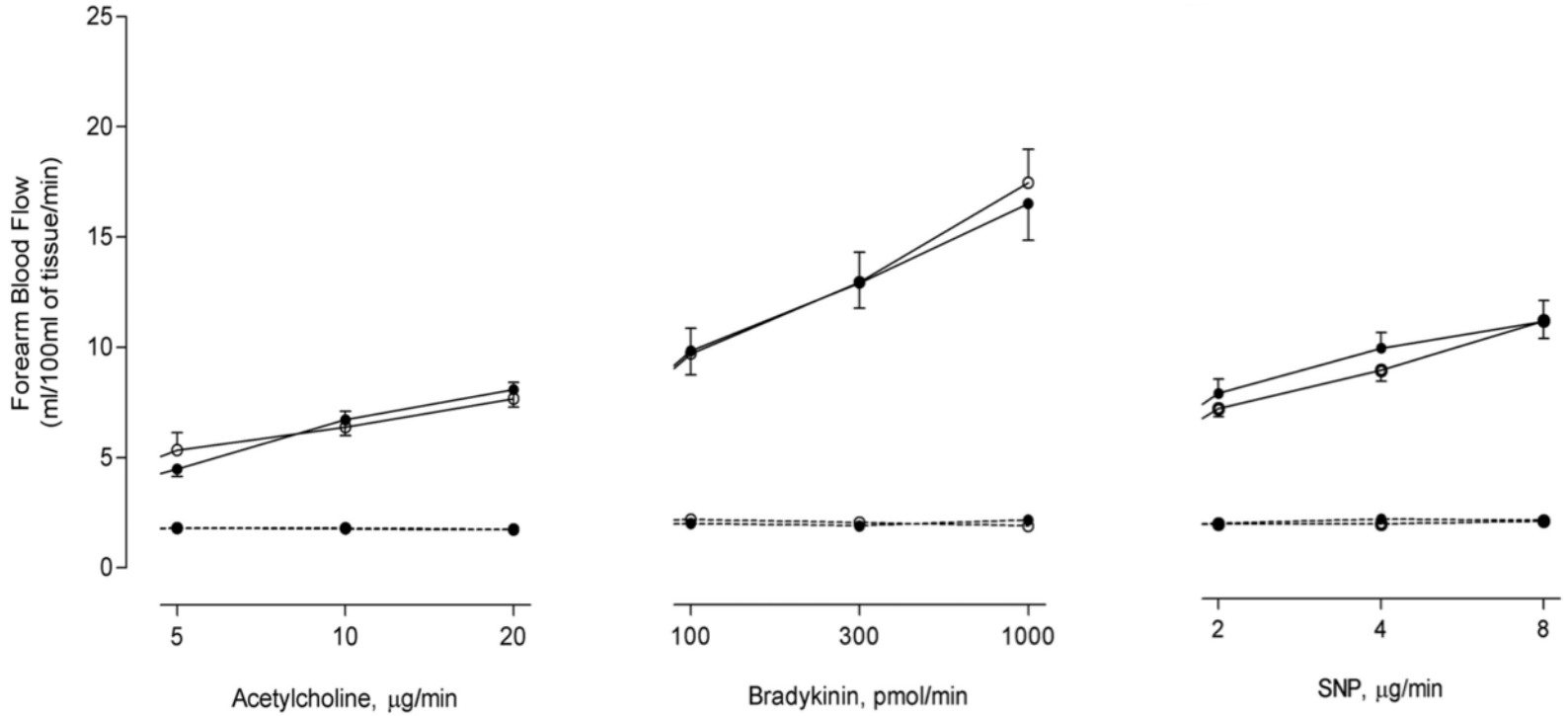
Ozone, 250ppb



Three hour exposure to ozone (250 ppb) or filtered air (n=14) did not effect heart rate, blood pressure, cardiac output, and muscle sympathetic nerve activity (MSNA) at rest, during deep breathing, maximum-inspiratory breath hold, and a Valsalva maneuver at 22 hours

Tank et al PLoS ONE 2011

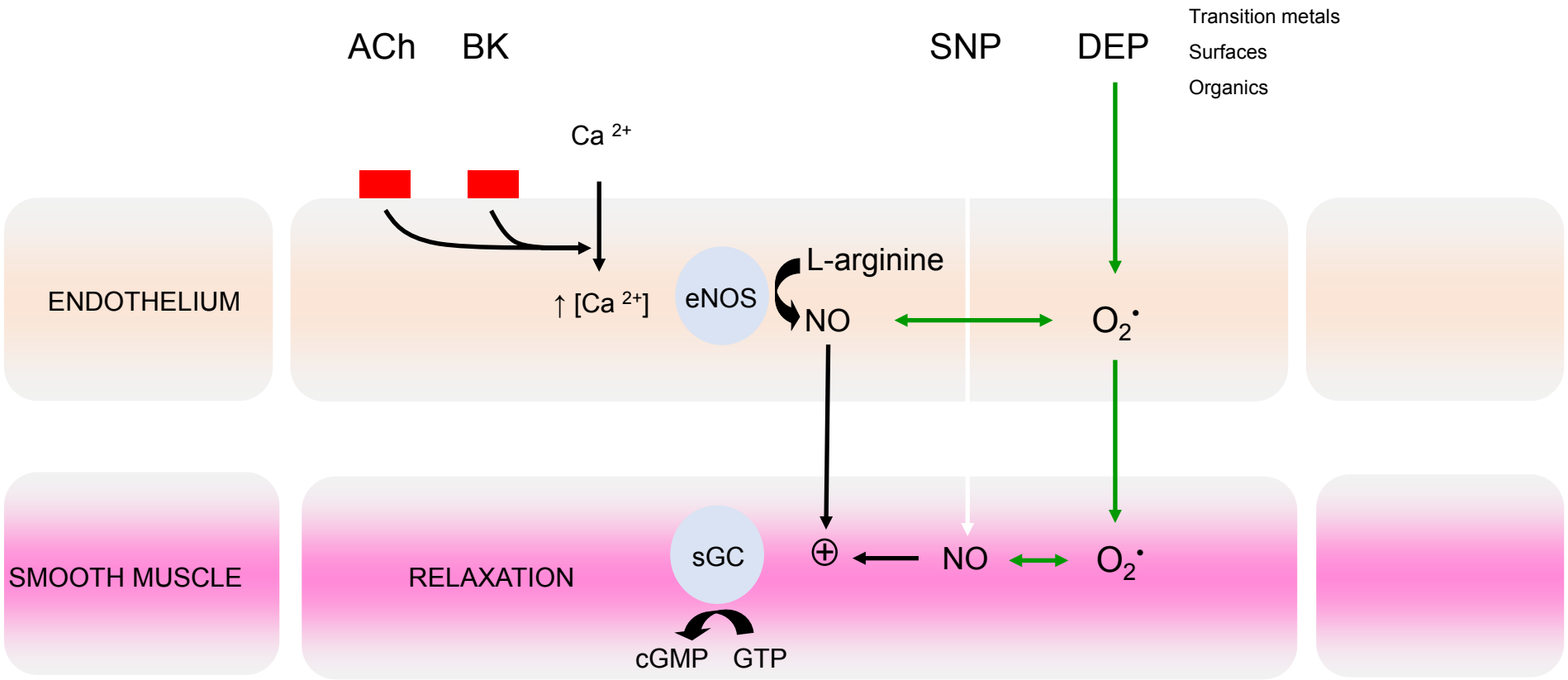
Ozone and forearm blood flow



Short-term exposure to ozone (75 mins) at 300ppb was compared to filtered air (n=36) and did not impair endothelial dependent or independent vascular function, fibrinolysis inflammation or heart rate variability in healthy young men

Barath et al. Toxicological Sciences 2012

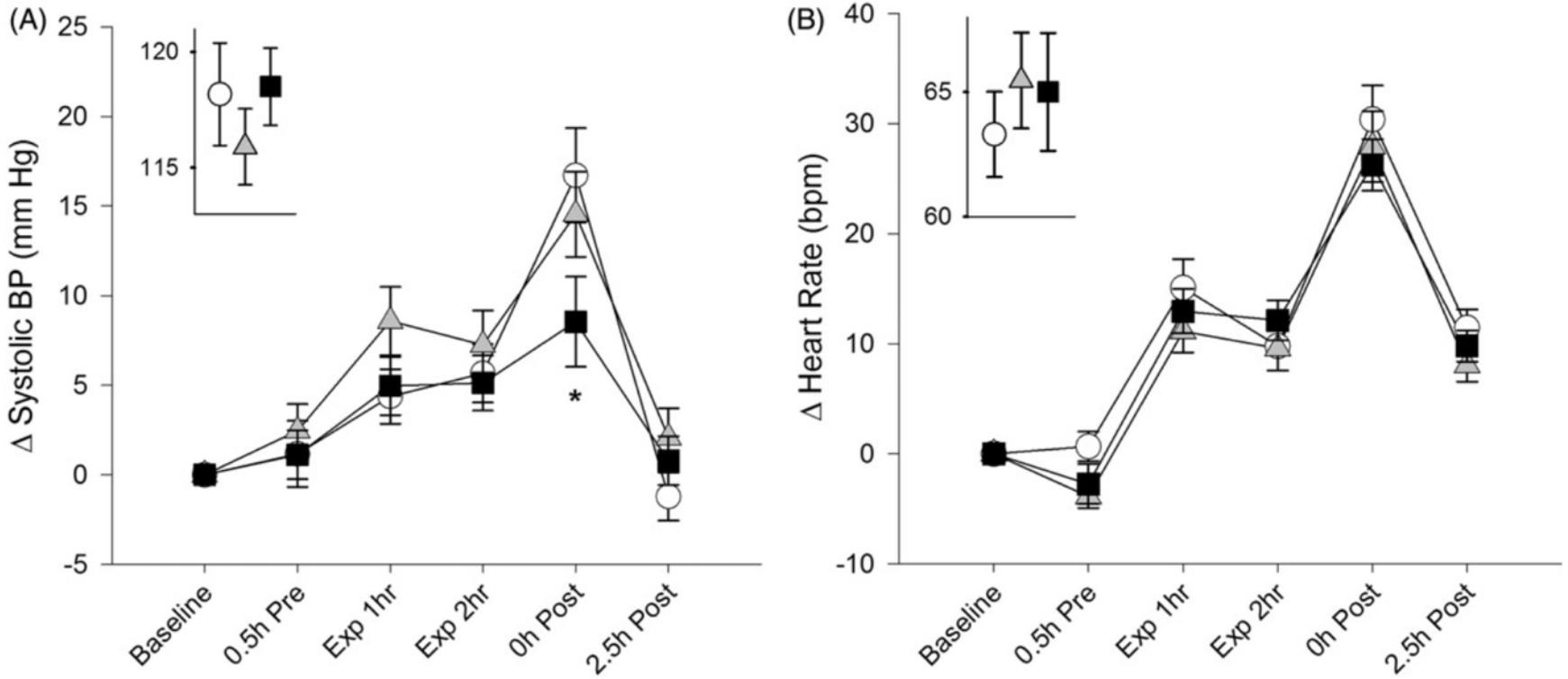
Adverse vascular effects of air pollution – oxidative stress?



Adverse vascular effects of diesel exhaust exposure could be explained by increased reactive oxidant species and nitric oxide consumption

Miller et al. Future Cardiol 2011;8:577-602

Ozone, cardiopulmonary effects, and impaired anti-oxidant defences



Three hour exposure to ozone (100 and 200 ppb) or filtered air (n=24) in healthy non-smokers stratified by glutathione-S-transferase gene deletion (n=12) did not affect vital signs, spirometry, arterial and venous blood nitrite levels, impedance cardiography, peripheral arterial tonometry, estimation of pulmonary capillary blood volume (Vc), and blood microparticles or platelet activation

Framptom et al Inh Tox 2015

Controlled exposure studies - the effect of ozone and particles

Royal Botanic Gardens, Edinburgh

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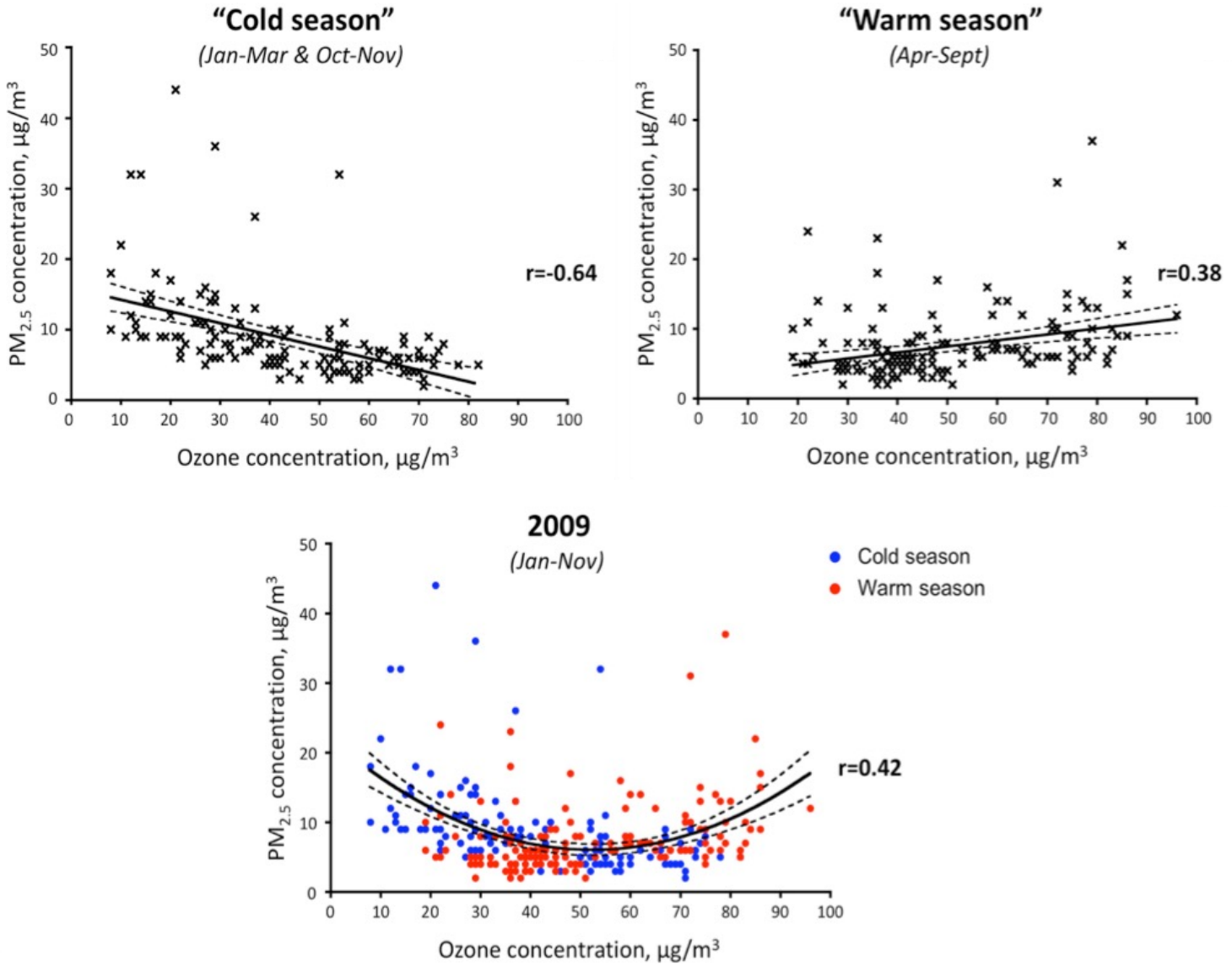
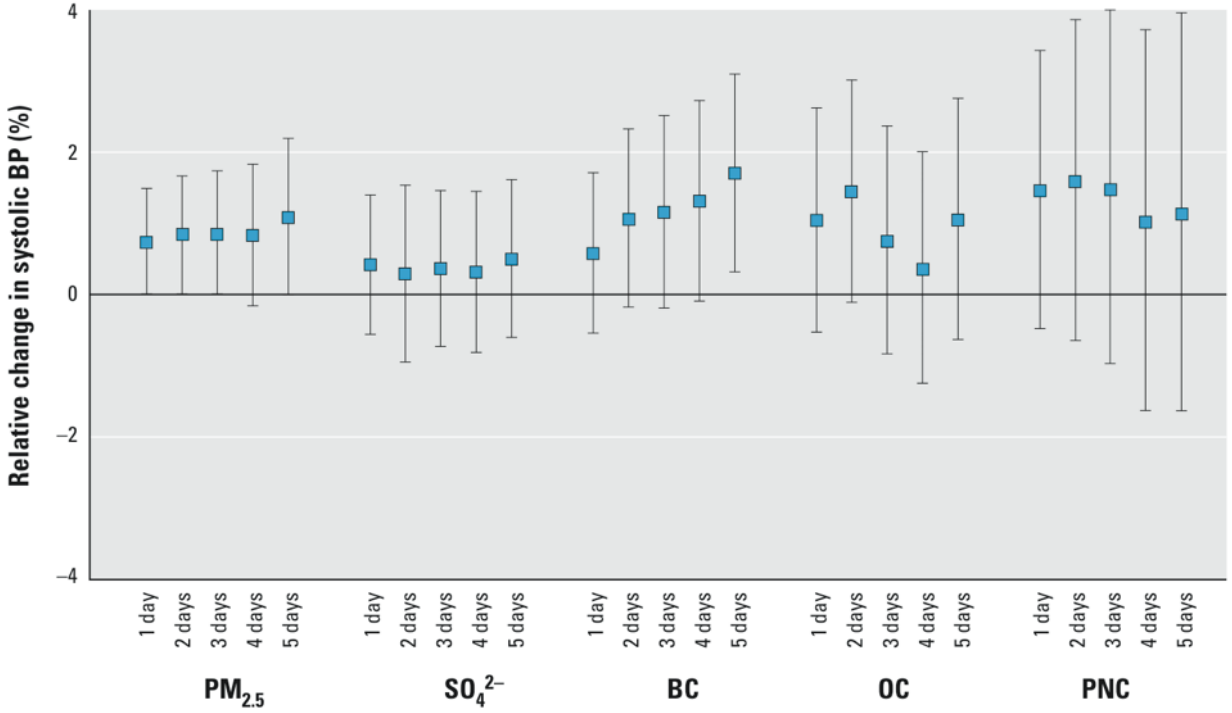
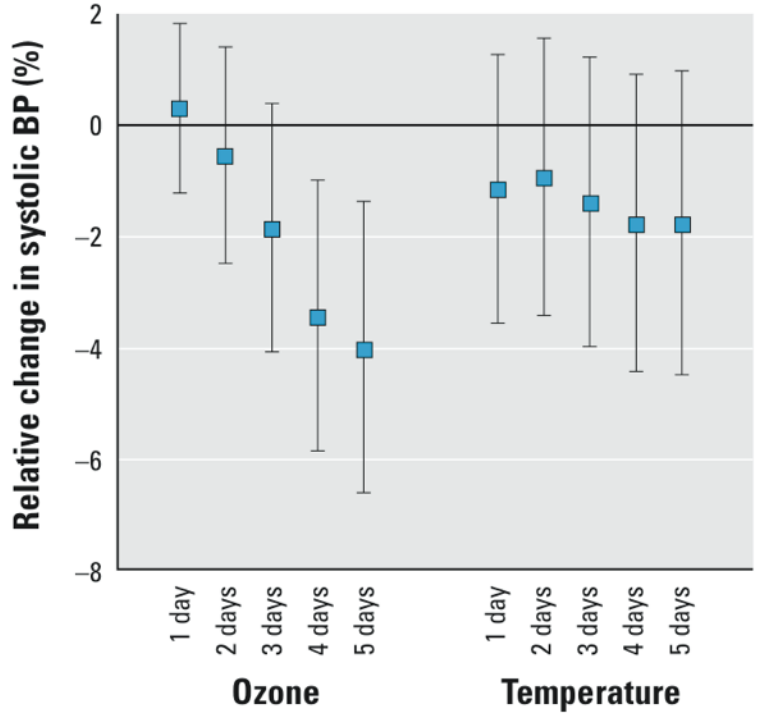
Relationship between ozone, particulates and temperature



Langrish et al. Heart 2009

Panel studies and interpretation of the effects of single pollutants

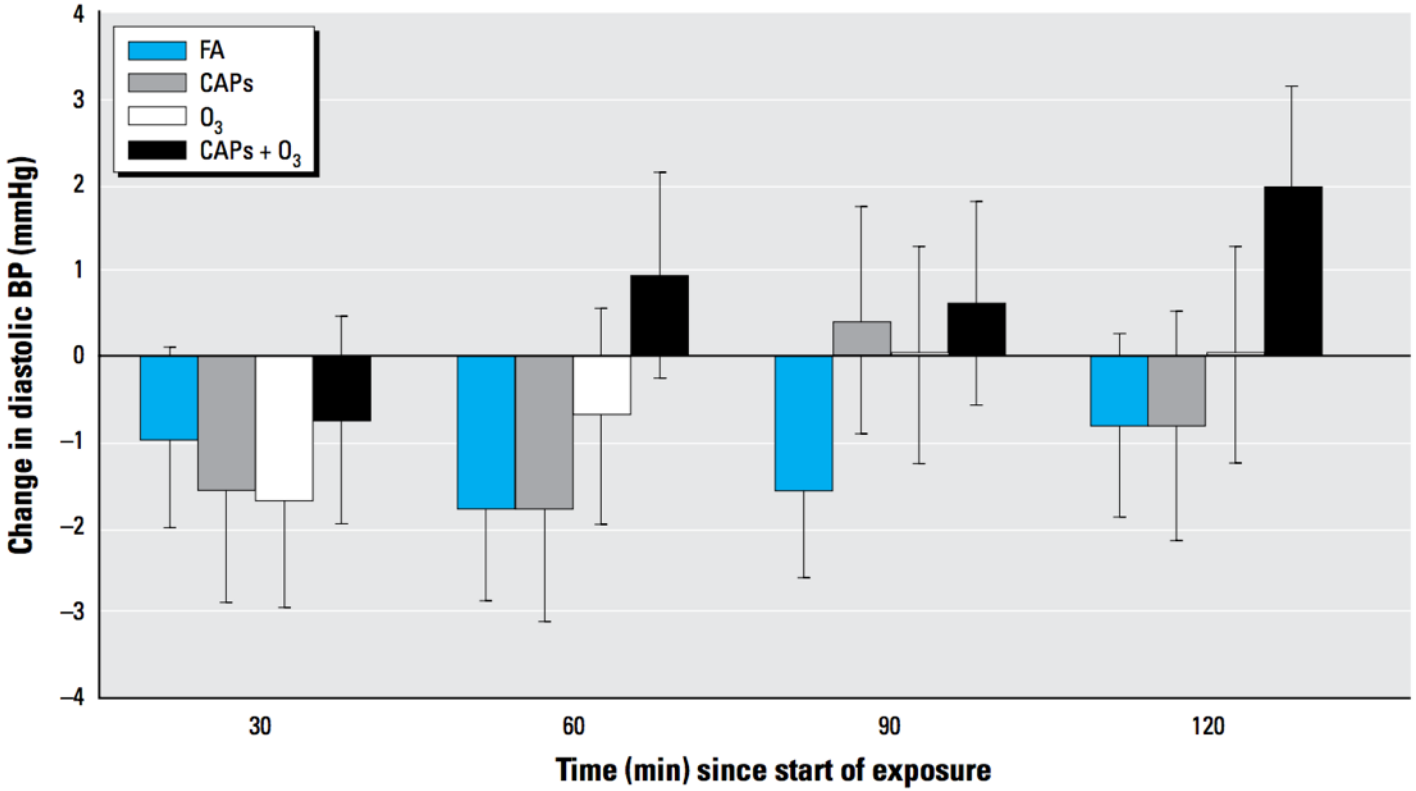




Panel study of patients with diabetes mellitus (n=70) with measures of BP every 2 weeks (5 occasions) an IQR increase in in PM2.5 and carbon black was associated with an increase in systolic BP of 1.4 mmHg and 2.2 mmHg but a decrease of 5.2 mmHg with ozone

Hoffmann et al. EHP 2012

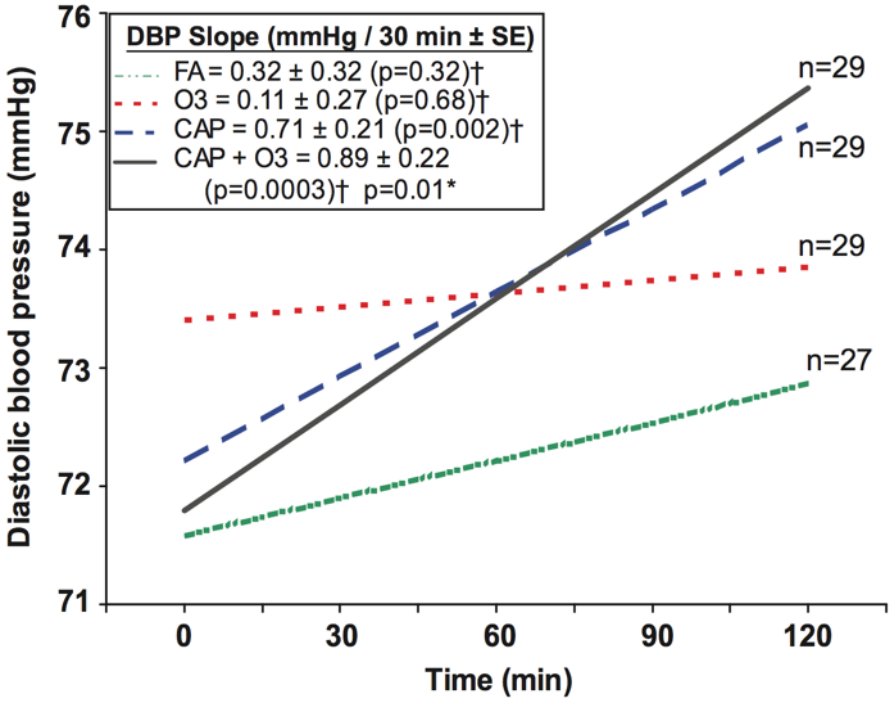
Ozone + fine particulate and blood pressure



Two hour exposure to ozone (113 ppb), concentrated ambient particulates (CAPs; 120 microgram/m3) or ozone with CAPs (n=50) did not effect HRV, but there appeared to be an interaction with ozone suggesting it may be potentiating the effects of CAPs on diastolic blood pressure

Fakhri et al Environ Health Perspect 2009

Ozone + fine particulate and blood pressure



Two hour exposure to ozone (120 ppb), concentrated ambient particulates (CAPs; 150 microgram/m3) or ozone with CAPs (n=81) increased diastolic blood pressure although the effect appears to be related to ambient particulate exposure rather than ozone here

Brook et al Hypertension 2009

Summary and conclusions

- Multiple meta-analysis suggest acute cardiovascular effects of exposure to air pollution are strongest for particulate matter
- Exposure to dilute diesel exhaust promotes vascular dysfunction, thrombosis and exercise induced myocardial ischemia (consistent, coherent and biologically plausible)
- Exposure to ozone (100-300 ppb) has been associated with effects on systemic inflammation, blood pressure and autonomic function
- Limited evidence of synergy between particulate matter and ozone in mediating the cardiovascular effects of air pollution exposure

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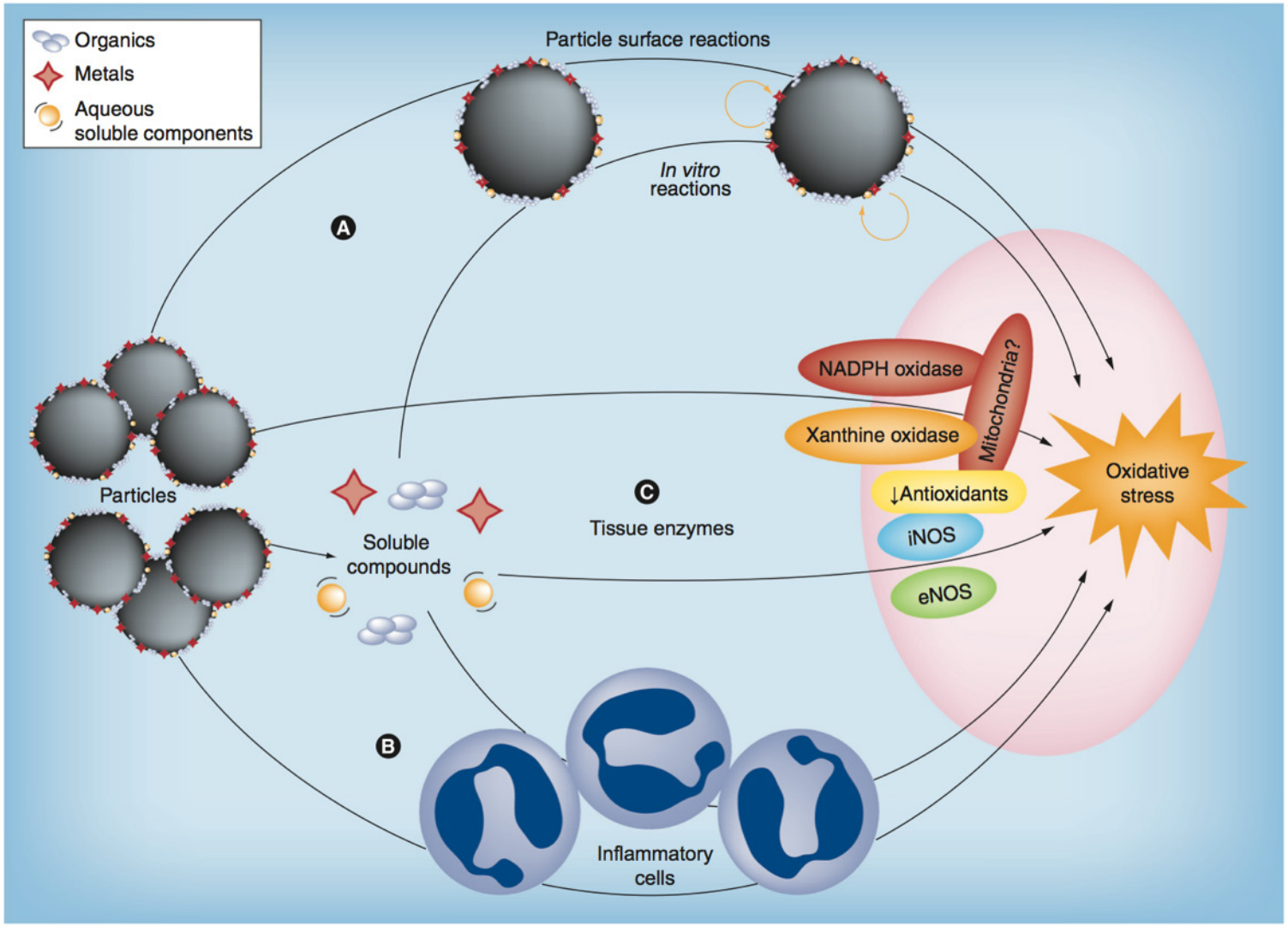
Cellular mechanisms of toxicity - combustion derived nanoparticles



Royal College of Physicians of Edinburgh

Miller et al. Future Cardiol 2011;8:577-602

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