Swiss TPH

Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Chronic Disease Epidemiology

Health Consequences of Ultrafine Particles
an exposome perspective

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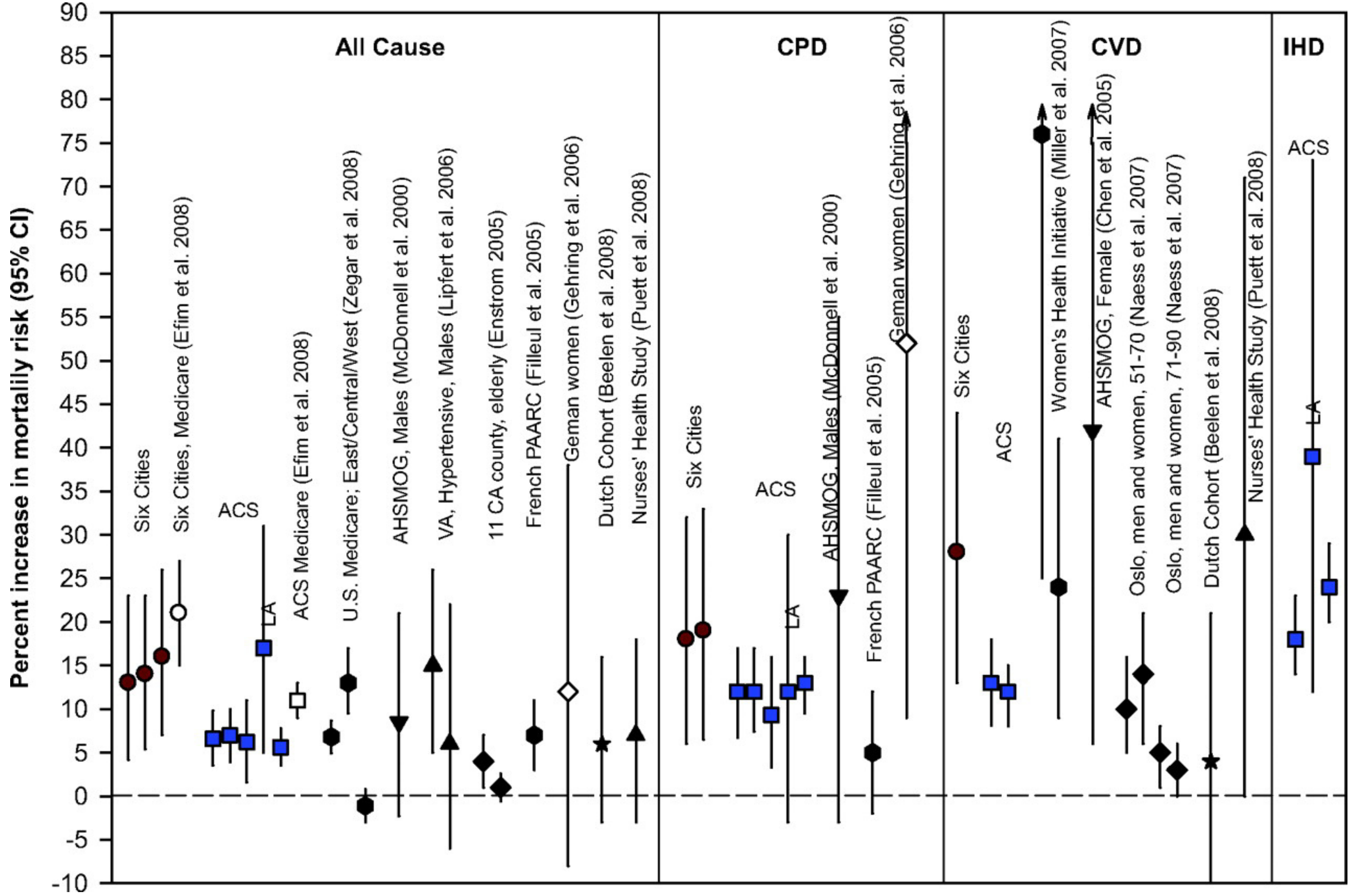
Head Chronic Disease Epidemiology

PI SAPALDIA Cohort & Biobank

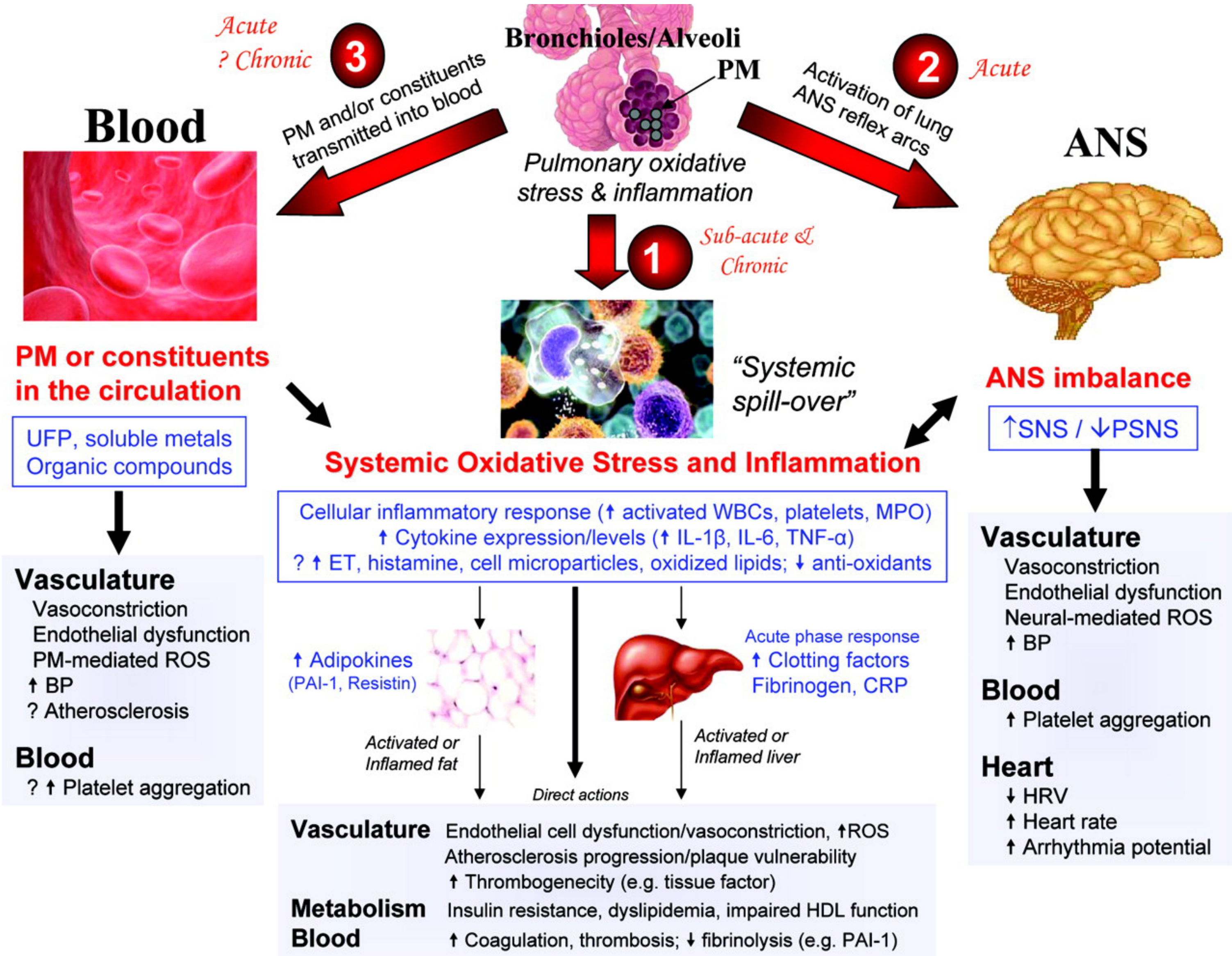
Chronic PM10/2.5 exposure and cardiovasuclar mortality

Brook Circulation 2010



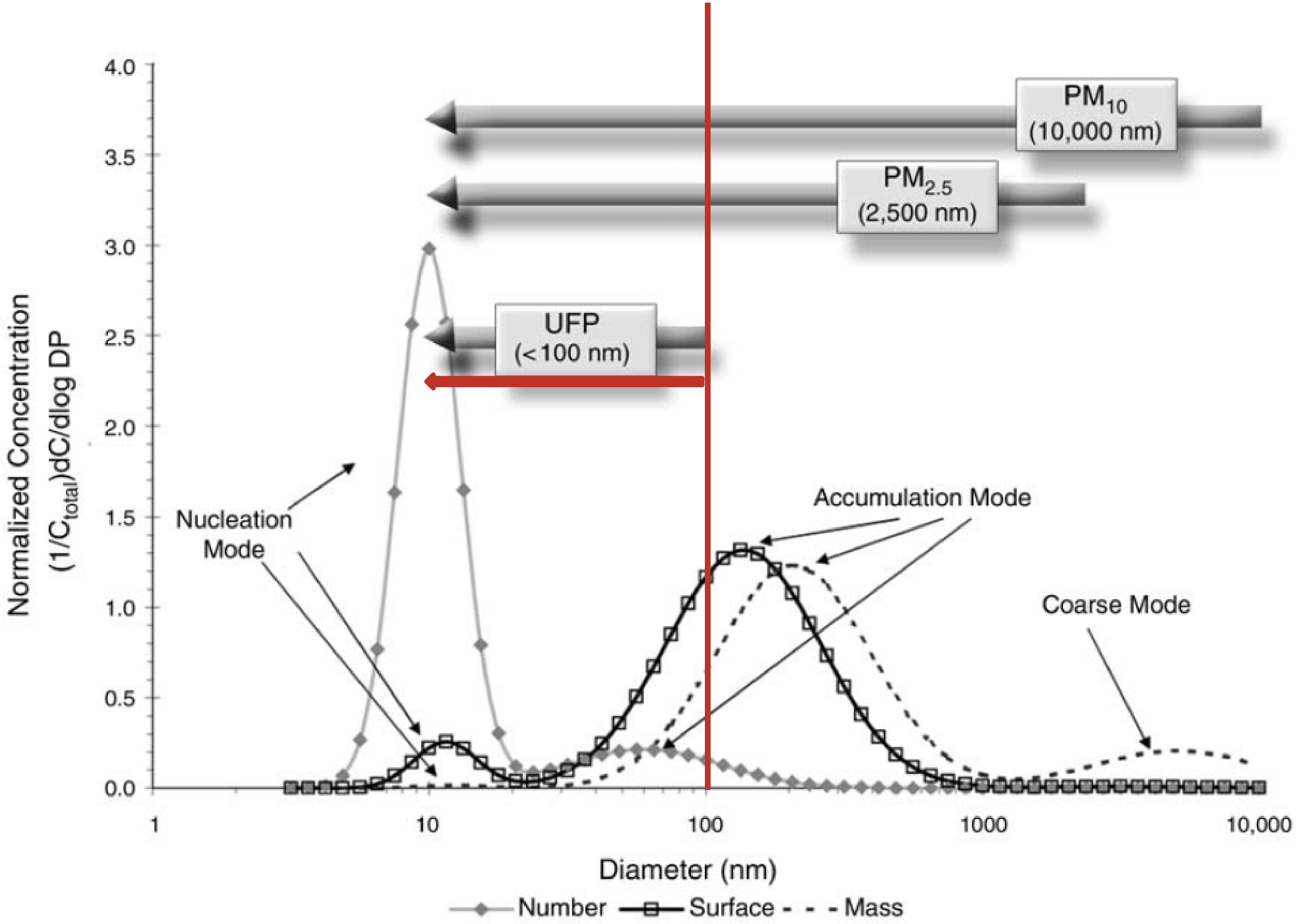
Biological pathways: ambient particles to CVD

Brook Circulation 2010



Normalized Particle Size Distributions of Roadway Aerosol

HEI Perspective 3 2013



Why are ultrafine particles potentially of specific concern
?

Concerns related to UFP health effects

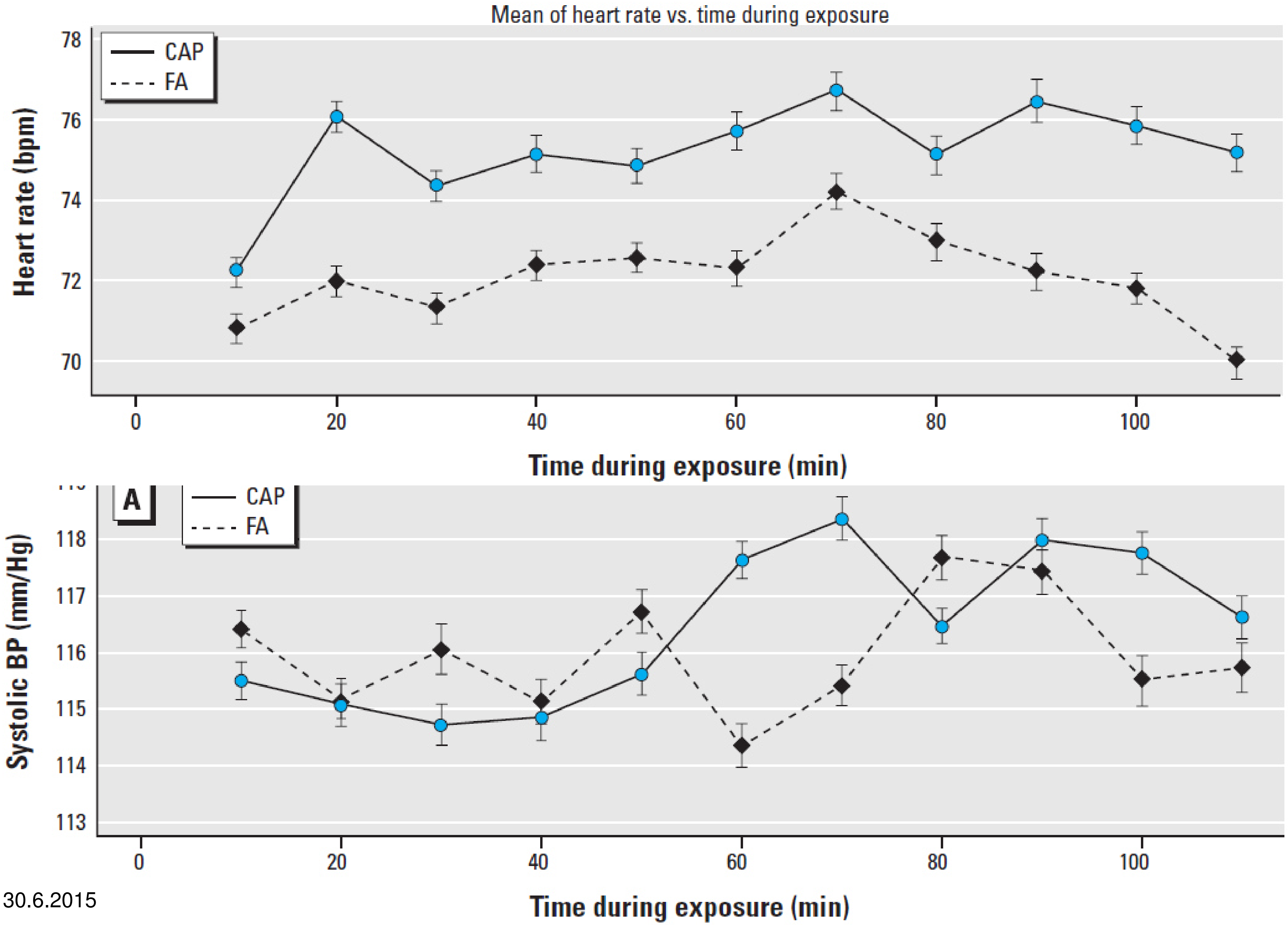
Araujo et al. Particle Fibre Toxicol 2009

- larger number of particles – larger surface – different composition – largely traffic-related
- larger redox activity
- pattern of lung deposition – reach alveoli
- lower clearance from the lung
- enter cells more easily – escape phagocytosis
- translociation across lung – reach distant organs (e.g. brain; translocation in humans not substantial)

Health effects of coarse PM air pollution from rural location

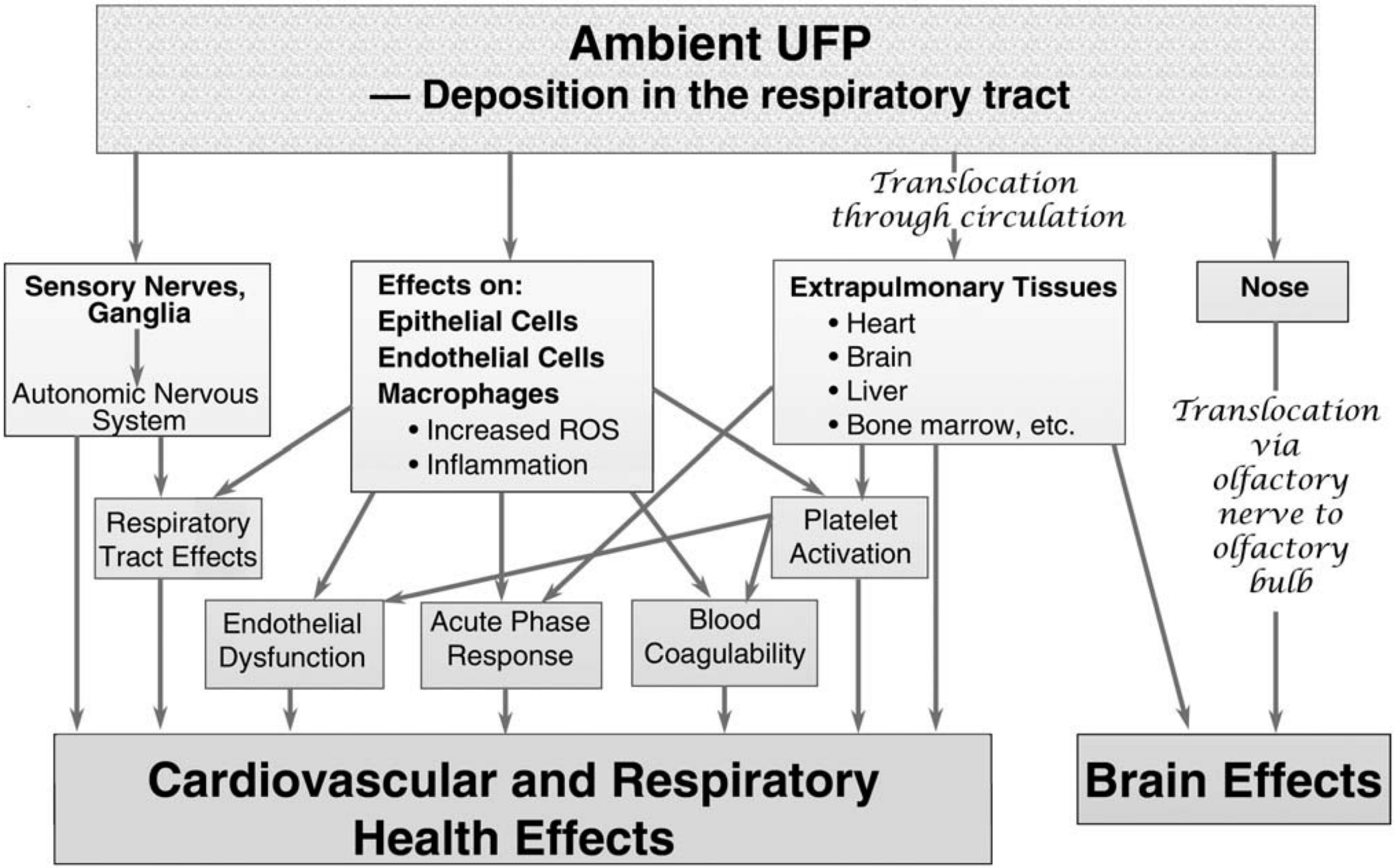
randomized double-blind crossover study

Brook RD et al. EHP 2015



Inhaled UFP impact on cardio-respiratory system and brain: hypothesized pathways

HEI Perspective 3 2013

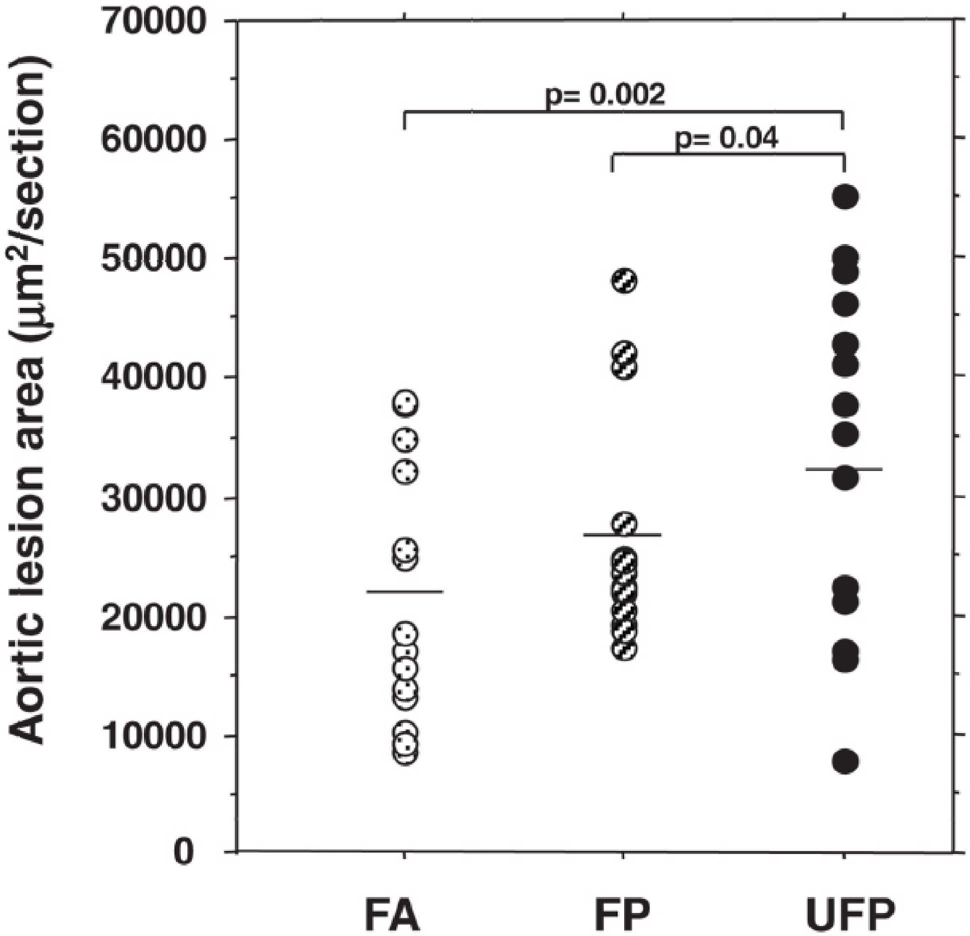


What is the evidence for (stronger/specific) health effects of ultrafine particles

?

Mouse model of atherosclerosis: PM2.5 vs. UFP

Araujo et al. Circ Res 2008



# sub-0.18 μm (particles/cm³)			
	~ 5,000	$3.88x10^5$	$5.59x10^5$

Health Effects Institute 2013

Understanding the health effects of ambient ultrafine particles

experimental & epidemiological evidence

on short-term effects

mortality (strongest for CVD)

cardiorespiratory acute morbidity

- hospital admissions
- respiratory symptoms
- pulmonary function
- allergy & atopy
- heart rate variability; arrhythmia
- ischemia (ST-segment changes)
- vascular reactivity/thrombogenic/endothelial function
- blood pressure
- soluble markers/brain inflammation

→

- **similar to fine particles**
- **limited consistency**
- **some evidence for CVD effects in absence of lung inflammation**
- **susceptible subgroups**

Health Effects Institute 2013

Understanding the health effects of ambient ultrafine partciles

Epidemiological evidence on long-term effects

- no long-term cohort studies – limited UFP monitoring

Health Effects Institute 2013

Understanding the health effects of ambient ultrafine partciles

Methodological challenges in assigning UFP specific effects

co-pollutant confounding

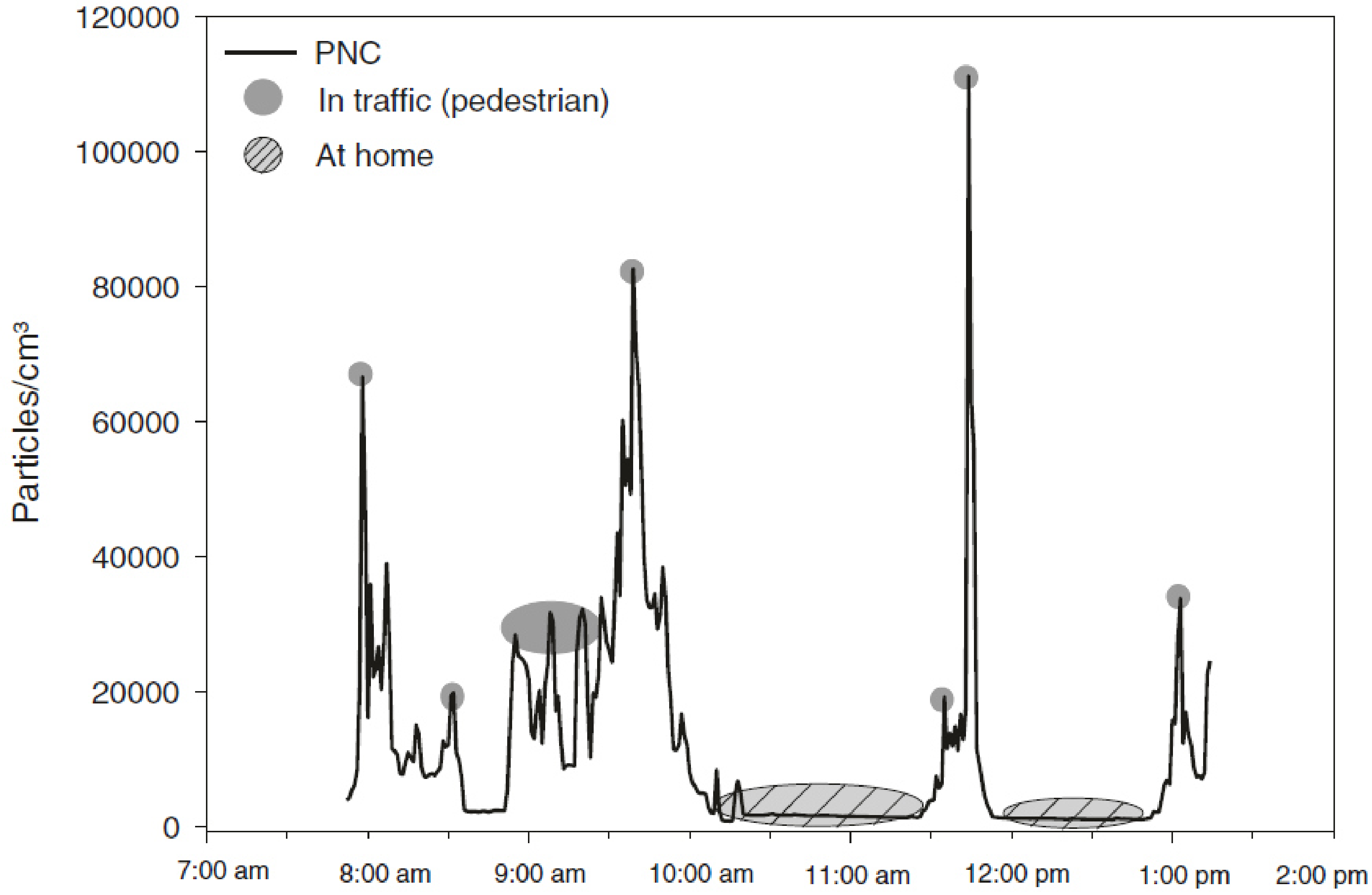
- correlations between exposure metrics (longterm observational studies; correlation of temporal variability of exposure metrics)

exposure measurement error

- large small-scale spatial variation
- non-consideration of indoor sources
- UFP exposure metrics (particle number vs. mass concentration; source; composition)

Personal PNC measurement

Peters Particle Fibre Toxicol 2015



need for new metric to capture intradurnal variability and peaks

Relevant post-HEI report evidence for (stronger/specific) short-term health effects of ultrafine particles ?

Short-term UFP (PNC) and mortality

Meta-Analysis of the published evidence

Atkinson et al. J Expo Sci Environ Epidem 2015

RMID	Author	City	Year	Age	Mode	Size	Range
All Cause							
517	Atkinson	London	2010	All	PNC	-	10,166
2051	Branis	Prague	2010	All	Accumulation	0.21-0.49	1,000
2051	Branis	Prague	2010	All	Aitken	0.05-0.21	1,000
2051	Branis	Prague	2010	All	Nucleation	0.015-0.05	1,000
2051	Branis	Prague	2010	All	PNC	0.015-0.49	1,000
1954	Breitner	Erfut	2009	>1 yr.	Aitken	0.03-0.05	1,483
1954	Breitner	Erfut	2009	>1 yr.	Aitken	0.05-0.1	805
1954	Breitner	Erfut	2009	>1 yr.	Nucleation	0.003-0.03	5,336
Cardiovascular							
517	Atkinson	London	2010	All	PNC	-	10,166
2051	Branis	Prague	2010	All	Accumulation	0.21-0.49	1,000
2051	Branis	Prague	2010	All	Aitken	0.05-0.21	1,000
2051	Branis	Prague	2010	All	Nucleation	0.015-0.05	1,000
2051	Branis	Prague	2010	All	PNC	0.015-0.49	1,000
205	Breitner	Beijing	2011	>15yr.	Aitken	0.03-0.1	6,250
205	Breitner	Beijing	2011	>15yr.	Nucleation	0.003-0.03	10,203
205	Breitner	Beijing	2011	>15yr.	PNC	<0.8	13,790
238	Halonen	Helsinki	2009	65+ yr.	Accumulation	0.1-0.29	287
238	Halonen	Helsinki	2009	65+ yr.	Aitken	0.03-0.1	2,467
238	Halonen	Helsinki	2009	65+ yr.	Nucleation	<0.03	3,583
Respiratory							
517	Atkinson	London	2010	All	PNC	-	10,166
2051	Branis	Prague	2010	All	Accumulation	0.21-0.49	1,000
2051	Branis	Prague	2010	All	Aitken	0.05-0.21	1,000
2051	Branis	Prague	2010	All	Nucleation	0.015-0.05	1,000
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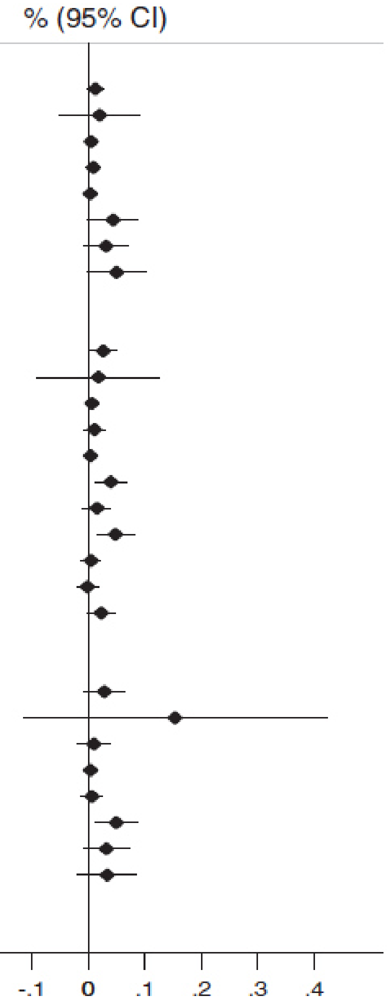


little evidence for association - lack of adjustment for co-pollutants

Short-term UFP and respiratory mortality/morbidity

UFIREG Project 2014

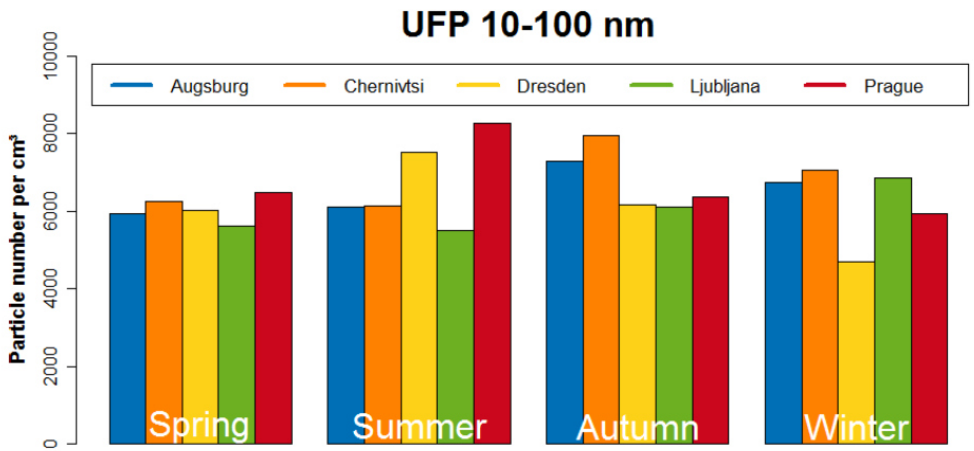


Figure 7. Seasonal variation of particle number concentration (10-100 nm) in UFIREG cities from May 2012 to April 2014 (Chernivtsi: January 2013 – April 2014).

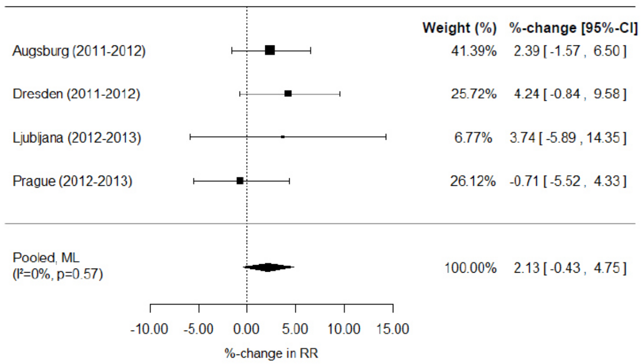


Figure 18. Percent change in respiratory mortality associated with each 1,000 particles/cm³ increase in daily UFP (lag 5).

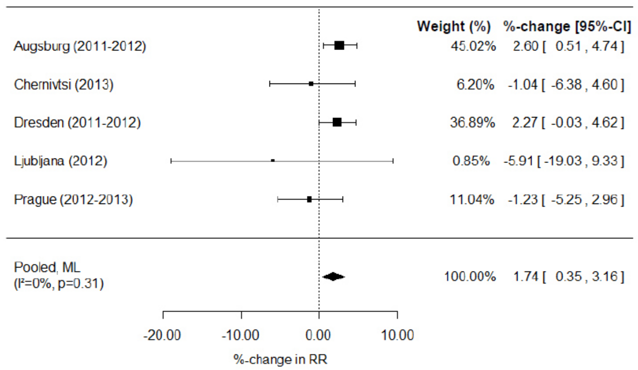
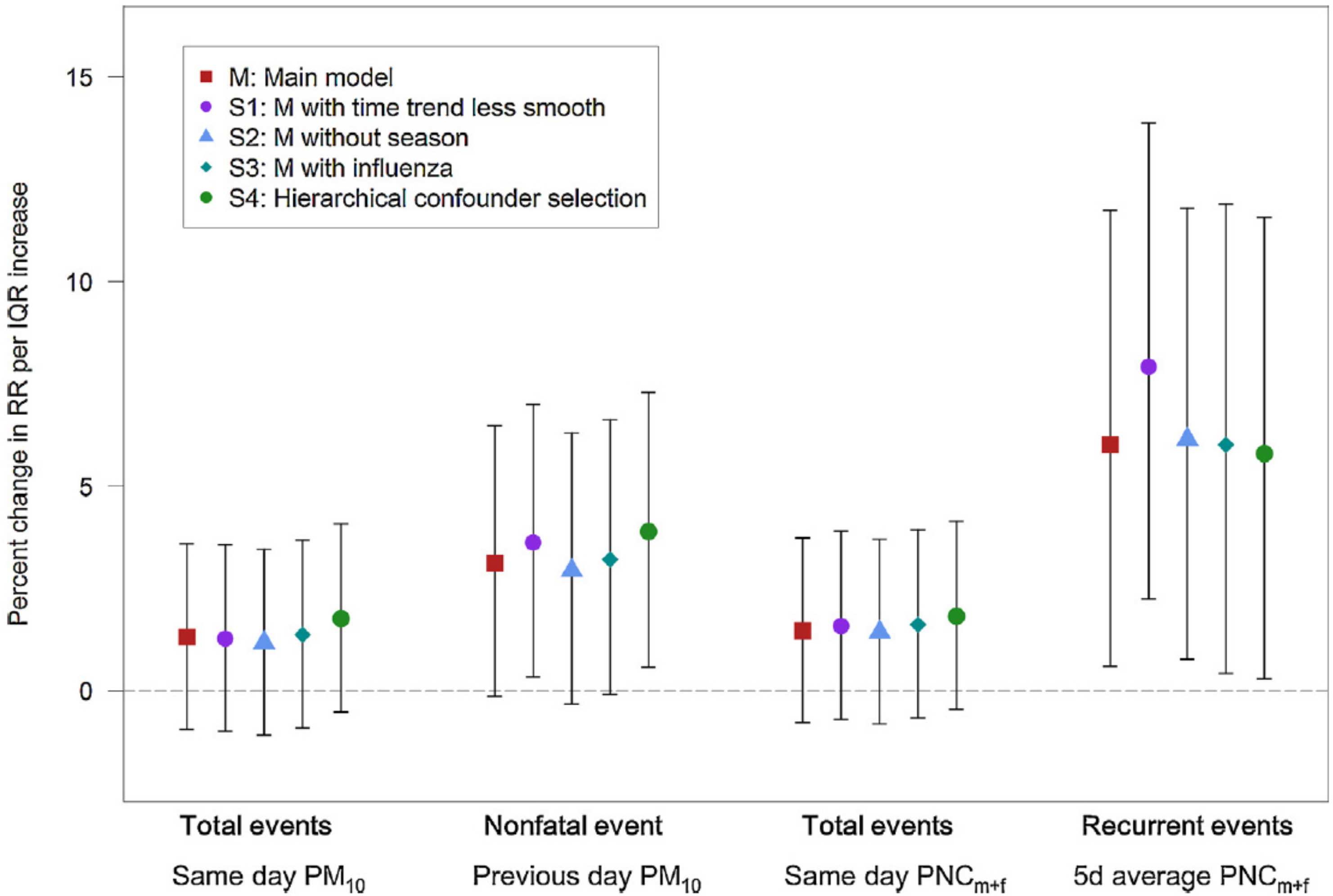


Figure 20. Percent change in respiratory hospital admissions associated with each 1,000 particles/cm³ increase in daily UFP (6-day average: lag 0-5).

effects on acute cardiovascular morbidity were heterogenous

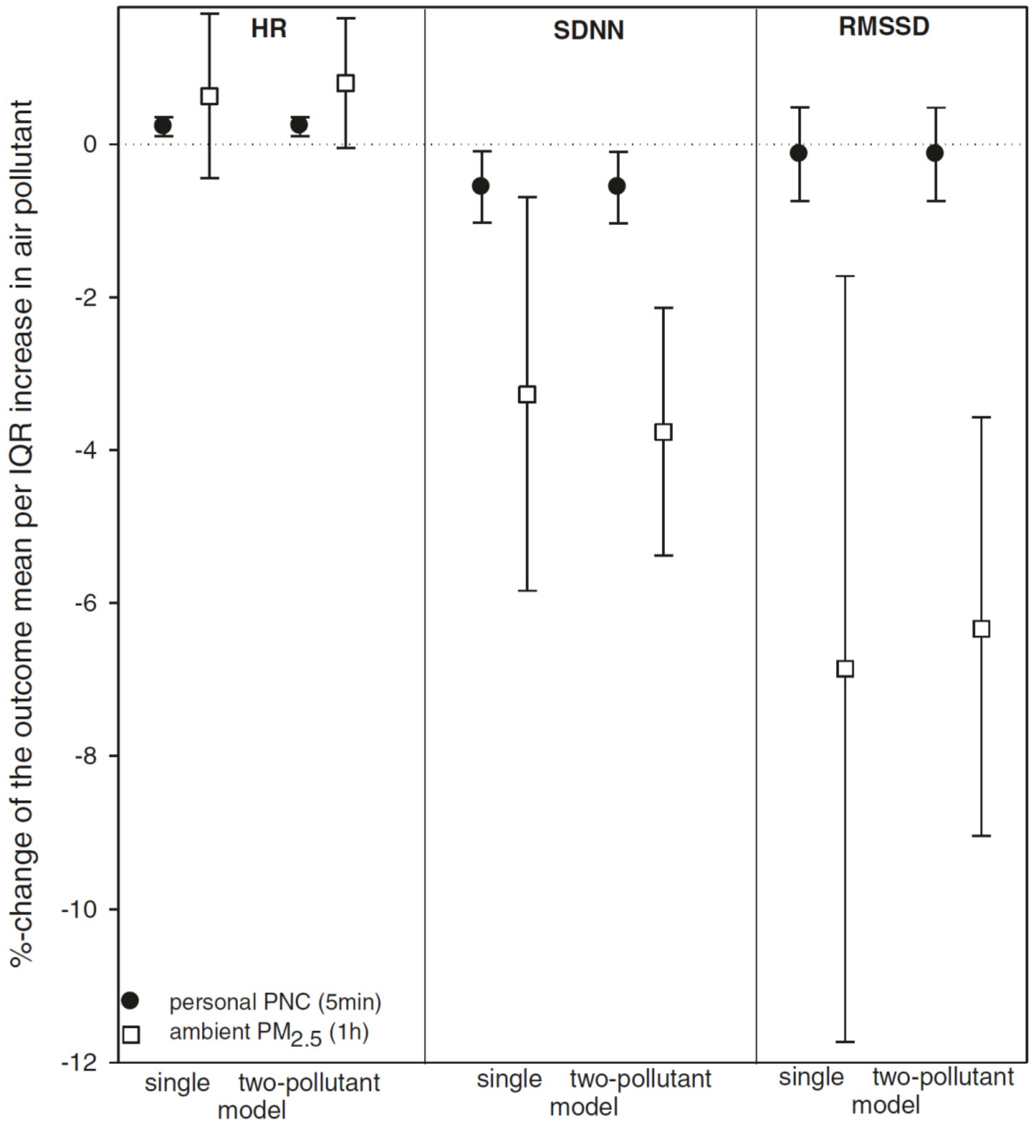
Registry-based myocardial infarction and short-term exposure to PM10 and UFP

Wolf K et al. Int J Hygiene and Environ Health 2015



Personal exposure PNC induced immediate changes in HRV
persons with impaired glucose tolerance /diabetes

Peters Particles Fibre Toxicol 2015



Size-fractioned UFP and HRV

diabetics and IGT from Shanghai

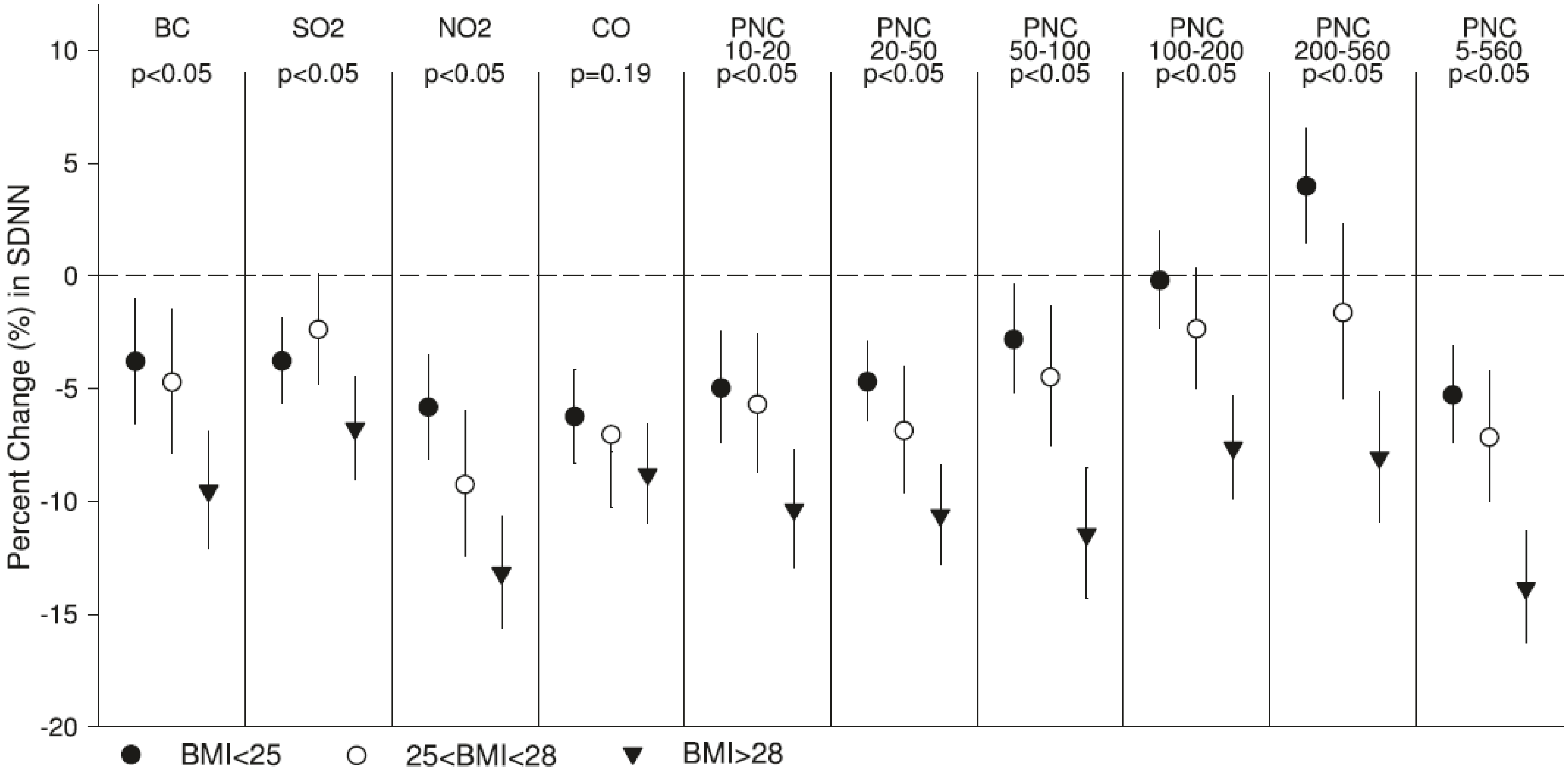
Sun et al. Particle Fibre Toxicol 2015

Table 4 Percent change in SDNN per IQR increases in proceeding 4-hour moving average exposures to ambient pollutants estimated in single-, and two-pollutant mixed-effects models

	Single-pollutant	Two-pollutant			
		Adj. for BC	Adj. for NO_2	Adj. for O_3	Adj. for CO
BC	-6.14 (-8.12,-4.11)	-6.14 (-8.12,-4.12)	1.09 (-1.72,3.98)	-5.18 (-7.31,-3)	0.07 (-2.7,2.91)
NO_2	-8.98 (-10.72,-7.18)	-9.56 (-11.85,-7.2)	-8.97 (-10.72,-7.18)	-9.33 (-11.34,-7.27)	-6.43 (-8.64,-4.17)
CO	-7.33 (-8.91,-5.73)	-7.37 (-9.43,-5.25)	-7.05 (-8.95,-5.11)	-6.68 (-8.52,-4.81)	-4.22 (-6.19,-2.21)
SO_2	-4.36 (-5.85,-2.86)	-2.91 (-4.66,-1.13)	-0.56 (-2.38,1.30)	-3.24 (-4.83,-1.62)	-1.25 (-3.02,0.55)
O_3	1.55 (-0.13,3.27)	0.51 (-1.22,2.27)	1.55 (-0.14,3.28)	0.94 (-0.77,2.68)	-1.73 (-3.51,0.09)
PNC_{5-560}	-7.89 (-9.69,-6.07)	-6.82 (-8.87,-4.72)	-7.73 (-9.57,-5.85)	-7.47 (-9.65,-5.24)	-4.54 (-6.82,-2.21)
PNC_{10-20}	-7.0 (-8.88,-5.08)	-7.05 (-8.92,-5.14)	-7.21 (-9.14,-5.24)	-6.73 (-8.65,-4.77)	-6.18 (-8.1,-4.21)
PNC_{20-50}	-6.57 (-8.07,-5.04)	-5.77 (-7.34,-4.17)	-6.36 (-7.92,-4.77)	-6.07 (-7.77,-4.33)	-4.32 (-6.07,-2.53)
PNC_{50-100}	-5.37 (-7.34,-3.35)	-2.76 (-5.29,-0.16)	-5.65 (-7.69,-3.56)	-3.49 (-6.03,-0.89)	1.52 (-1.32,4.45)
$PNC_{100-200}$	-2.98 (-4.63,-1.3)	2.53 (-0.29,5.42)	-2.53 (-4.26,-0.77)	0.3 (-1.84,2.49)	2.83 (0.71,4.99)
$PNC_{200-560}$	-0.45 (-2.43,1.56)	5.15 (2.53,7.84)	0.09 (-1.96,2.18)	3.25 (0.97,5.59)	4.46 (2.22,6.75)

Stronger UFP effects in obese persons

Sun et al. Particle Fibre Toxicol 2015

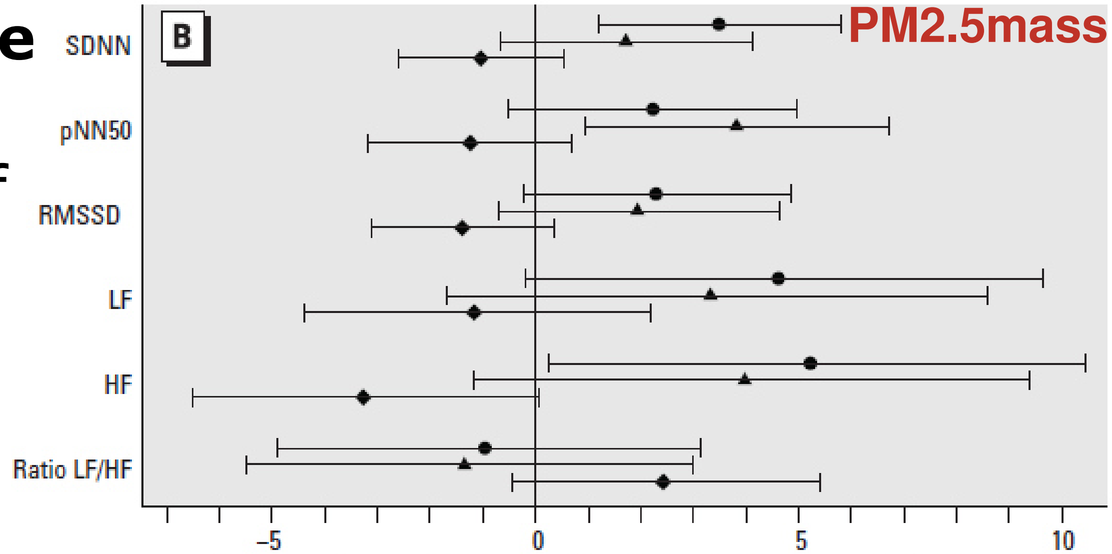


UFP LDSA & traffic noise

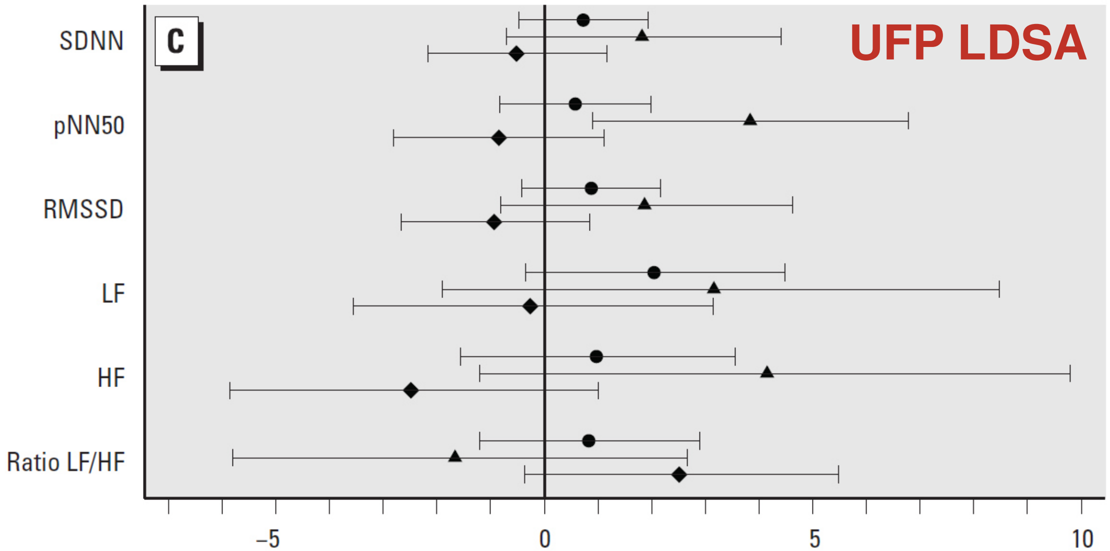
HRV

short-term exposure of highway maintenance workers

Meier R EHP 2014



Percent change (95% CI) with a 10-μg/m^3 increase in $PM_{2.5Mass}$ (circles), 1-dB(A) increase in noise at work (triangles), 1-dB(A) increase in noise after work (diamonds)

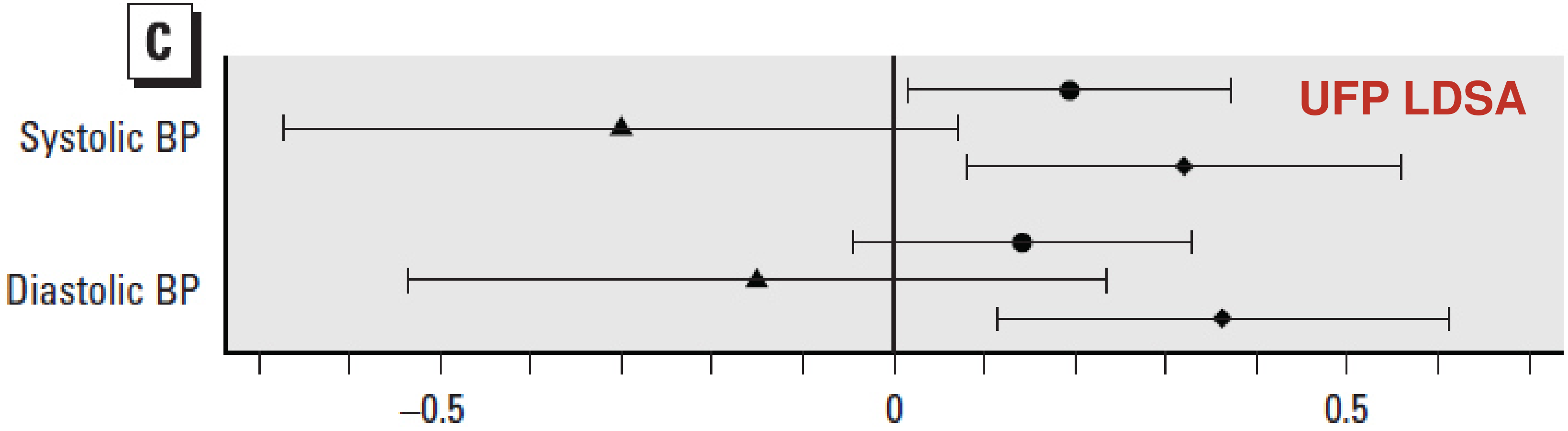


Percent change (95% CI) with a 10-μm^2/cm^3 increase in UFP LDSA (circles), 1-dB(A) increase in noise at work (triangles), 1-dB(A) increase in noise after work (diamonds)

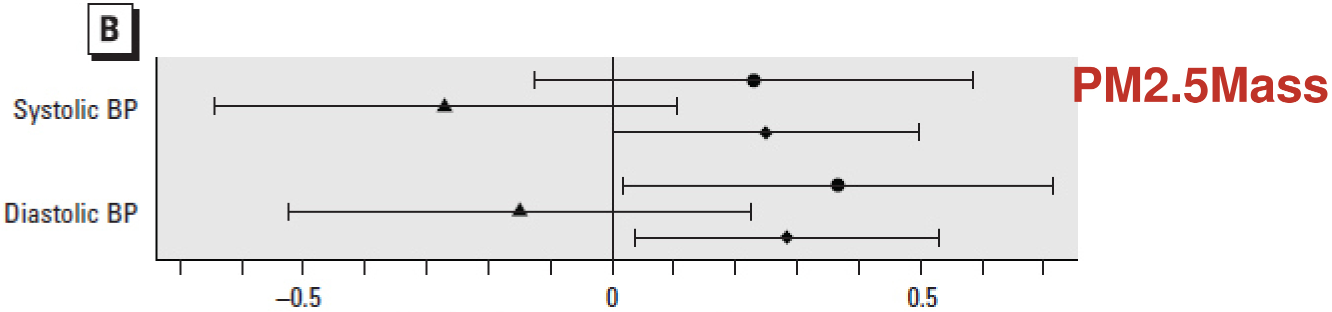
UFP LDSA & traffic noise: blood pressure

short-term exposure of highway maintenance workers

Meier R EHP 2014



Percent change (95% CI) with a 10-µm²/cm³ increase in UFP LDSA (circles), 1-dB(A) increase in noise at work (triangles), 1-dB(A) increase in noise after work (diamonds)



Percent change (95% CI) with a 10-µg/m³ increase in $PM_{2.5Mass}$ (circles), 1-dB(A) increase in noise at work (triangles), 1-dB(A) increase in noise after work (diamonds)

Particle exposure and blood markers

highway maintencance workers

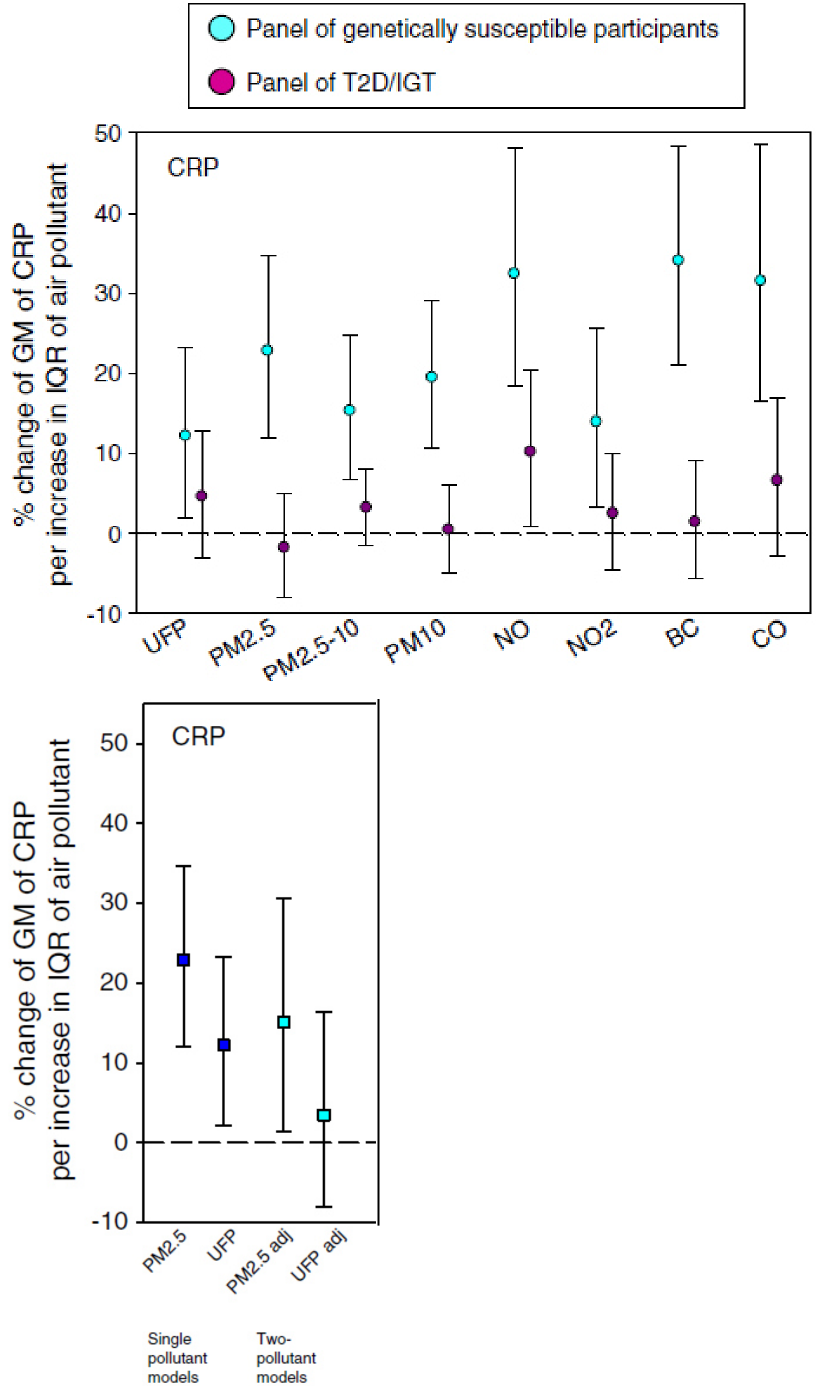
Meier et al. EHP 2014

Table 3. Associations of particle exposures during work and proinflammatory and prothrombotic markers in the blood [percent differences (95% CI)].[a]

Outcome	$PM_{2.5Realtime}$	$PM_{2.5Mass}$	LDSA
IL-6	−1.18 (−2.60, 0.26)	−1.52 (−3.98, 1.00)	−0.65 (−1.98, 0.70)
TNFα	−0.25 (−0.58, 0.08)	−0.60 (−1.15, −0.04)	0.02 (−0.31, 0.35)
CRP	1.97 (−0.62, 4.62)	5.56 (1.05, 10.27)	1.38 (−0.88, 3.70)
SAA	1.23 (−0.79, 3.29)	3.56 (0.04, 7.21)	1.00 (−0.88, 2.91)
vWF	0.30 (−0.55, 1.15)	0.41 (−1.06, 1.88)	0.17 (−0.66, 0.99)
Tissue factor	−0.96 (−2.24, 0.32)	−0.56 (−2.80, 1.69)	−0.84 (−2.05, 0.37)

5-day average exposure to air pollutants and inflammatory blood markers in panel of genetically susceptible

Rückerl
Environ International 2014



Particles & systemic biomarkers in single blind cross-overs study

UFP and urinary 8-OHdG

Liu e tal. EHP 2015

Table 3. Mean changes in urinary biomarker concentrations (95% CI) per 100-µg/m^3 increase in CAP mass concentration in single- and two-pollutant models.

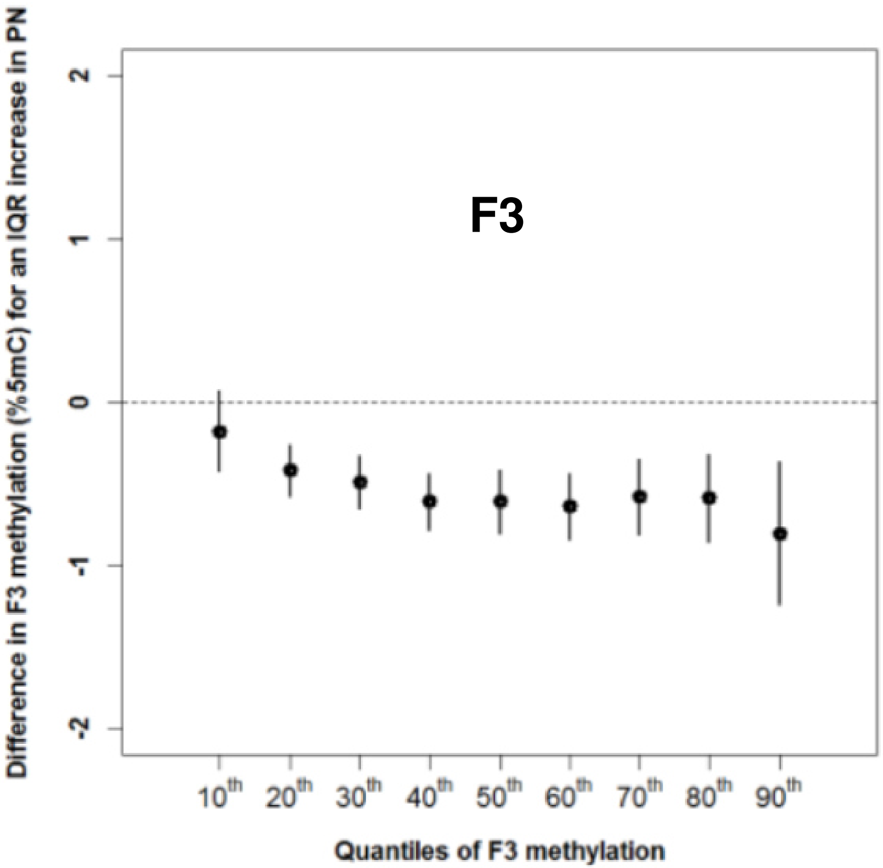
	Coarse CAP		Fine CAP		Ultrafine CAP	
Biomarker/model	1 hr postexposure	21 hr postexposure	1 hr postexposure	21 hr postexposure	1 hr postexposure	21 hr postexposure
8-OHdG (ng/mg creatinine)						
CAP alone	0.24 (–0.02, 0.50)*	0.01 (–0.26, 0.27)	–0.19 (–0.55, 0.17)	–0.19 (–0.50, 0.13)	0.69 (0.09, 1.29)**	0.19 (–0.41, 0.79)
+ SO_2	0.29 (0.02, 0.56)**	0.06 (–0.22, 0.35)	–0.20 (–0.58, 0.18)	–0.20 (–0.52, 0.13)	0.72 (0.09, 1.34)**	0.18 (–0.42, 0.78)
+ O_3	0.22 (–0.07, 0.51)	–0.03 (–0.32, 0.27)	–0.23 (–0.60, 0.15)	–0.18 (–0.51, 0.15)	0.68 (0.09, 1.26)**	0.19 (–0.40, 0.79)
+ NO_2	0.27 (–0.03, 0.57)*	–0.05 (–0.38, 0.27)	–0.20 (–0.62, 0.21)	–0.33 (–0.67, 0.01)*	0.76 (0.15, 1.38)**	0.22 (–0.40, 0.84)
+ CO	0.30 (0.04, 0.57)**	0.02 (–0.26, 0.30)	–0.12 (–0.50, 0.26)	–0.18 (–0.51, 0.16)	0.57 (0.00, 1.15)**	0.29 (–0.34, 0.91)

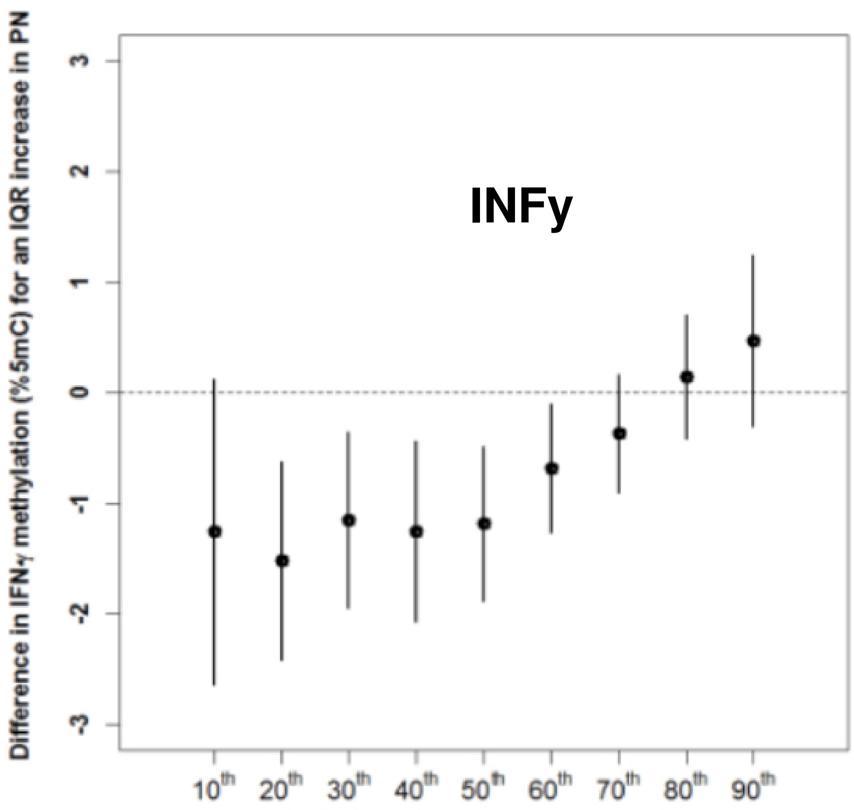
Association of particle air pollution

4-week moving average

with gene-specific methylation

Bind M-A EHP 2015





Particle Number and DNA metylation

Relevant post-HEI report evidence for (stronger/specific) long-term health effects of ultrafine particles ?

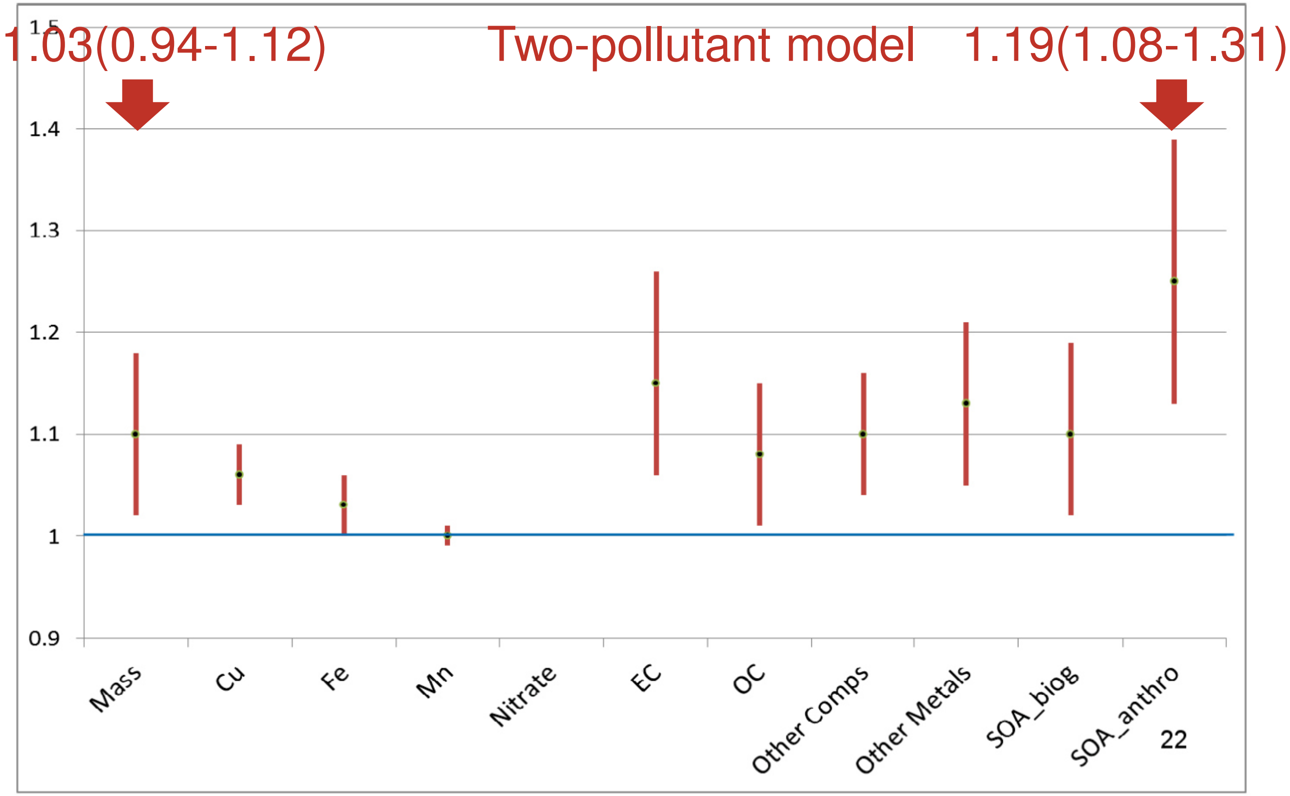
Long-Term Effect of Fine and Ultrafine Particles

Ischemic Heart Disease Mortality in California Teachers

Ostro et al. EHP 2015

Association of $PM_{0.1}$ Constituents with IHD Mortality

(Hazard Ratios and 95% CI Using IQR)



association with IHD, but not overall/ pulmonary mortality

UFP provided slightly better fit than PM2.5

accumulation of damaage

Acute effect studies – myocardial infarction

Nawrot et al meta-analysis, Lancet

2% increase per 10μg/m³ PM2.5

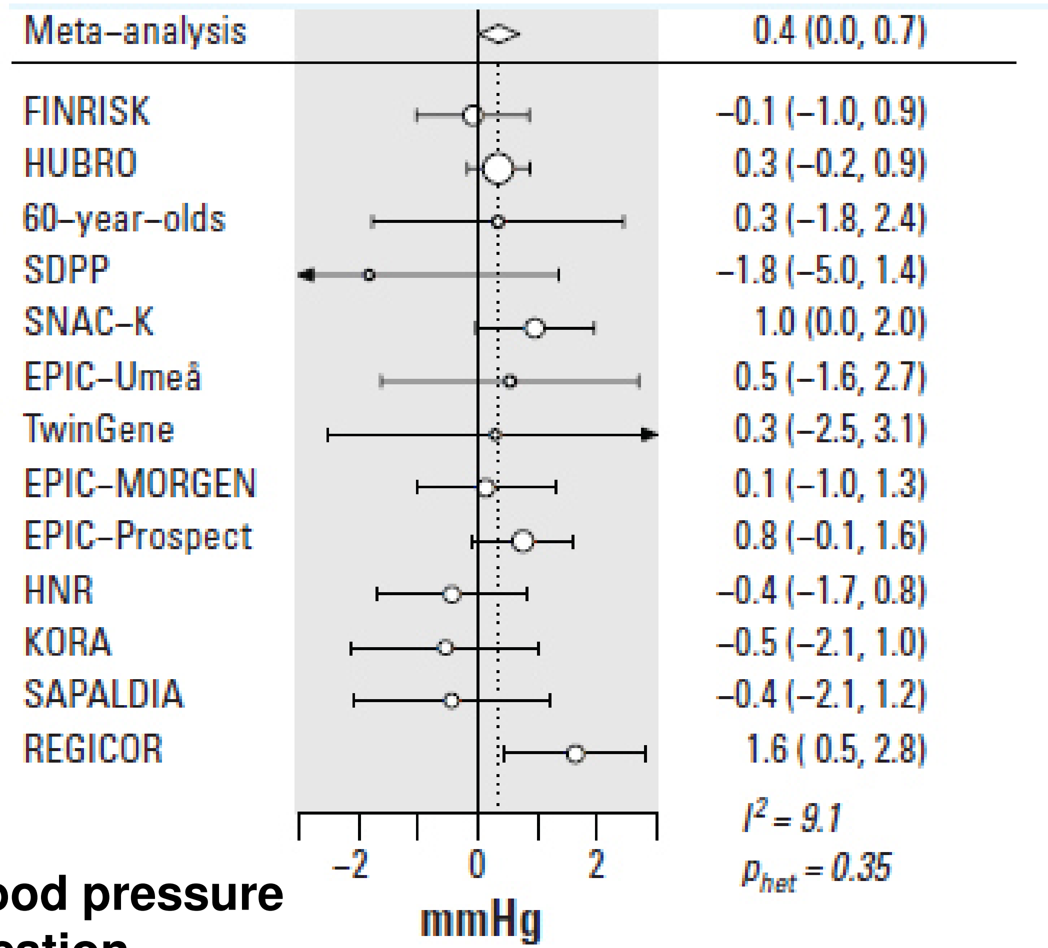
Long-term effect studies –coronary events in ESCAPE

Cesaroni et al, BMJ 2014

26% increase per 10μg/m³ PM2.5

Systolic blood pressure and traffic load on major roads within 100 m – ESCAPE Study

Fuks EHP 2015

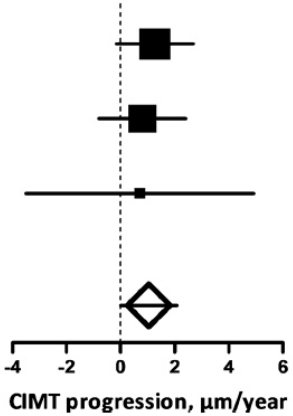


In persons without blood pressure lowering medication

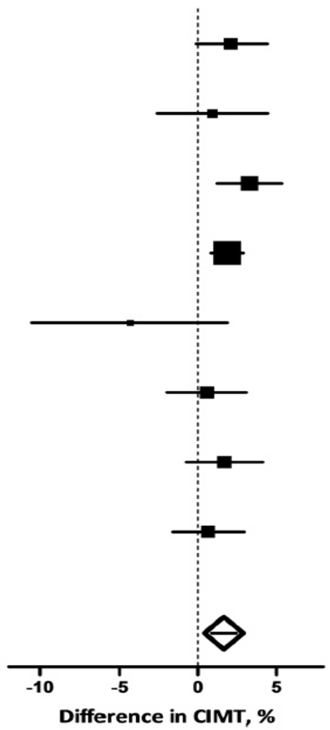
Atherosclerosis – main underlying pathology of CVD - association with longterm PM2.5 exposure

Nawrot PLoS One 2015

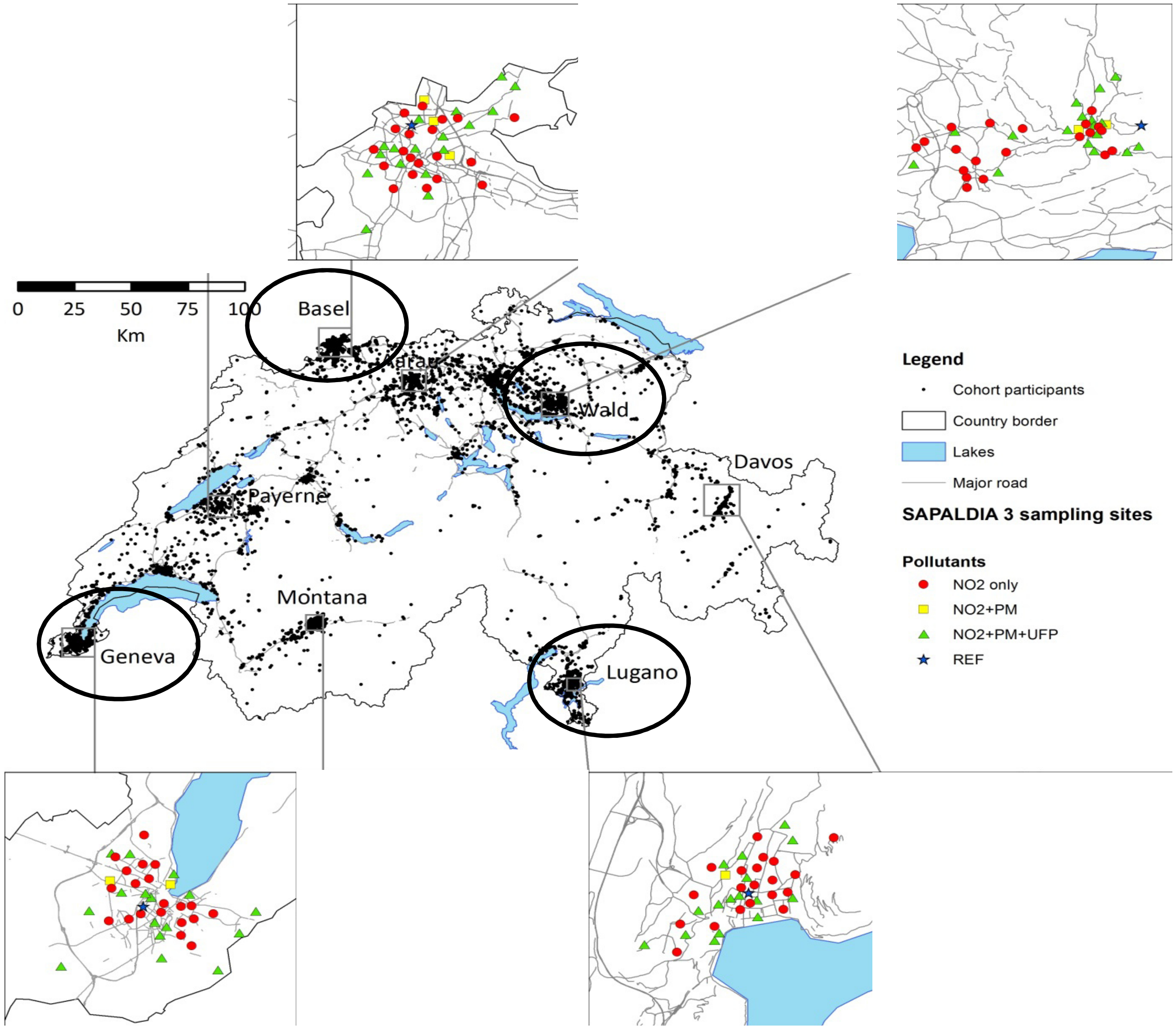
Source	Number of participants	Relative Study Weight, %	Estimated Change (95% CI), %
Künzli *et al.* [26] 2010	1,483	52.5	1.27 (-0.16 to 2.69)
Adar *et al.* [23] 2013	5,276	41.5	0.80 (-0.80 to 2.40)
Gan *et al.* [28] 2014	509	6.0	0.71 (-3.51 to 4.93)
Combined (I^2=0%; Cochran Q, *P*=0.9)	7,268		1.04 (0.01 to 2.07) *P*=0.048



Source	Number of participants	Relative Study Weight, %	Estimated Change (95% CI), %
Künzli *et al.* [19] 2005	798	11.2	2.10 (-0.10 to 4.45)
Lenters *et al.* [21] 2010	745	4.9	0.94 (-2.59 to 4.47)
Tonne *et al.* [22] 2012	2,347	13.3	3.30 (1.24 to 5.36)
Adar *et al.* [23] 2013	5,276	38.9	1.85 (0.83 to 2.89)
Perez *et al.* [24] 2015 ESCAPE: IMPROVE-Stockholm	487	1.6	-4.32 (-10.53 to 1.90)
Perez *et al.* [24] 2015 ESCAPE: HNR	3,759	9.1	0.57 (-1.98 to 3.11)
Perez *et al.* [24] 2015 ESCAPE: KORA	2,646	9.9	1.70 (-0.74 to 4.14)
Perez *et al.* [24] 2015 ESCAPE: REGICOR	2,291	11.1	0.65 (-1.63 to 2.94)
Combined (I^2=11%; Cochran Q, *P*=0.34)	18,349		1.66 (0.86 to 2.46) *P*<0.0001



SAPALDIA
PM monitoring sites for long-term spatial modelling



SAP3 Monitoring Methods

NO_2

- Passive Passam tubes
- 2-week sampling periods

Gravimetric $PM_{2.5}$/PM_{10}

- $PM_{2.5}$ & PM_{10} w/ Harvard Impactors (@ 4 L/min)
- 37mm Teflon filter (23±2 ^{0}C, 35±5% RH)
- 2-week sampling periods

Particle Number & Size

- miniDiSC (1-sec resolution)
- 2 week monitoring period
- Dp >15 nm

SAPALDIA
CIMT association with home-outdoor pollutants
4 sites; 1500 subjects age >50
Aguilera et al – in preparation

	Main Model	Two-Pollutant Model	PNC estimate in two-pollutant model
Exposure, P90-P10 increase	**%change**	**%change**	**%change**
PM10 last year (5.5 µg/m3)	1.58	-0.05	2.13
PM2.5 last year (4.2 µg/m3)	**2.10**	1.73	0.63
Vehicular source of PM2.5	1.67	1.27	0.87
Crustal course of PM2.5	-0.58	-1.53	3.35
LDSA (30.5 µg/m3)	**2.32**	3.41	-1.11
PNC (12’639 particles/m3)	**2.06**	n.a.	n.a.

Pearson PNC with LSDA, PM10, PM2.5, Vehicular PM2.5: >.085

SAPALDIA
CIMT association with home-outdoor pollutants
modificaton by anti-inflammatory, CIMT-related SNP

	% change	95% CI		P-value
PM 2.5 biannual mean (10 µg/m3 increase)				
Genotype 1	4.764	-1.419	10.985	0.131
Genotype 2	19.132	5.128	33.332	0.007
Genotype 3	33.707	6.120	62.050	0.016
LDSA (10µm2/m3 increase				
Genotype 1	0.914	-0.201	2.029	0.108
Genotype 2	3.325	0.766	5.891	0.011
Genotype 3	5.743	0.721	10.790	0.025

Longterm exposure to traffic PM & Incident Diabetes

Weinmayer EHP 2015

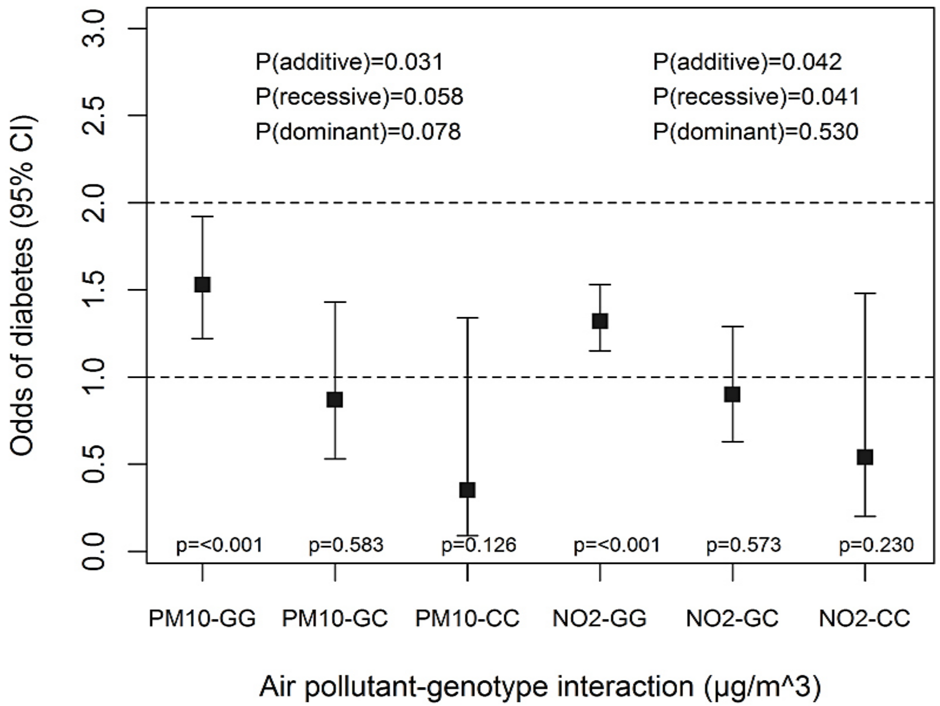
			Increase in PM equivalent to the IQR		Increase of 1 μg/m³ PM	
		IQR	Crude model	Main model[a]	Crude model	Main model[a]
Total PM	PM_{10ALL}	3.78	1.08 (0.96;1.21)	1.20 (1.01;1.42)	1.02 (0.99;1.05)	1.05 (1.00;1.10)
	$PM_{2.5All}$	2.29	1.03 (0.92;1.15)	1.08 (0.89;1.29)	1.01 (0.96;1.06)	1.03 (0.95;1.12)
Traffic	PM_{10TRA}	0.33	1.15 (1.05;1.27)	1.11 (0.99;1.23)	1.54 (1.15;2.05)	1.36 (0.98;1.89)
	$PM_{2.5TRA}$	0.32	1.15 (1.04;1.26)	1.10 (0.99;1.23)	1.53 (1.15;2.05)	1.36 (0.97;1.89)
Distance to major road (>200 m reference) (N = 3186)	<= 100 (N = 180)				1.31 (0.99;1.75)	1.37 (1.04;1.81)
	>100-200 (N = 339)				0.81 (0.60;1.12)	0.77 (0.57; 1.04)

[a] main model adjusted for age, gender, lifestyle variables, BMI, individual and neighbourhood SES, and city

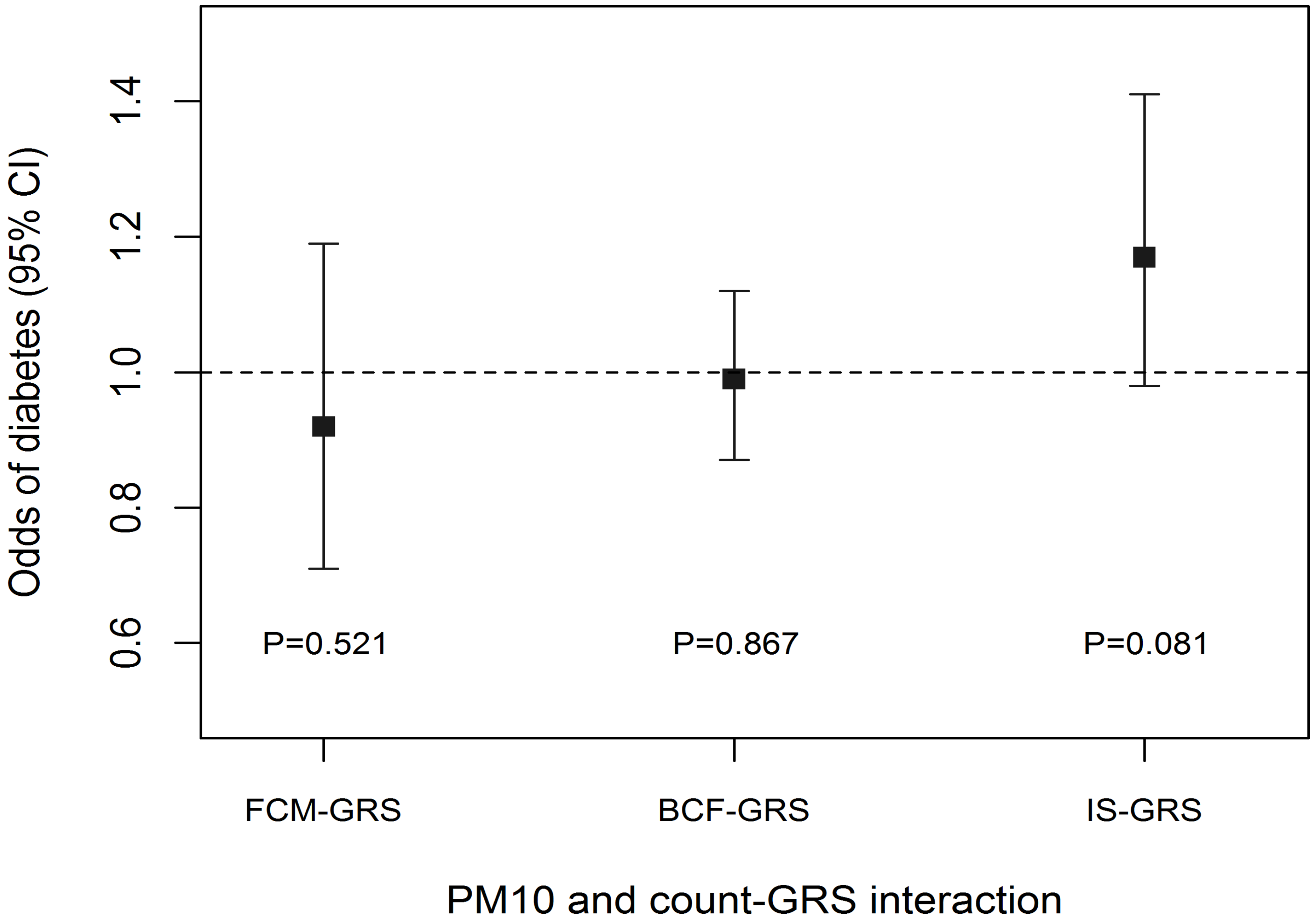
Longterm exposure to traffic air pollution
modification of association with diabetes and HRV modified by IL6 gene variants

Adam M PLoOne 2014; Eze in preparation

HRV parameters	*IL6*-174 G/C	Estimate[a]	95% CI		p_{TPM10} (by genotype)[c]	$p_{interaction}$ (genetic model)[d]
SDNN	GG	**−1.77**	−3.51	0.01	0.051	**0.028 (1)**
	GC	**1.06**	−0.47	2.62	0.177	
	CC	**0.73**	−1.62	3.14	0.545	

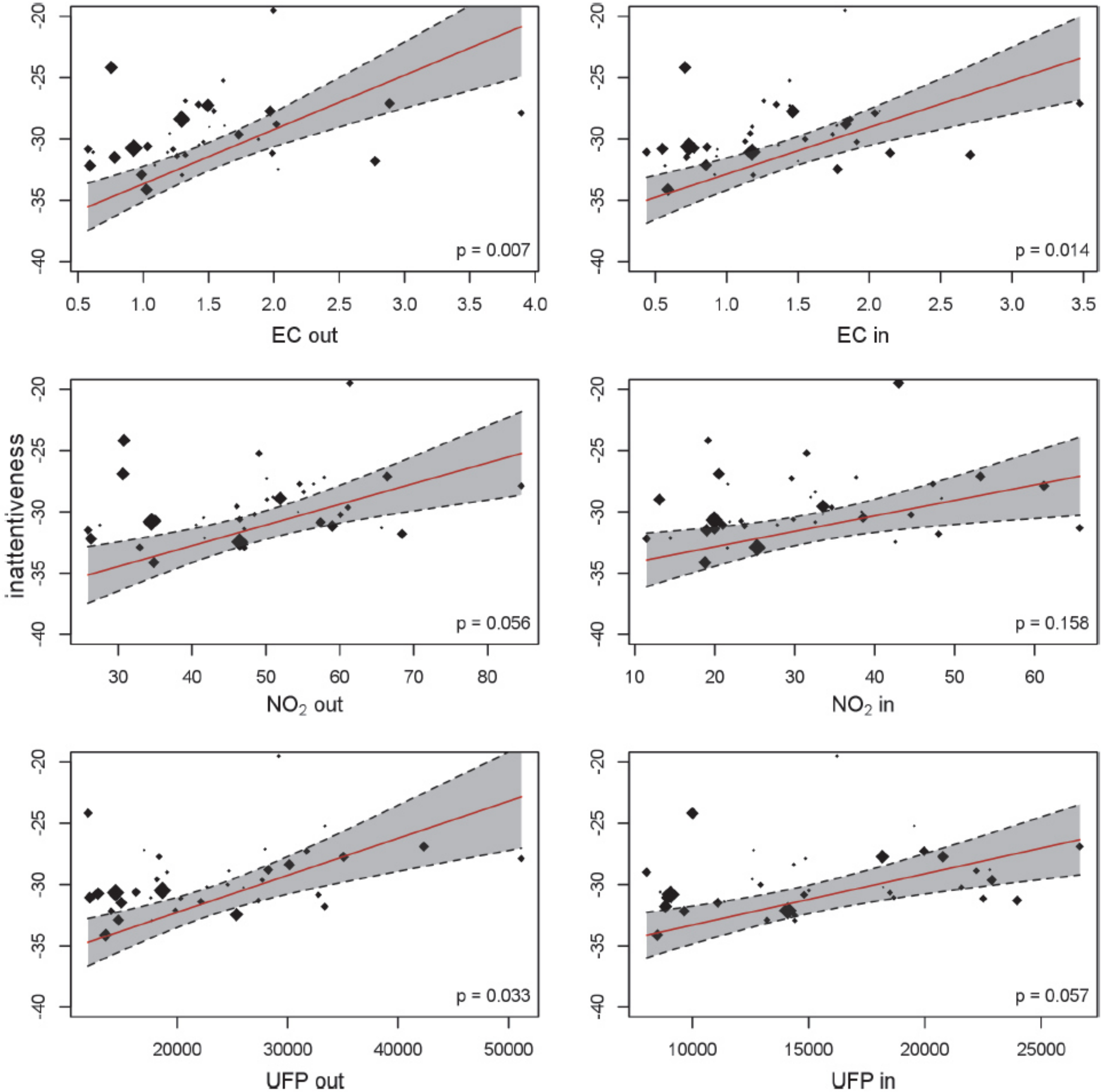


Longterm PM10 and diabetes:
modification by diabetes gene scores
Eze / Probst-Hensch, unpublished



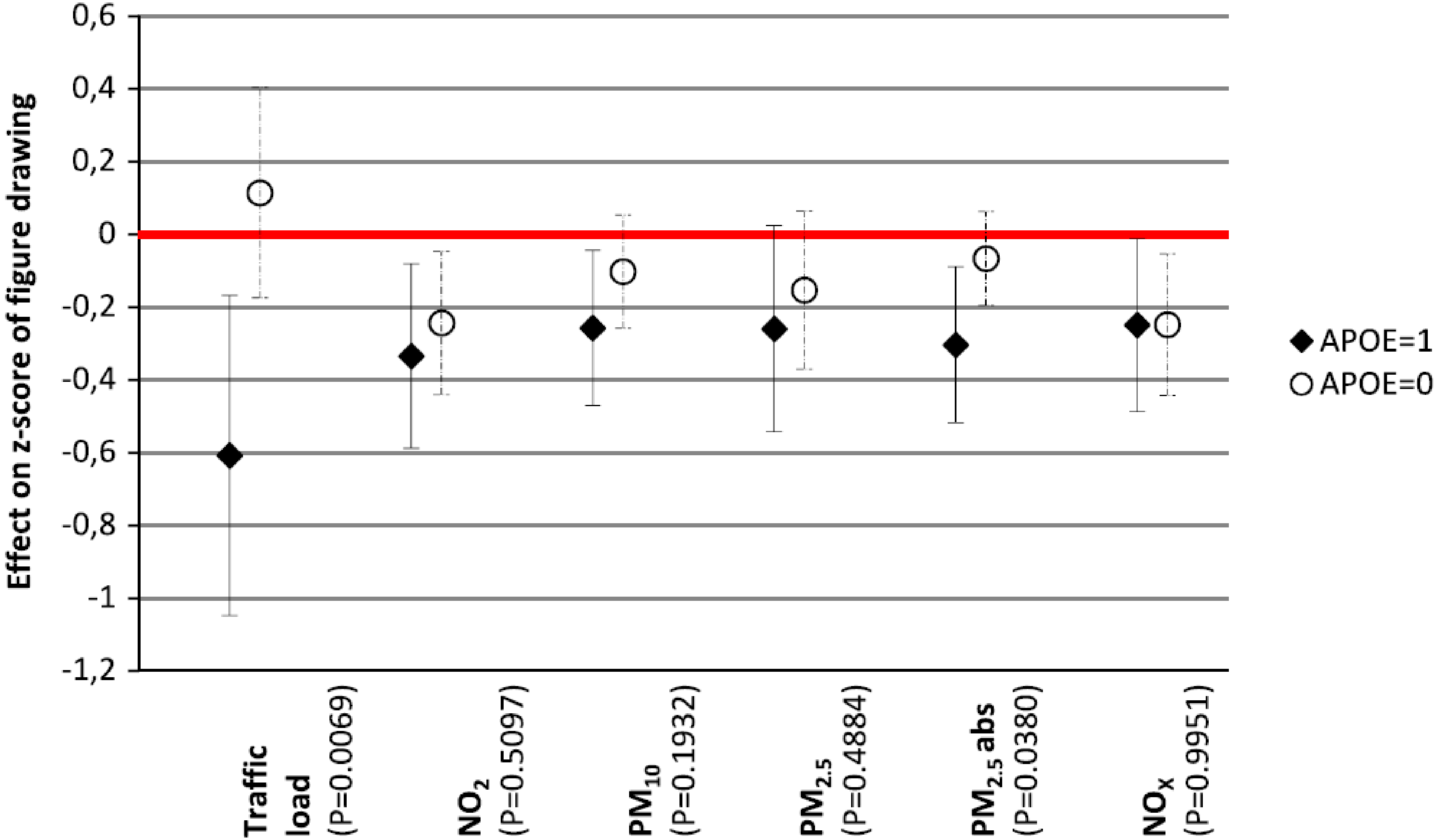
Traffic Air Pollution in Schools and Cognitive Development in School Children

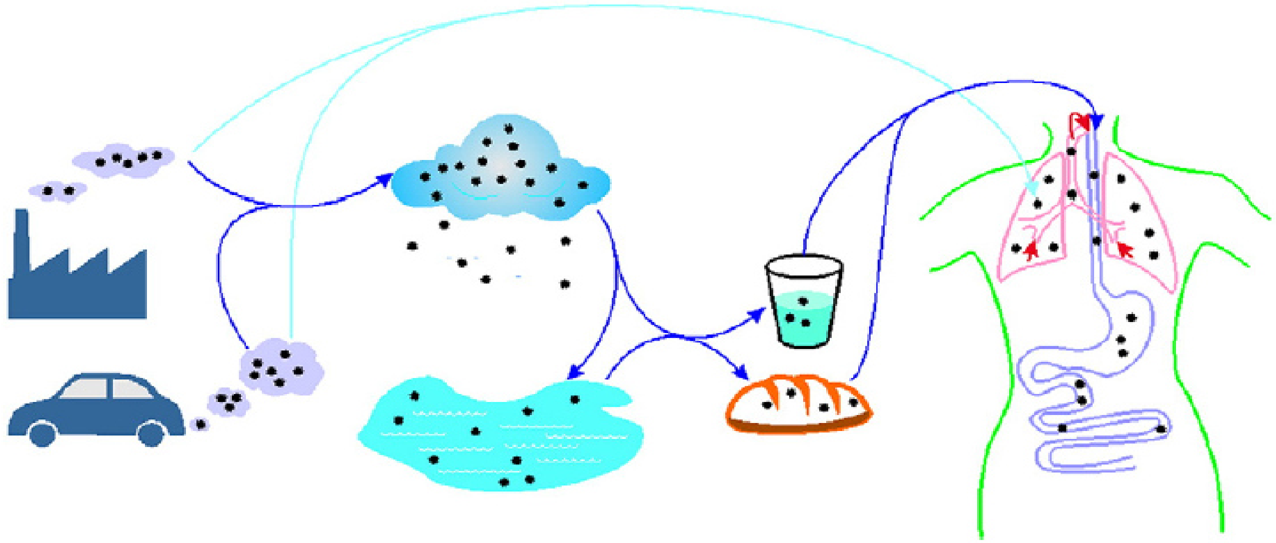
Sunyer J et al. PLoS Med 2015



Air pollution and cognitive function in women: modification by apoE gene variants

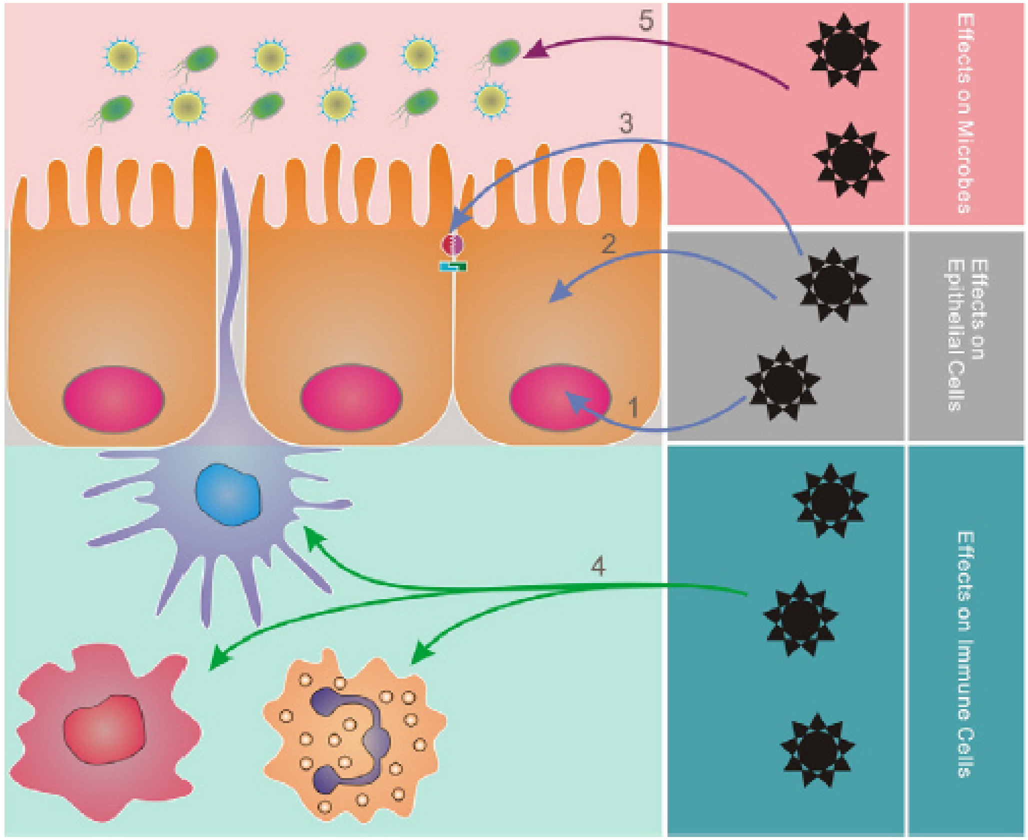
Schikowski T Environ Res 2015





UFP – role in gastrointestinal disorders ?

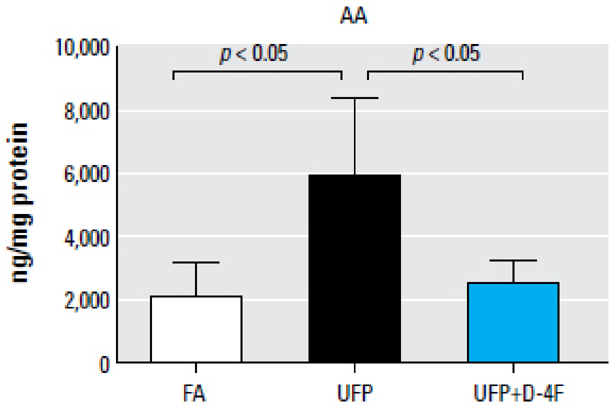
Beamish
J Crohns & Colitis 2011

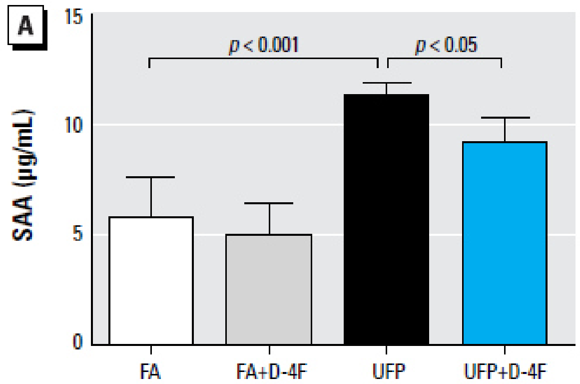


UFP effects on lipid metabolism and inflammation in mouse digestive system

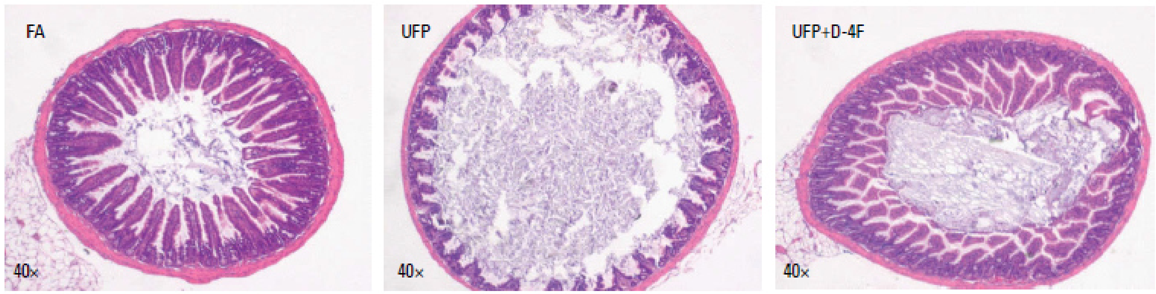
Li R EHP 2015

arachidonic acid

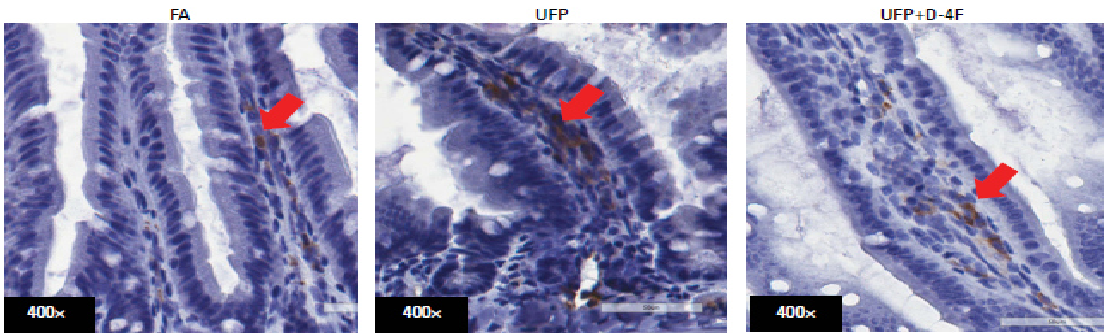




shortening of villi in small intestines

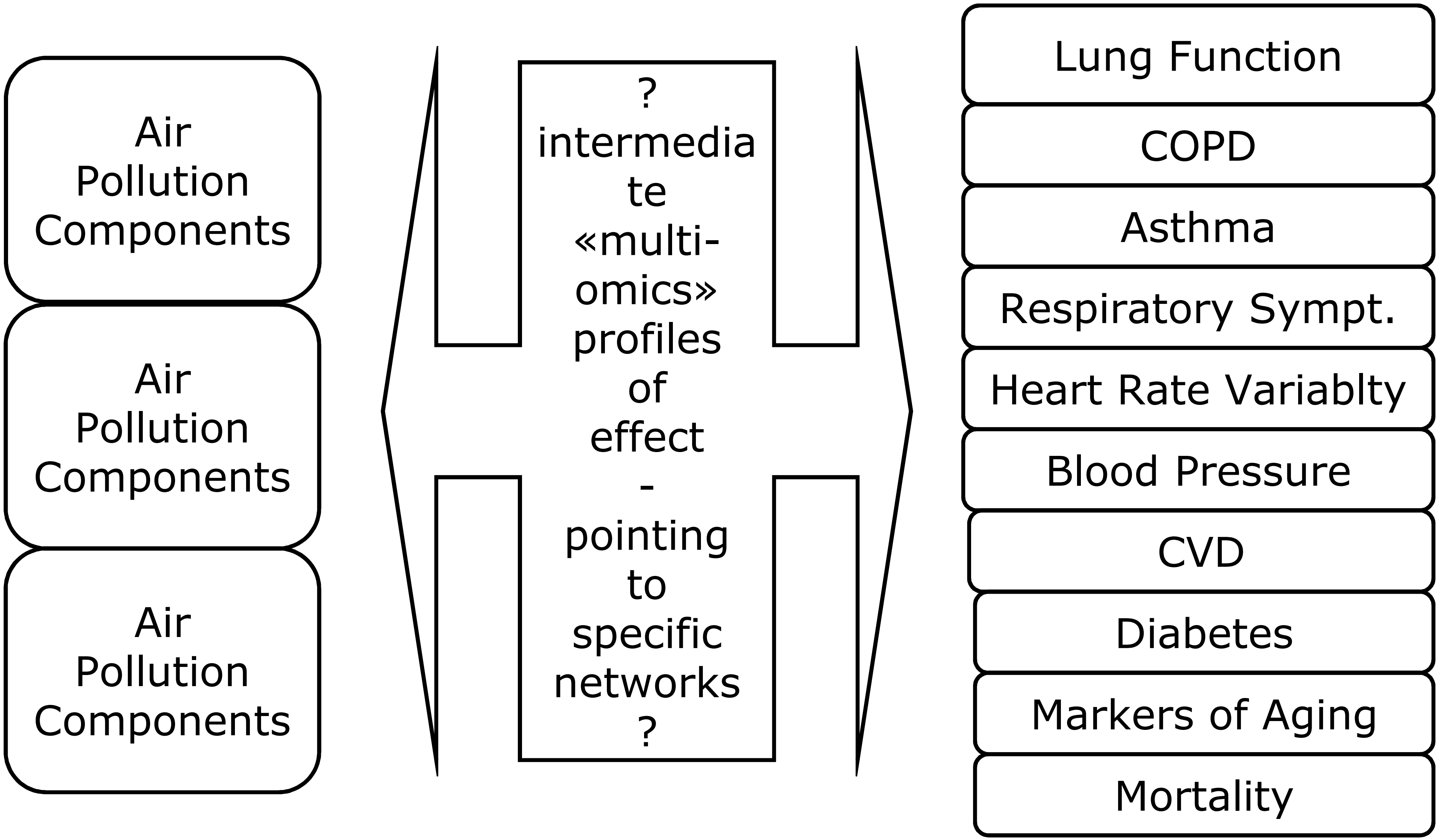


increased number of macrophages in small intestines



Can exposome approaches improve understanding of health effects of ultrafine particles ?

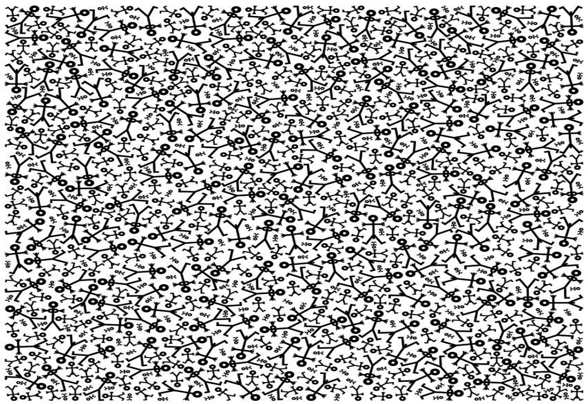
Air pollution exposome & phenome



SAPALDIA in Exposomics

EU 7th Framework Project, PI P. Vineis

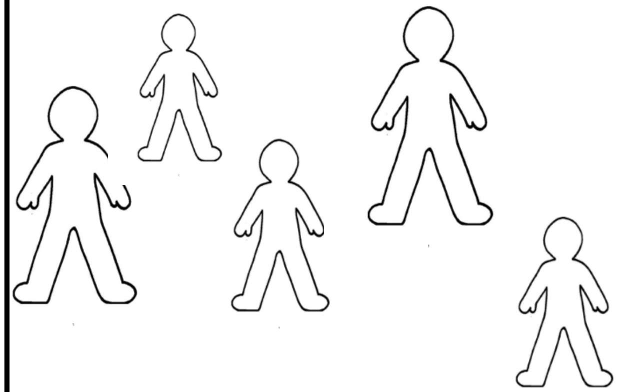
SAPALDIA



archived blood

historical health & pollution data

SAPALDIA subgroup



personalized air pollution measurements

blood for -omics

- omics biomarkers of health phenotypes

overlap – mechanisms

- omics biomarkers of specific air pollutants

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(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics