Gene-Air Pollution Interactions and Beyond

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Air pollution exposure is associated with a broad set of health effects. Genetic variants and the assessment of gene-air pollution interactions are important research tools to investigate causality and mechanisms underlying the observed associations and to study individual differences in susceptibility to pollutants.

It is assumed that oxidative and inflammatory properties of air pollutants mediate part of the adverse health effects on the lung and the heart. It is unlikely that c-reactive protein (CRP) plays a key role in mediating these effects, as studies applying the principle of Mendelian randomization do not point to CRP being a key risk markers for either coronary heart disease or COPD.

The well characterized population-based SAPALDIA cohort with its associated biobank belongs to the small set of longitudinal studies that allow investigating the long term impact of air pollution on cardiorespiratory morbidity and to study underlying mechanisms. First, we found single genetic variants in selected antioxidative genes such as glutathione S-transferase P1 to modify the beneficial effect of improvements in air quality as assessed based on PM10 in attenuating age related lung function decline. We observed that the lung function of some persons in the general population, based on their genetic make-up, did not benefit from the air quality improvement.Second, in a pathway analyses we studied genetic variation in over 150 genes involved in oxidative stress regulation. The interaction of oxidative stress gene variants with 11 year cumulative PM10 exposure on lung function decline in adults was contrasted to equivalent interactions with 11 year cumulative cigarette smoke exposure. The pathway approach suggested that gene variants modifying the lung function effects of PM10 and tobacco smoke, respectively, differed and suggests different mechanisms mediating the respiratory effects of inhaled particles from the ambient air and cigarette smoke. Third, we conducted agnostic genome wide environment interaction analyses (GWES) on the association of PM10 exposure and lung function decline, albeit with limited power. Pilot data from the GWES provide first evidence for potentially novel mechanisms underlying the PM10 effects on lung function.

Large air pollution and genetics research consortia must confirm the observed interactions with sufficient statistical power. As evidence by the example of inducible nitric oxide synthase both, genetic and epigenetic variation interact in highly complex manners in modifying the effect of air pollution on lung health. Novel exposome approaches in the future will rely on existing cohorts and biobanks to conduct environmental epidemiology beyond genetics by applying other –omics techniques and by refining exposure assessment.

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Gene Air Pollution Interactions
-
and Beyond……

Prof. Dr. phil.II et PhD Nicole Probst-Hensch

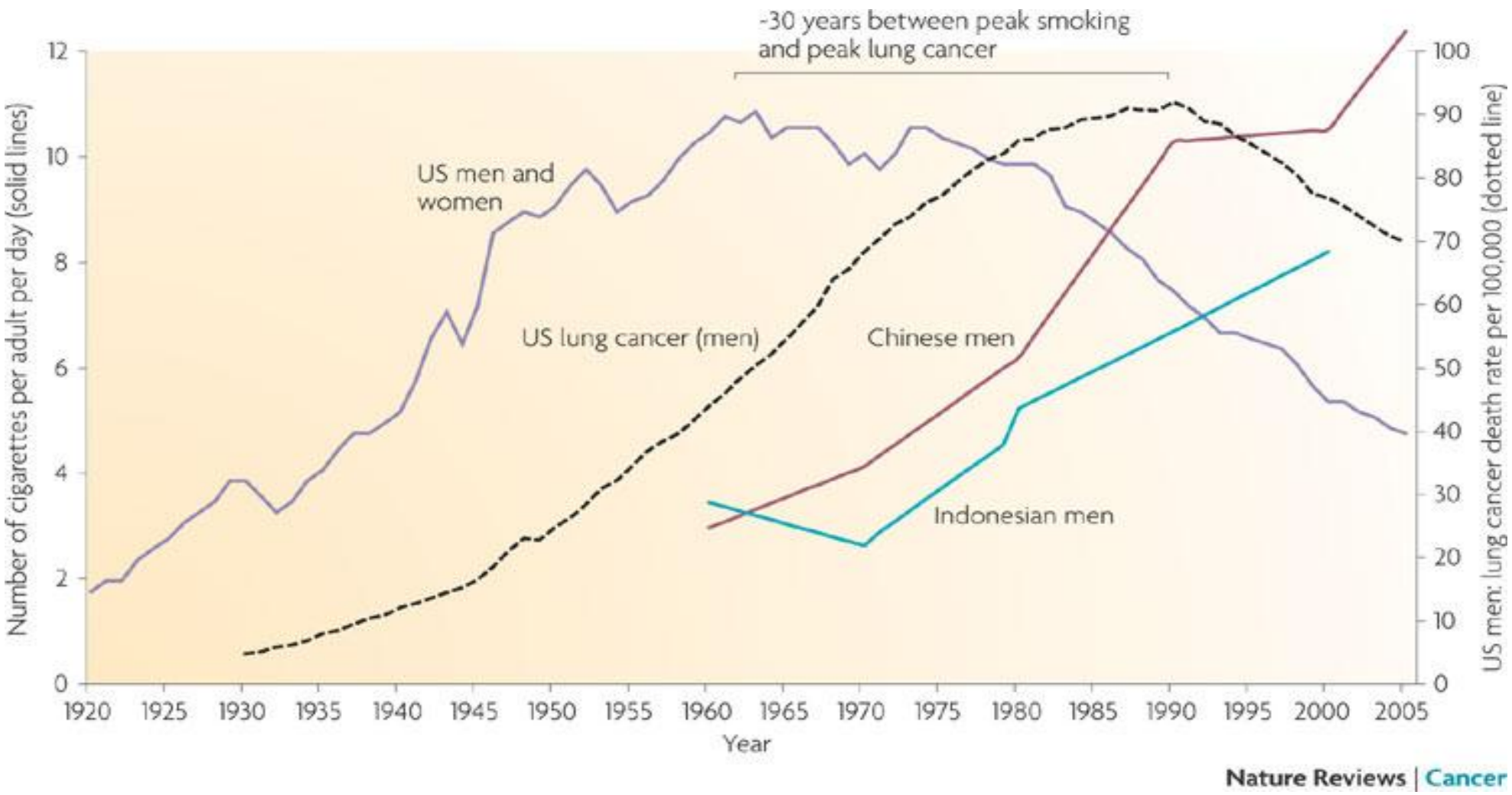
President Obama's wife convinced him to stop smoking……

……but not to reduce air pollution

Obama Administration Abandons Stricter Air-Quality Rules
New York Times, September 2, 2011
WASHINGTON — President Obama abandoned a contentious new air pollution rule on Friday…….

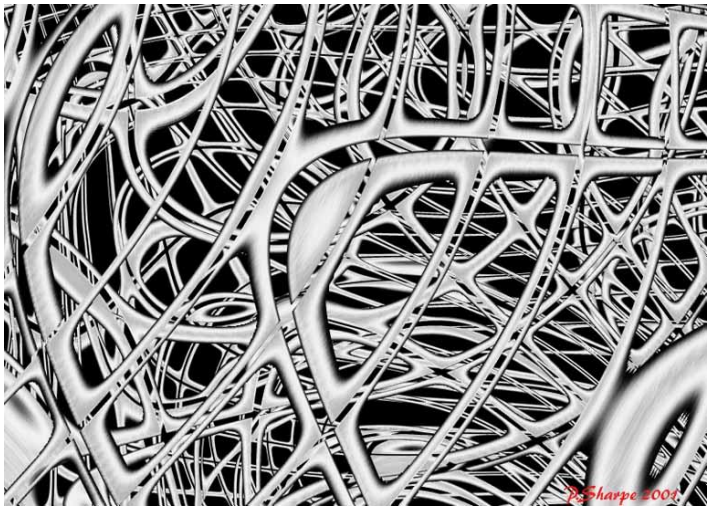
The lung cancer epidemic:it is about smoking…

Jha P. Nat Rev Cancer 2009



….the air pollution epidemic is just more complex

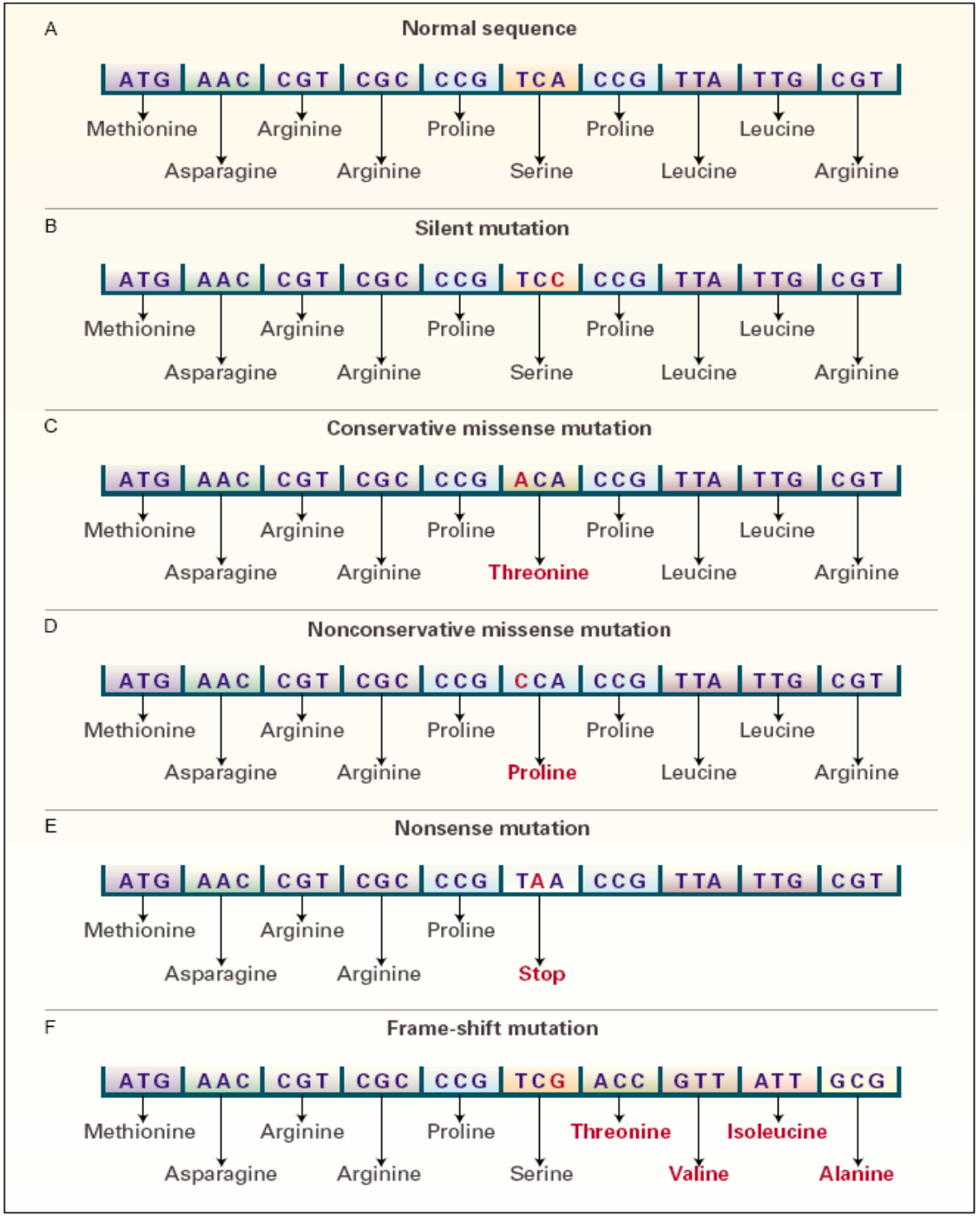
- small effects on an individual level
- exposurecorrelated with lifestyle, socio-demographic and other environmental factors



- Air Pollution and Health: a Complex Network
- **Genetic Variation: a Valuable Research Tool**
- Beyond Genetic Variation: a Broader –Omics Perspective

Single Nucleotide Polymorphisms SNPs

- most common type of genetic variant
- 20-50 common SNPs in a gene
- present in every cell of the body
- can lead to lifelong differences in molecular activities



Potential use of genetic variants and gene-environment interaction studies

not as GENE TEST for:

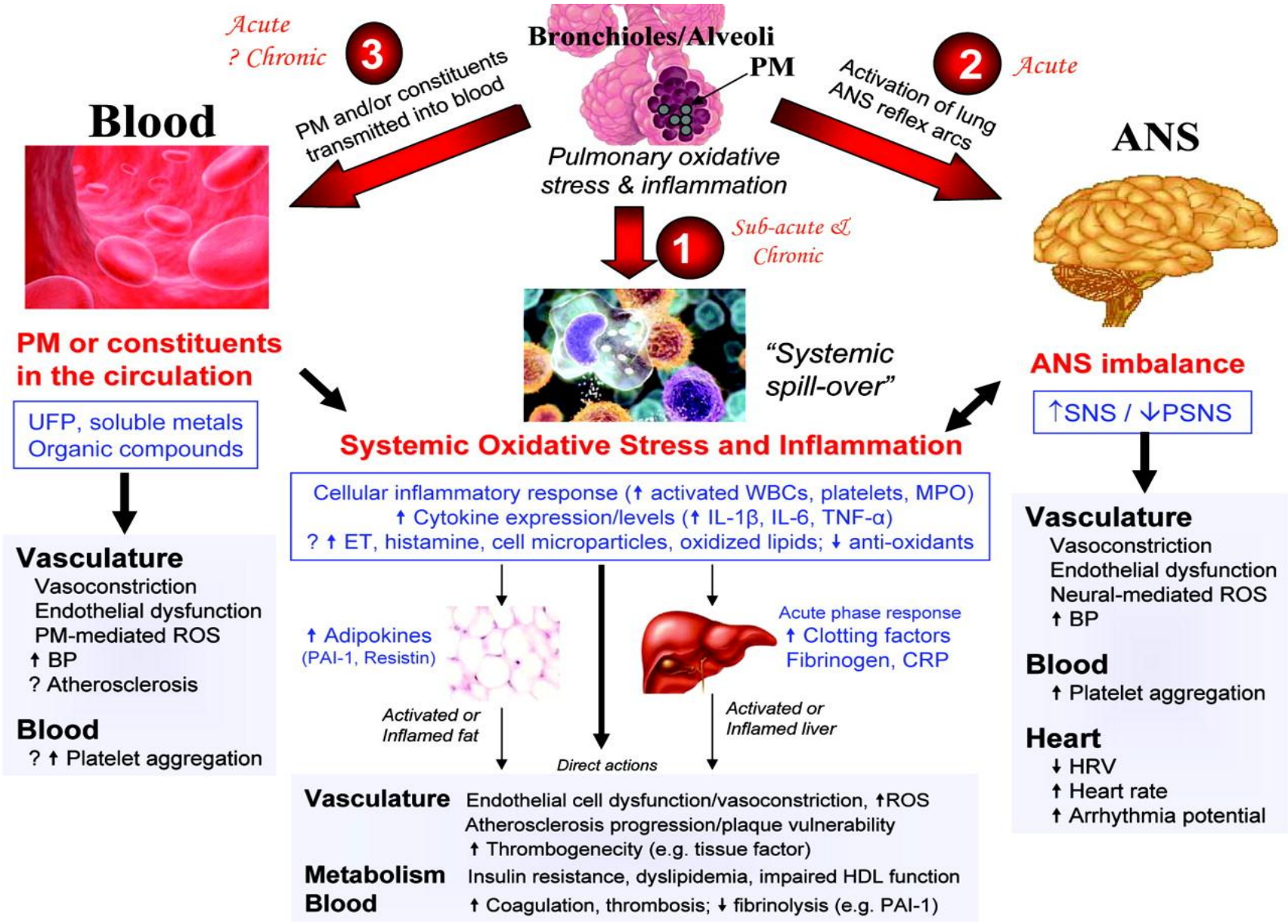
- personalized risk prediction

but as RESEARCH TOOL in policy and prevention for:

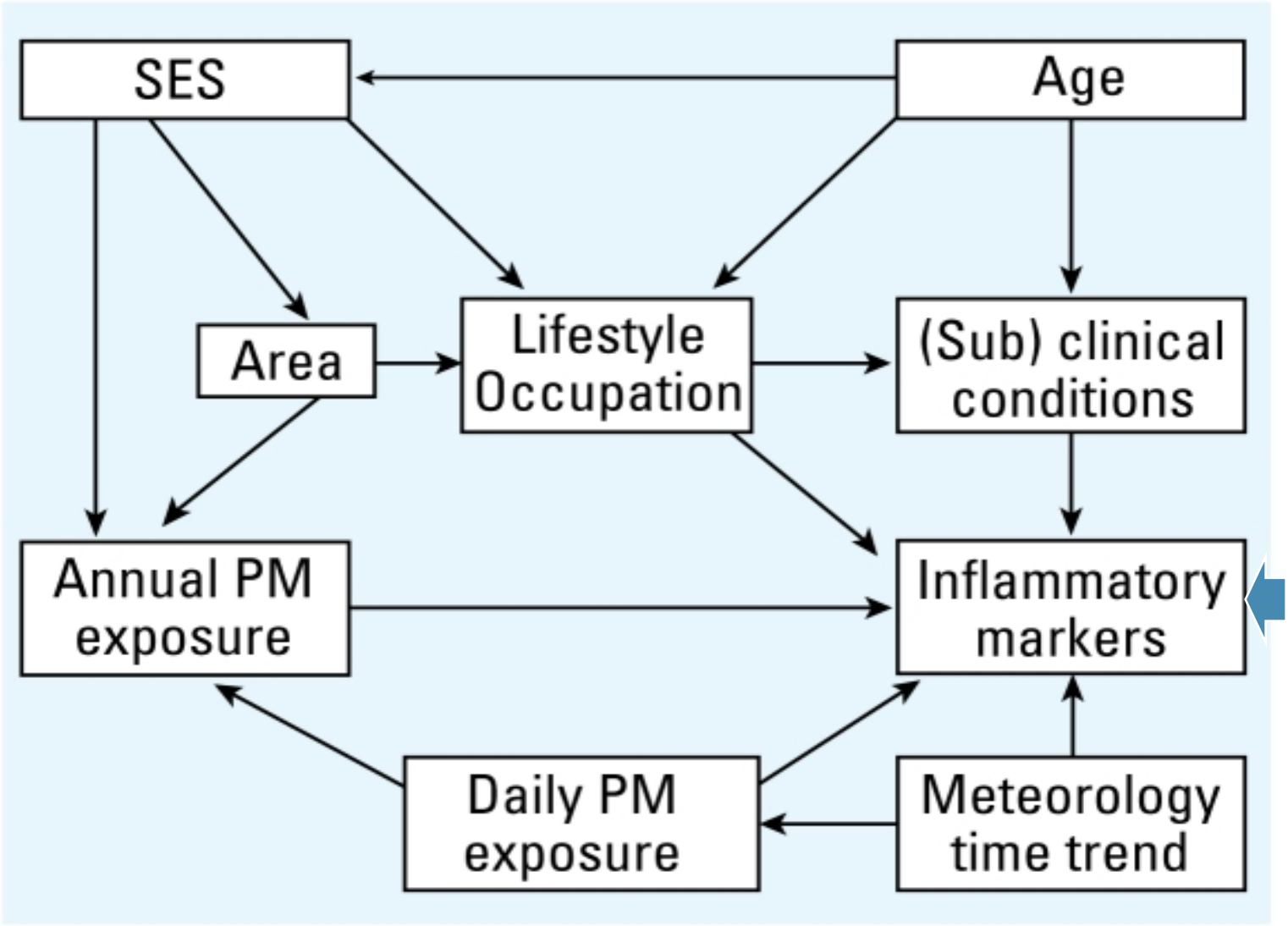
- identifying causal risk factors
- understanding causal biological mechanisms and relevant chemicals
- identifying susceptibility
- refining risk assessment

Biological pathways mediating particulate matter health effects

Brook RD Circulation 2010



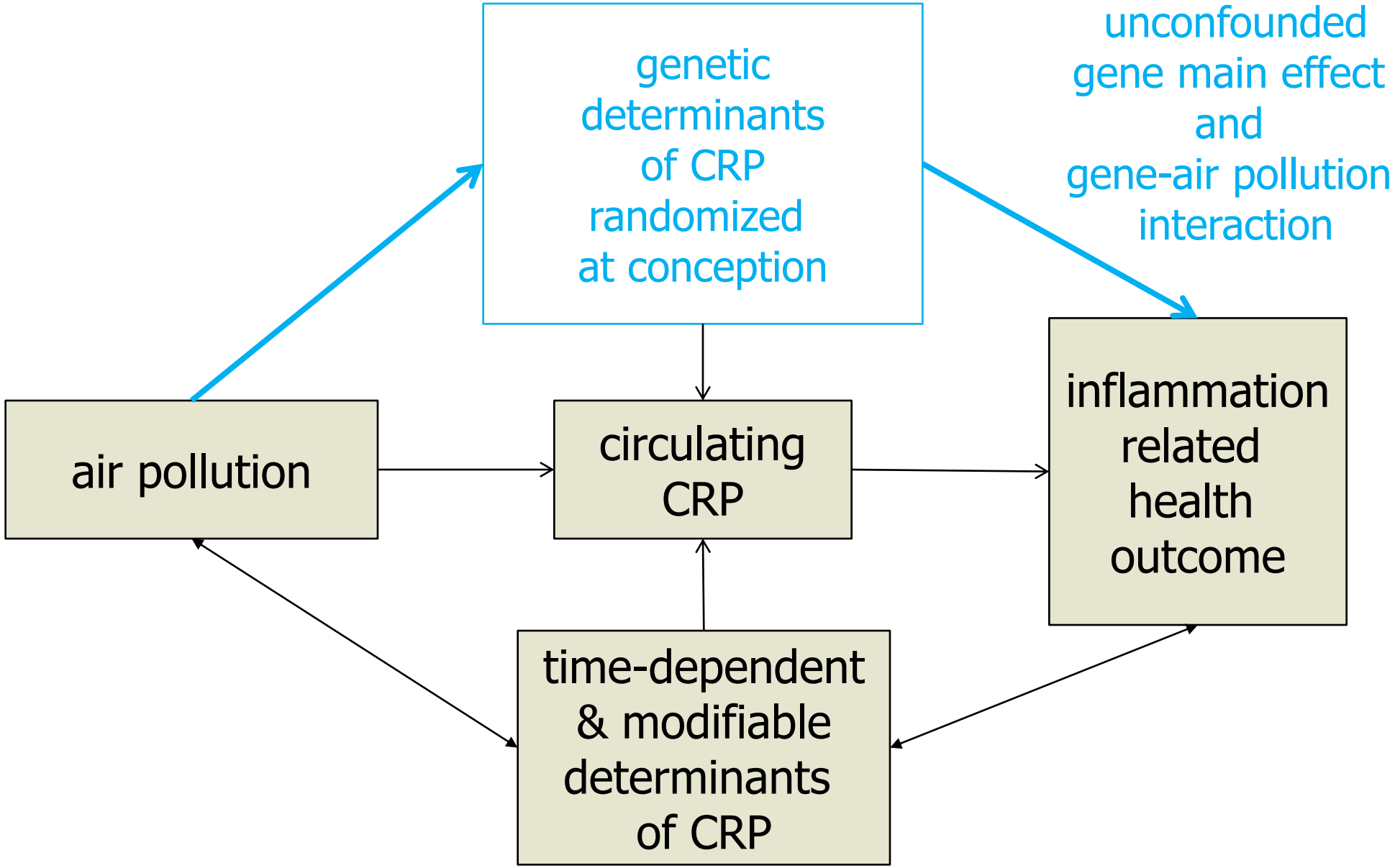
Air Pollution, Inflammation, and Health:
causal or confounded ?



i.e. C-reactive protein

Hoffmann et al. EHP 2009

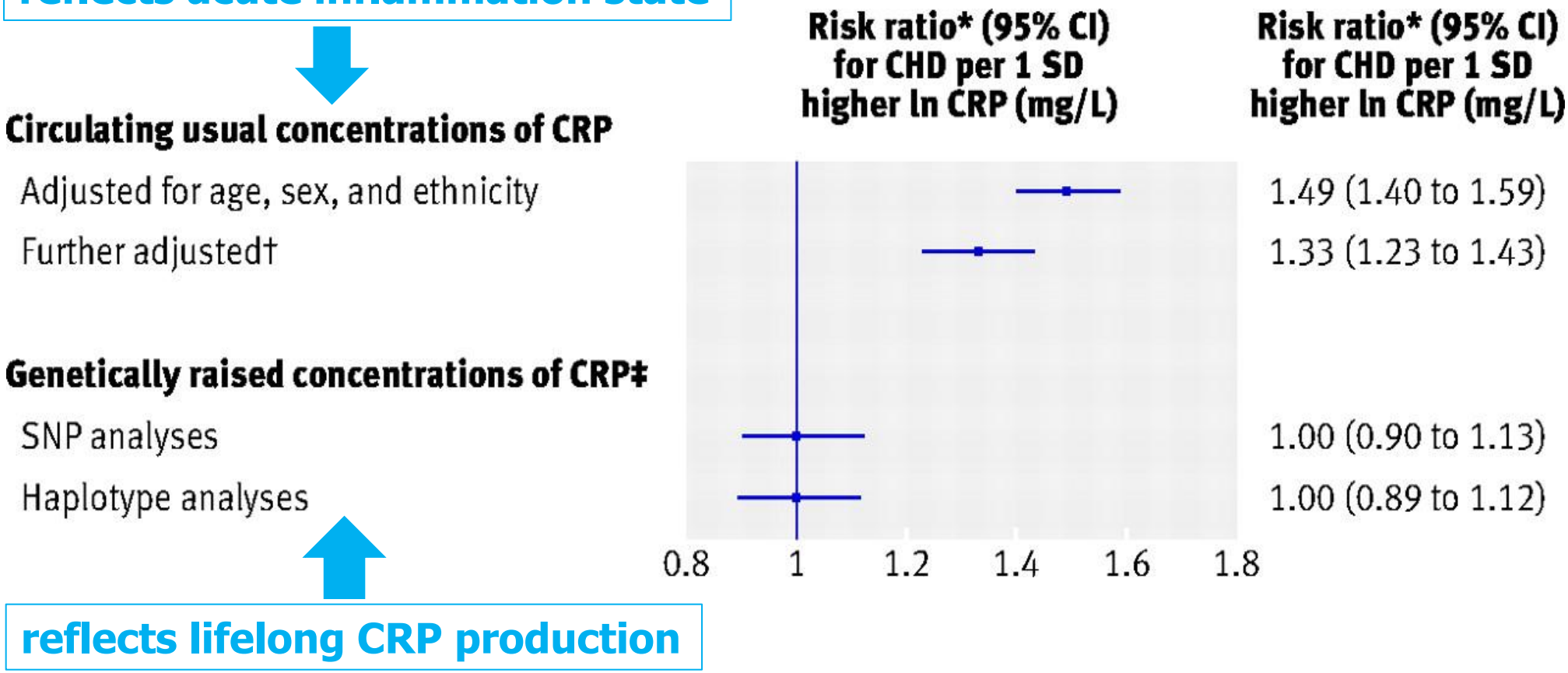
Causality and the Principle of Mendelian Randomization



Circulating CRP, CRP gene variants, and Coronary Heart Disease

Wensley et al. BMJ 2011t

reflects acute inflammation state

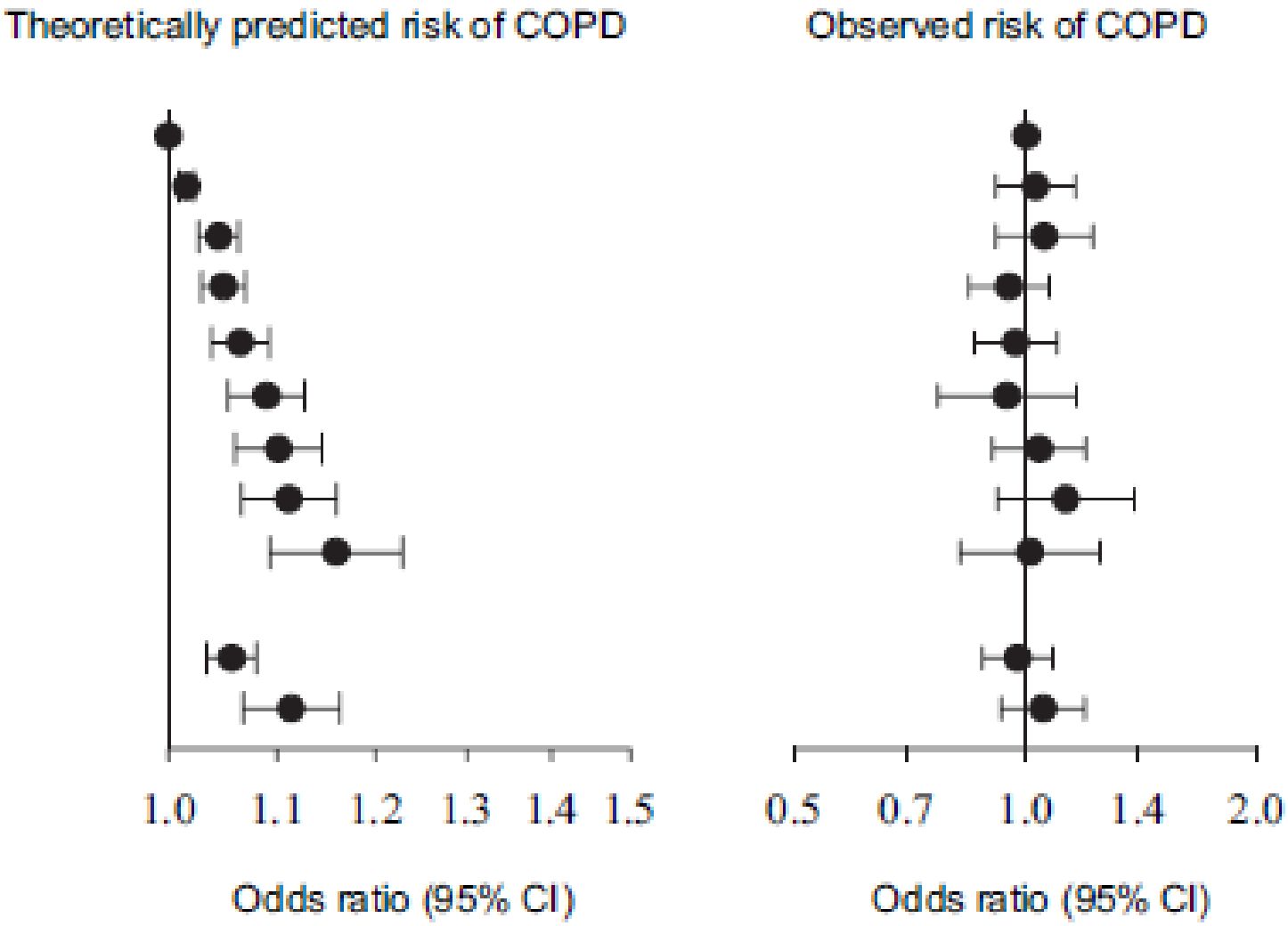


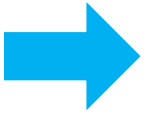
reflects lifelong CRP production

C-reactive protein and COPD:

predicted versus observed risk as a function of CRP genotype combinations (Mendelian Randomization)

Dahl et al. Thorax 2011





air pollution effects on heart and lung unlikely via CRP

What else have we learnt from interactions between genetic variants and air pollution?

candidate gene, knowledge-driven approach:

investigating the role of hypothesized mechanisms & genes

genome-wide, data-driven approach:

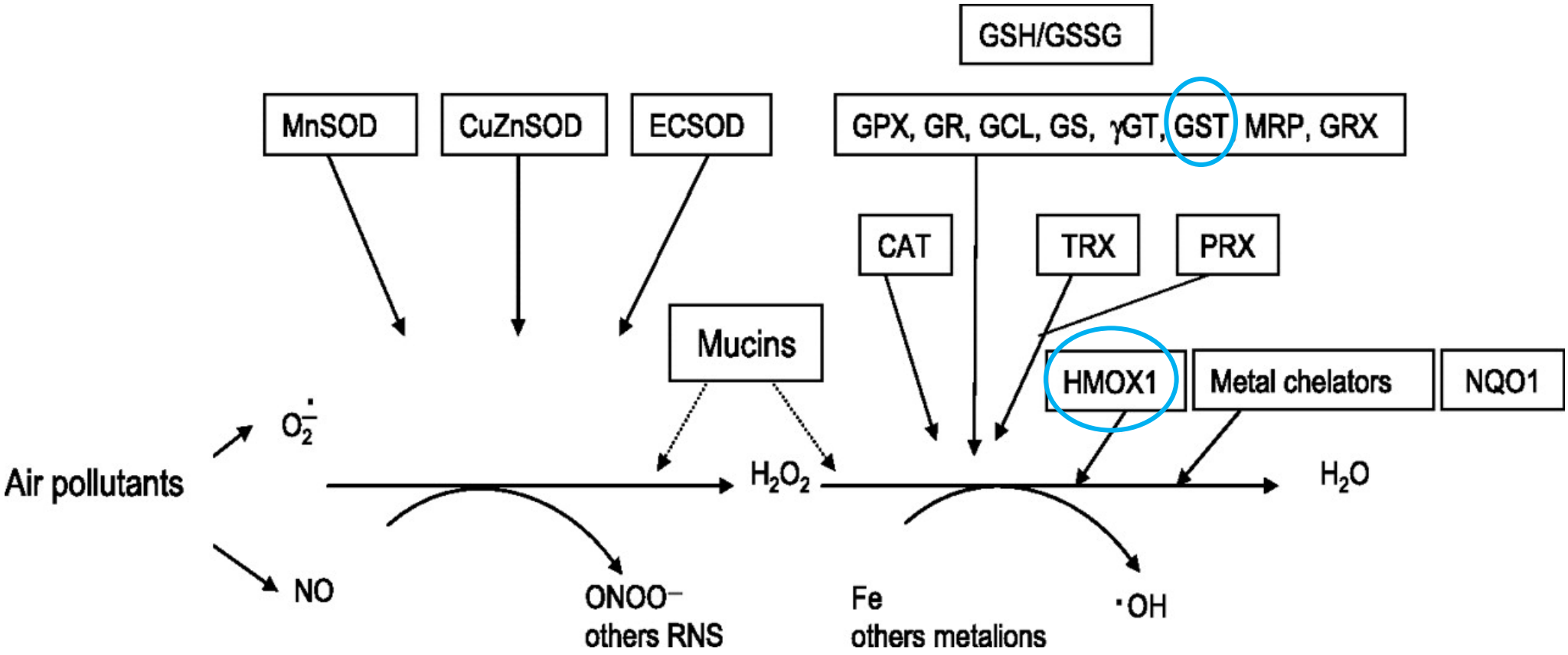
searching genome-wide for novel mechanisms

Gene-air pollution interactions and health:

evidence for a modifying role of antioxidative gene variants

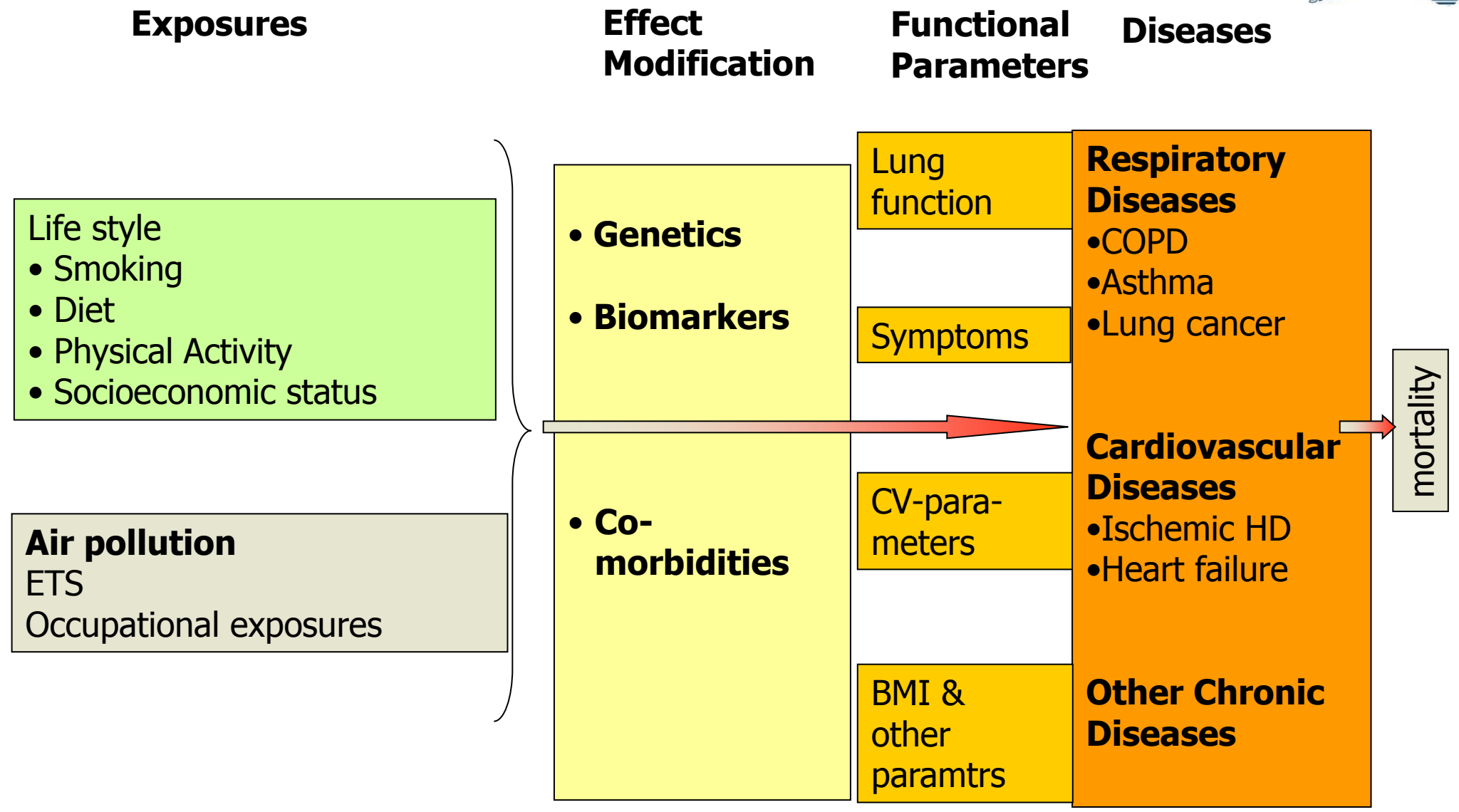
Romieu, Proc Am Thorac Soc 2010; Minelli C et al. Int J Epidemiol 2011

Zanobetti Prog Cardiovascular Dis 2011 (Review on gene-air pollution interactions and CVD outcomes

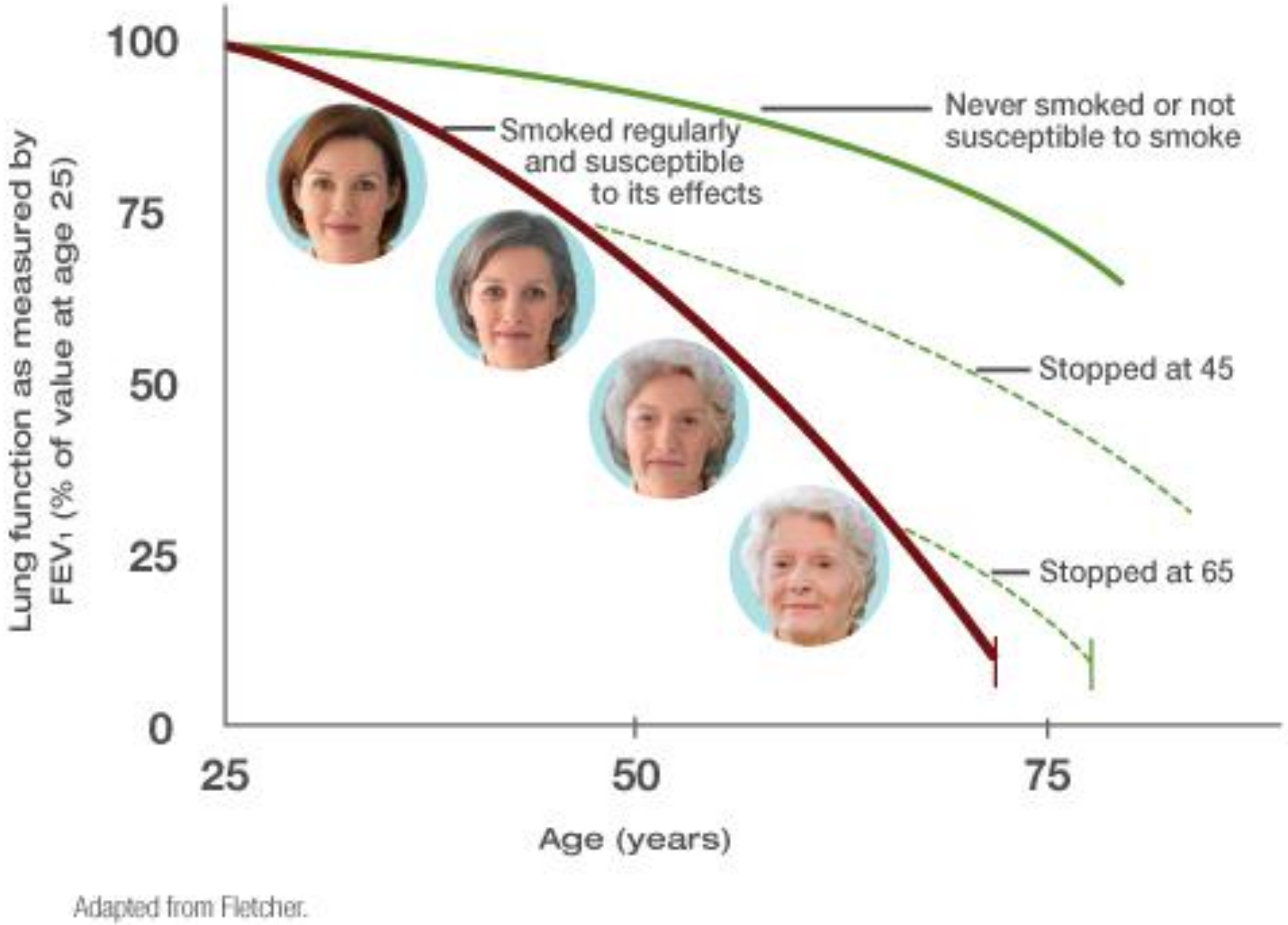


The SAPALDIA Cohort & Biobank

9000 participants, 1 mio. biospecimens, 20 years folllow-up



Lung function declines naturally with age:
more so in smokers; what about air pollution?



http://www.copdhelp.ca/en/about_copd/do_your_lungs_work/

Reduced exposure to PM10 and attenuated age-related decline in lung function: SAPALDIA

Downs SH et al. N Engl J Med 2007

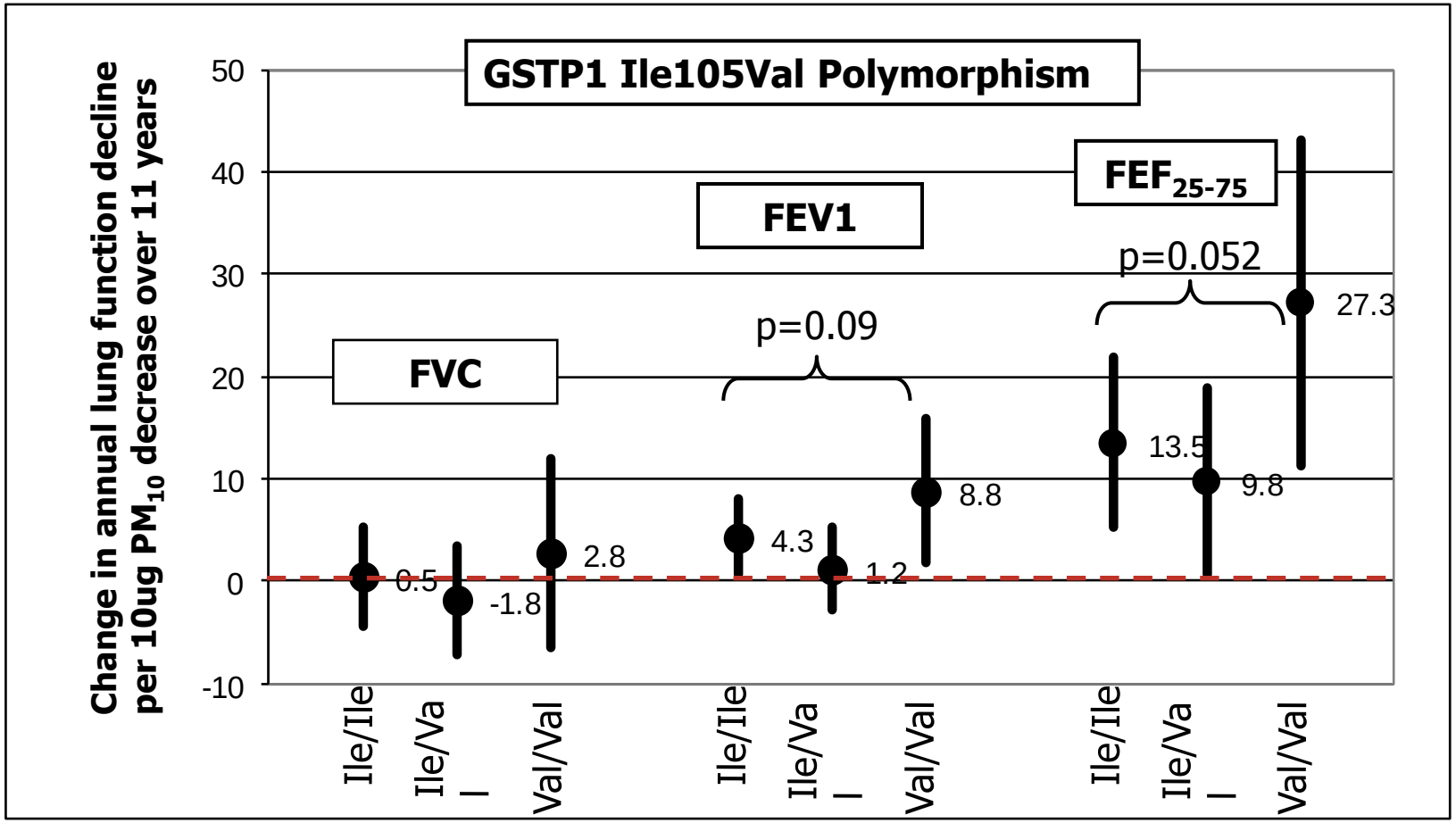
	% difference in annual decline FEF_{25-75} ml/s
all subjects	**16%**
never smokers	**18%**

Group	Lung function parameter	Effects for a 10 µg/m^3 decrease in PM_{10} between SAPALDIA 1 (1991) and SAPALDIA 2 (2002)			
		Effect	95% CI lower	95% CI upper	p-value
All (n=4742)	FVC [ml]	- 1.19	- 5.2	3.0	0.87
	FEV_1 [ml]	2.9	- 0.4	5.8	0.09
	FEV_1/FVC %	0.07	- 0.02	0.12	0.011
	FEF_{25-75} [ml/s]	12.7	4.7	18.6	0.001

Single Antioxidant Candidate Gene Variant:

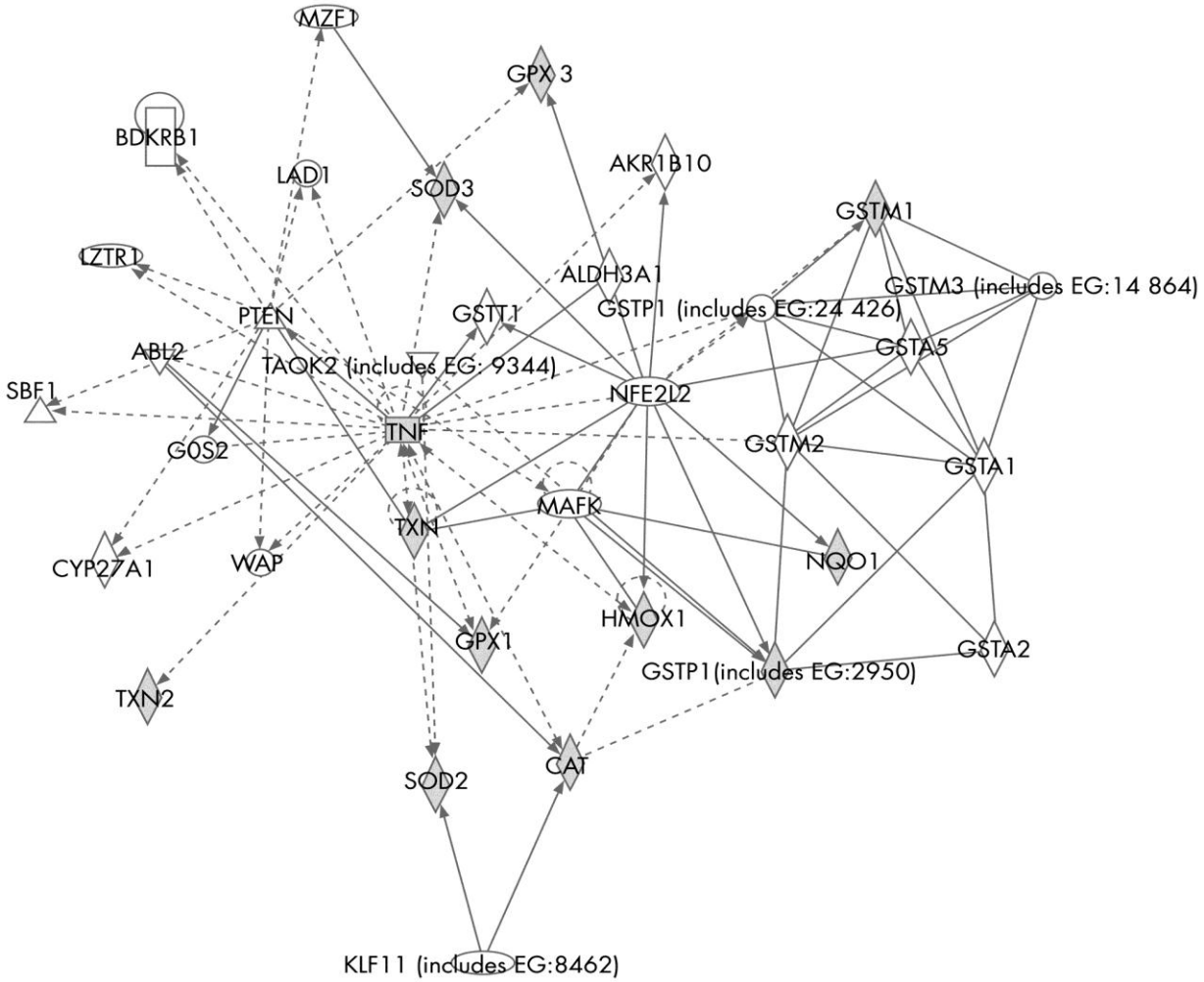
antioxidative GSTP1 variants modify beneficial effect of PM10 reduction on natural lung function decline

Curjuric ERJ 2010



Network of candidate oxidative stress genes

Yang I A et al. Postgrad Med J 2009;85:428-436



Assessment of oxidative stress related gene-PM10 interactions on gene- & pathway-level

Curjuric I, PLoSOne in press

Study sample: 669 non-asthmatic adults

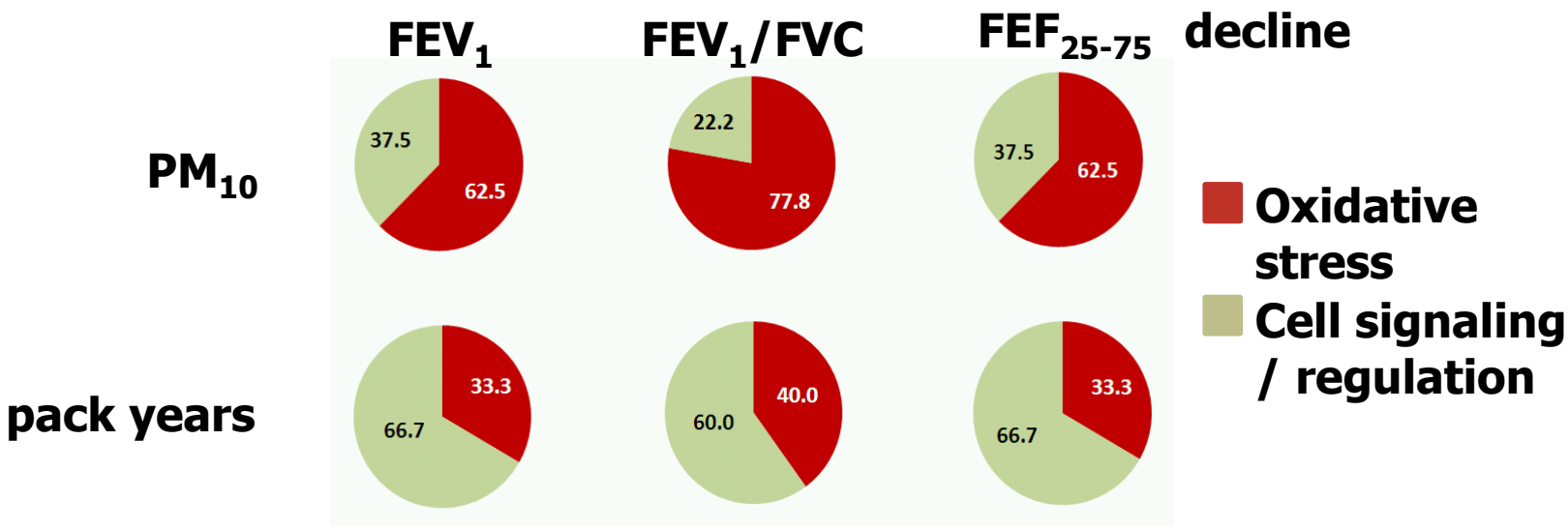
Outcome: Decline in lung function

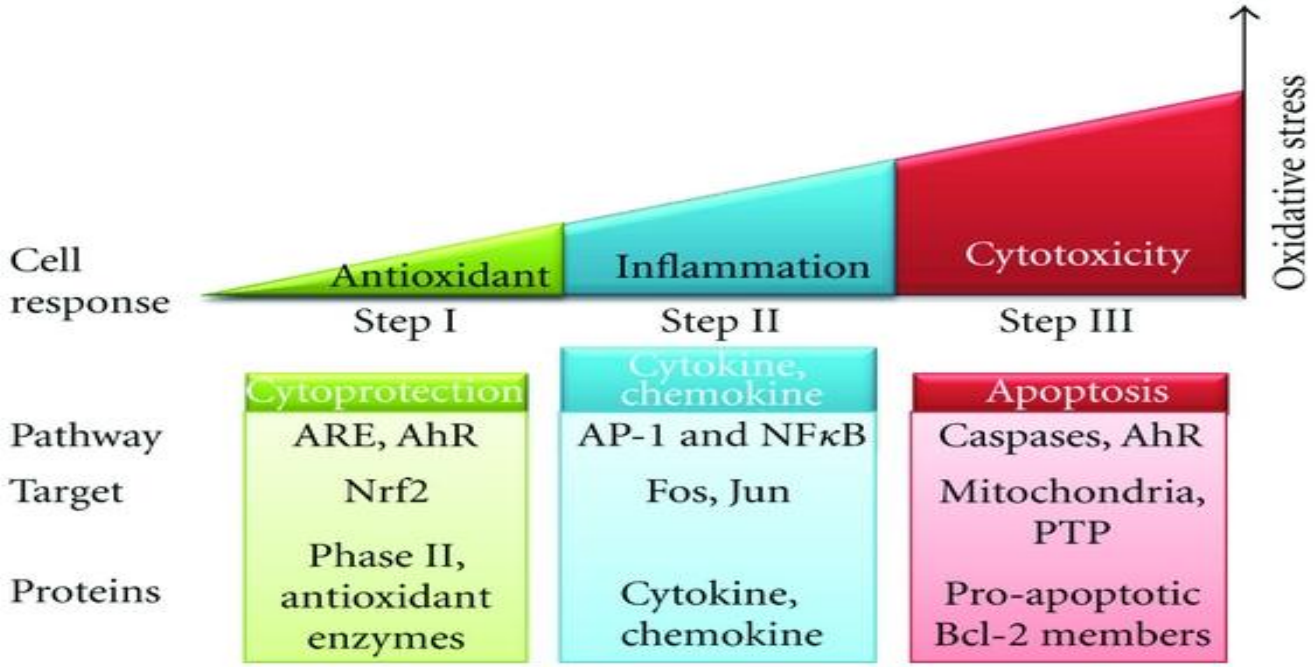
Genes: **152 oxidative stress genes**, 14 pathways, 12679 SNPs

Exposure: individual cumulative **PM10 or Packyears**

Model: derive gene- and pathway level interaction p-values
-running ARTP method [1)] on SNP interaction p-values

1) Yu K et al. *Genet Epidemiol* 2009 ; 33(8): 700–709.

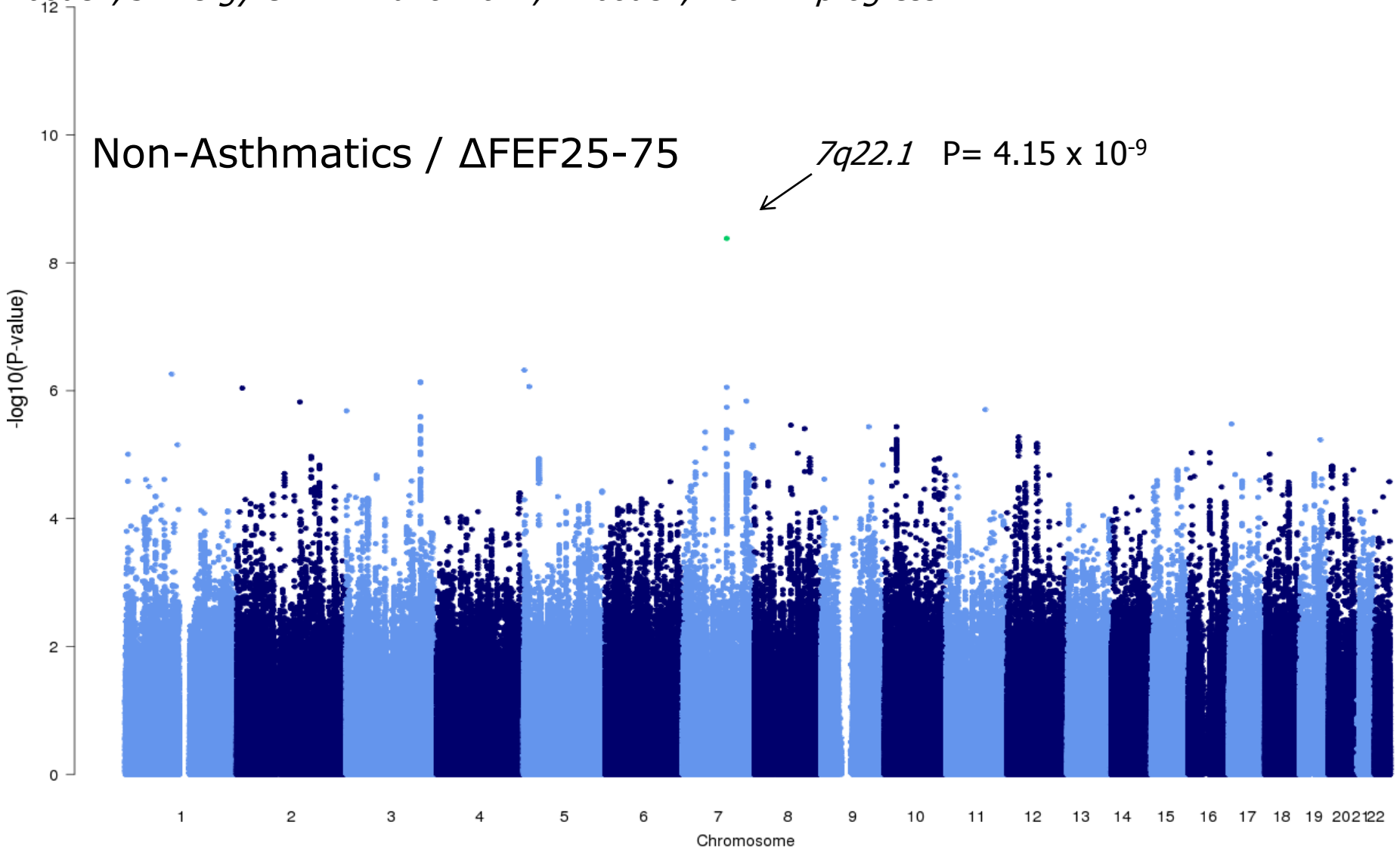

FEV1
FEV1/FVC
FEF25-75
decline
PM10
pack years
37.5
62.5
22.2
77.8
37.5
62.5
33.3
66.7
40.0
60.0
33.3
66.7
Oxidative stress
Cell signaling / regulation


Cell response
Antioxidant
Inflammation
Cytotoxicity
Oxidative stress
Step I
Step II
Step III
Cytoprotection
Cytokine, chemokine
Apoptosis
Pathway
ARE, AhR
AP-1 and NFκB
Caspases, AhR
Target
Nrf2
Fos, Jun
Mitochondria, PTP
Proteins
Phase II, antioxidant enzymes
Cytokine, chemokine
Pro-apoptotic Bcl-2 members

All common gene variants:

genome-wide interaction on ΔPM10 and lung function decline

Imboden, J Allergy Clin Immunol 2012; Imboden, work in progress



Gene-Air Pollution Interactions: Challenges

- sample size needs
- phenotypic heterogeneity
- accurate assessment of air pollution exposure & composition
- functionality of genetic variation

- Air Pollution and Health: a Complex Network
- Genetic Variation: a Valuable Research Tool
- **Beyond Genetic Variation:**
  a Broader –Omics Perspective

-omics approaches

Holloway Respirology 2012

from

gene

to

gene expression

to

protein function

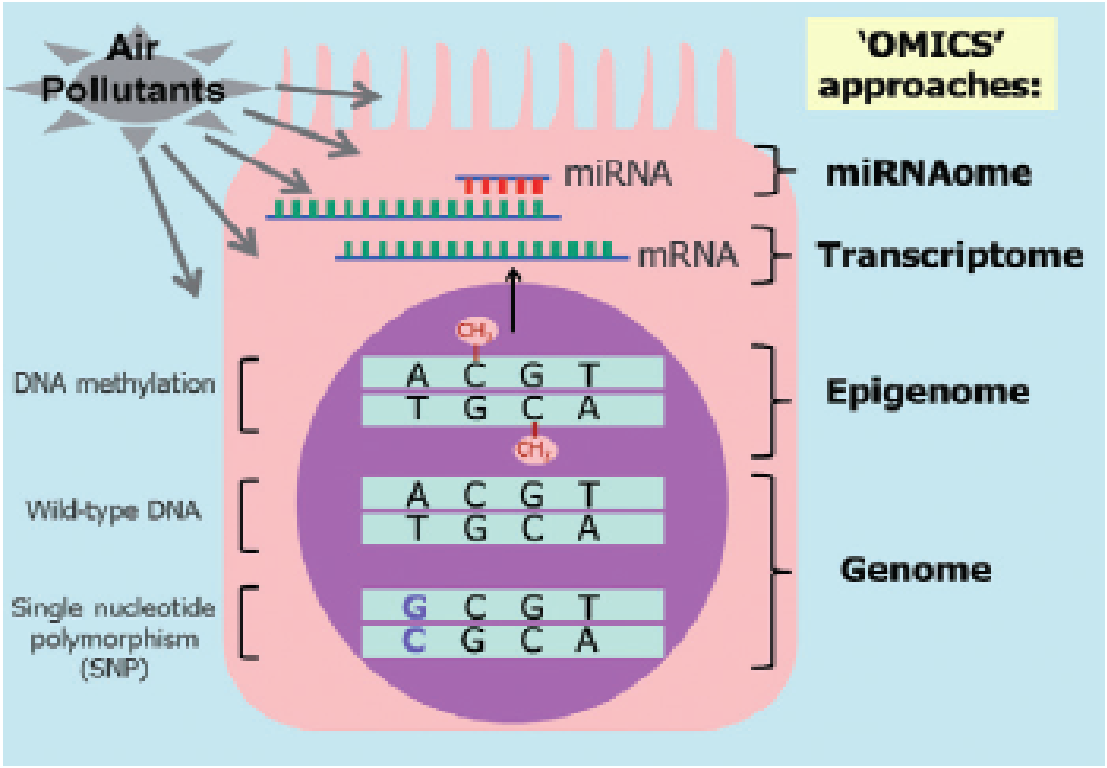
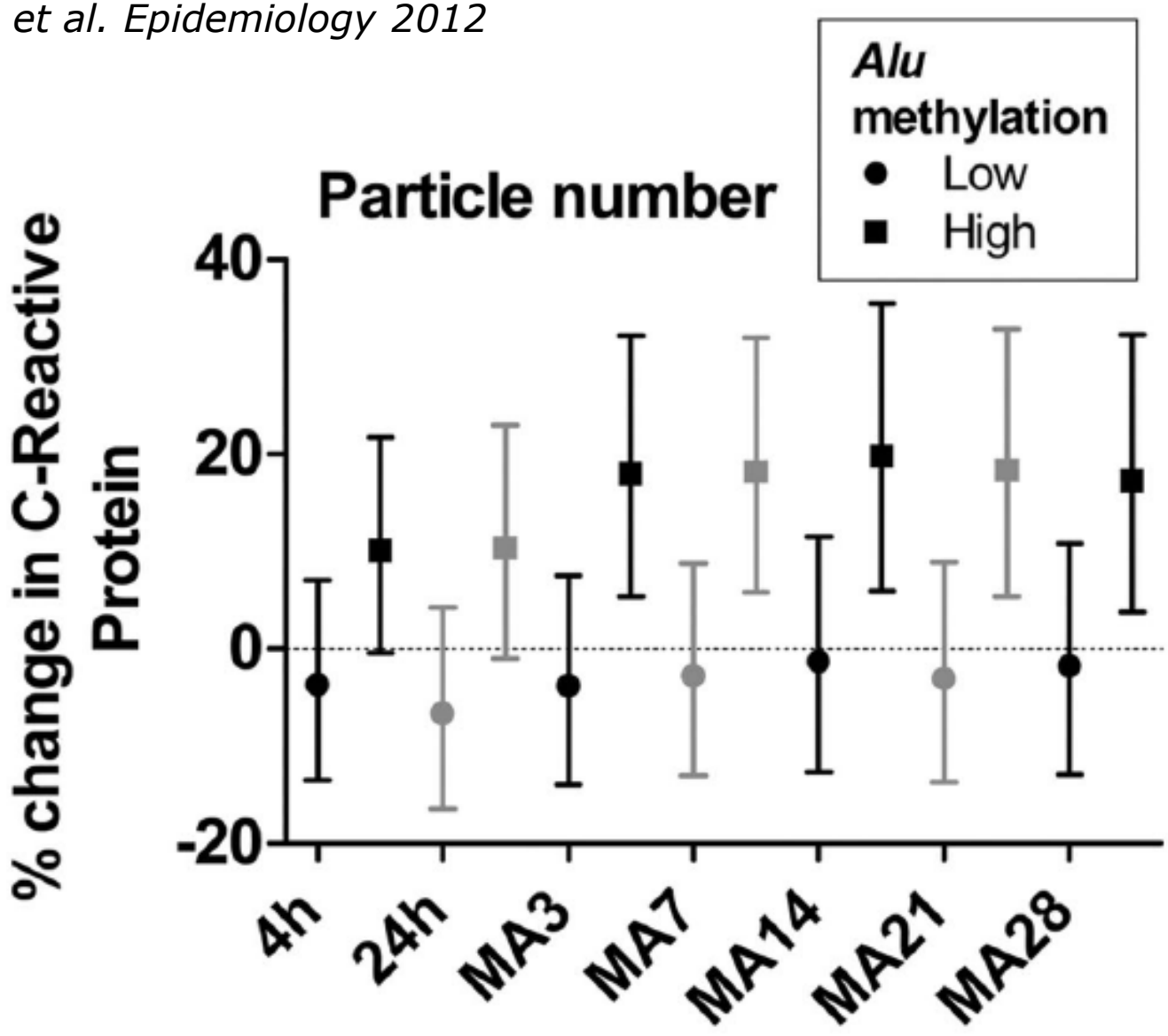


Figure 1 'Omics' approaches to studying the respiratory effects of air pollutant exposure. Response to air pollutant exposure in the lungs can be studied systematically at the genomic level. The response may vary based on SNP in DNA comprising the genome, differences in DNA methylation and other epigenomic changes, mRNA expression in the transcriptome and altered miRNA expression in the miRNAome. These genomic changes, arising as a result of gene-environment interaction, influence protein expression and function in a number of biological pathways, and ultimately influence cellular function in response to air pollution.

Epigenetics challenging Mendelian Randomization

Alu methylation status modifies the association of air pollution with circulating CRP *Bind M-A et al. Epidemiology 2012*



Epigenetics and Genetics Combined

Inducible nitric oxide synthase, PM, and exhaled nitric oxide in children

Salam MT J Allergy Clin Immunol 2012;219:232-9

- fractional concentration of exhaled nitric oxide (FENO) measurement : noninvasive assessment of airway inflammation
- FENO level predictive of future asthma risk in children & adults
- nitric oxide homeostasis: modulation of airway and vascular smooth muscle tone and inflammation

Short-term air pollution and genetic NOS2 variants influence iNOS promoter methylation

Salam J Allergy Clin Immunol 2012

TABLE II. Short-term air pollution exposures and iNOS promoter methylation

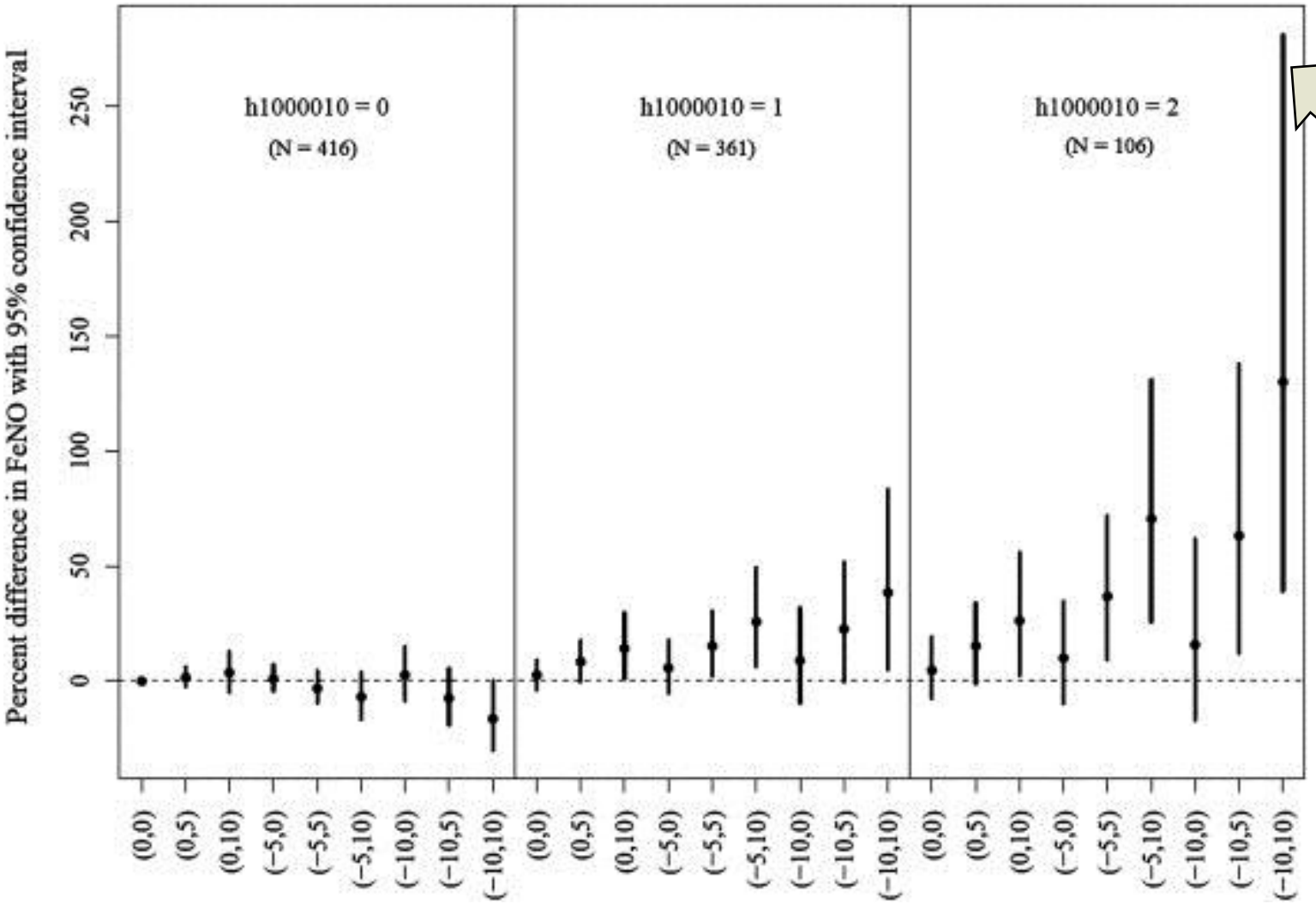
Air pollution exposure*	Percent methylation (95% CI)†	*P* value‡
$PM_{2.5}$	**−0.30 (−0.54 to −0.06)**	**.01**
PM_{10}	−0.07 (−0.22 to 0.08)	.38
NO_2	0.10 (−0.25 to 0.45)	.57
O_3	−0.02 (−0.35 to 0.32)	.92

TABLE III. *NOS2* promoter haplotypes and iNOS promoter methylation

	Haplotype frequency			
NOS2* haplotypes	**Hispanic white**	**Non-Hispanic white**	**Percent methylation (95% CI)†**	**Global *P* value‡**
h0000000 (H1)	0.19	0.16	Reference	6.2×10^{-8}
h0111101 (H2)	0.32	0.37	**−1.55 (−2.07 to −1.02)**	
h1000010 (H3)	0.36	0.25	**−1.21 (−1.72 to −0.70)**	
h0000010 (H4)	0.11	0.19	−0.49 (−1.12 to 0.14)	
Other haplotypes§	0.02	0.03	**−1.42 (−2.69 to −0.16)**	

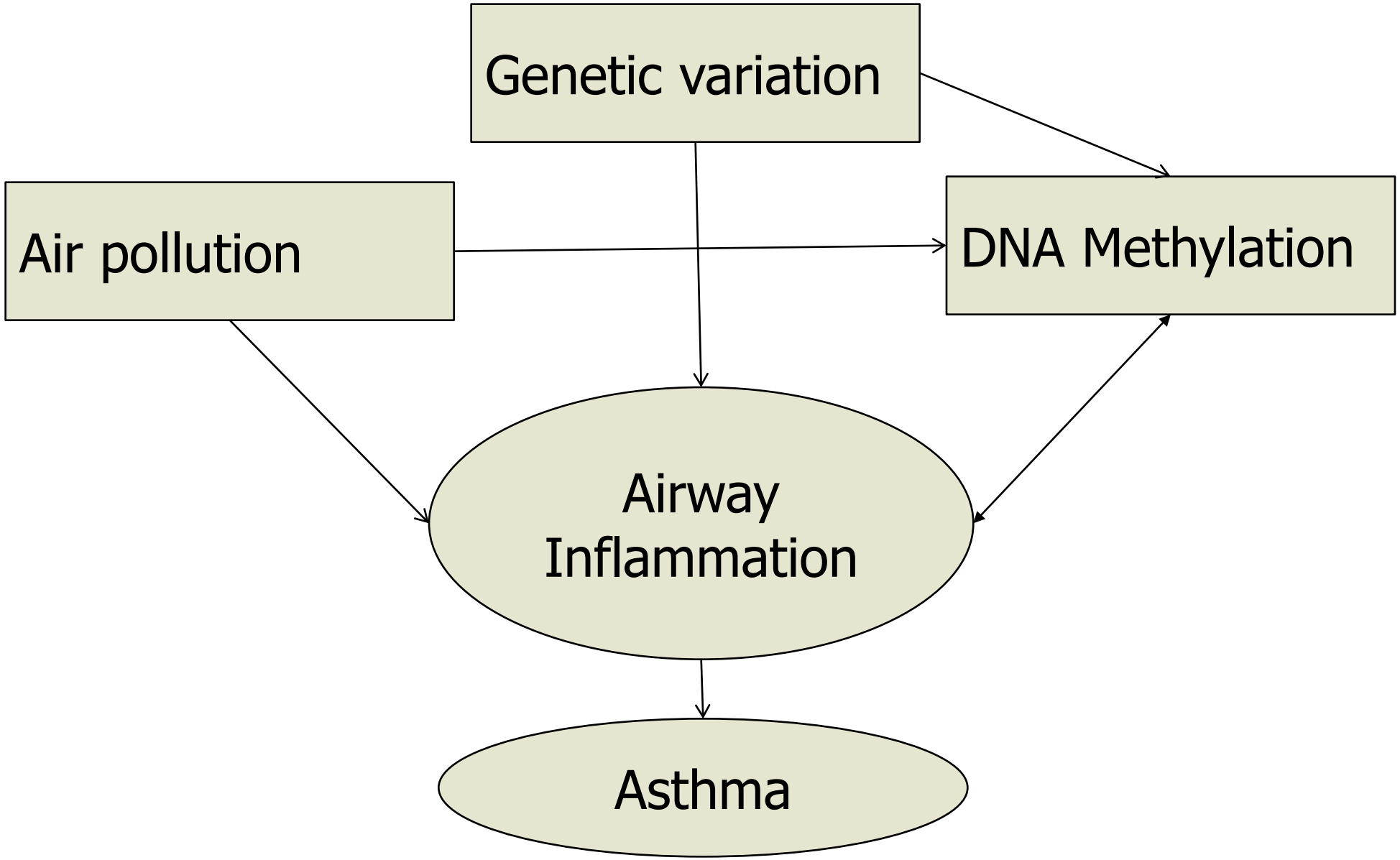
Joint effect of NOS2 gene variants, iNOS Methylation, and 7-day average PM*2.5 on FENO*

Salam J Allergy Clin Immunol 2012



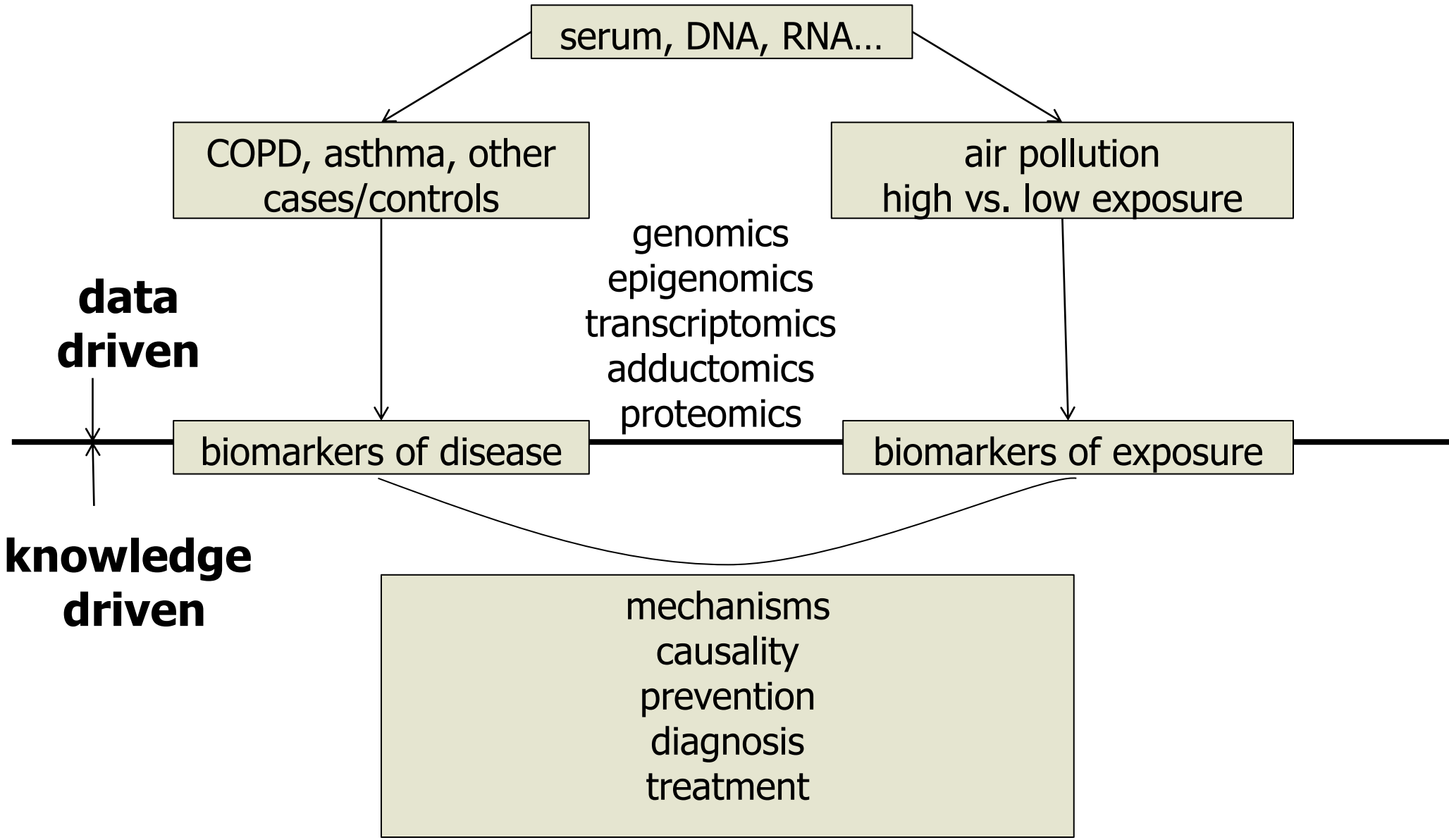
at risk haplotype
&
PM2.5 high
&
methylation high

The complex interplay between environment, genetics and epigenetics: iNOS example



Air pollution exposome and phenome

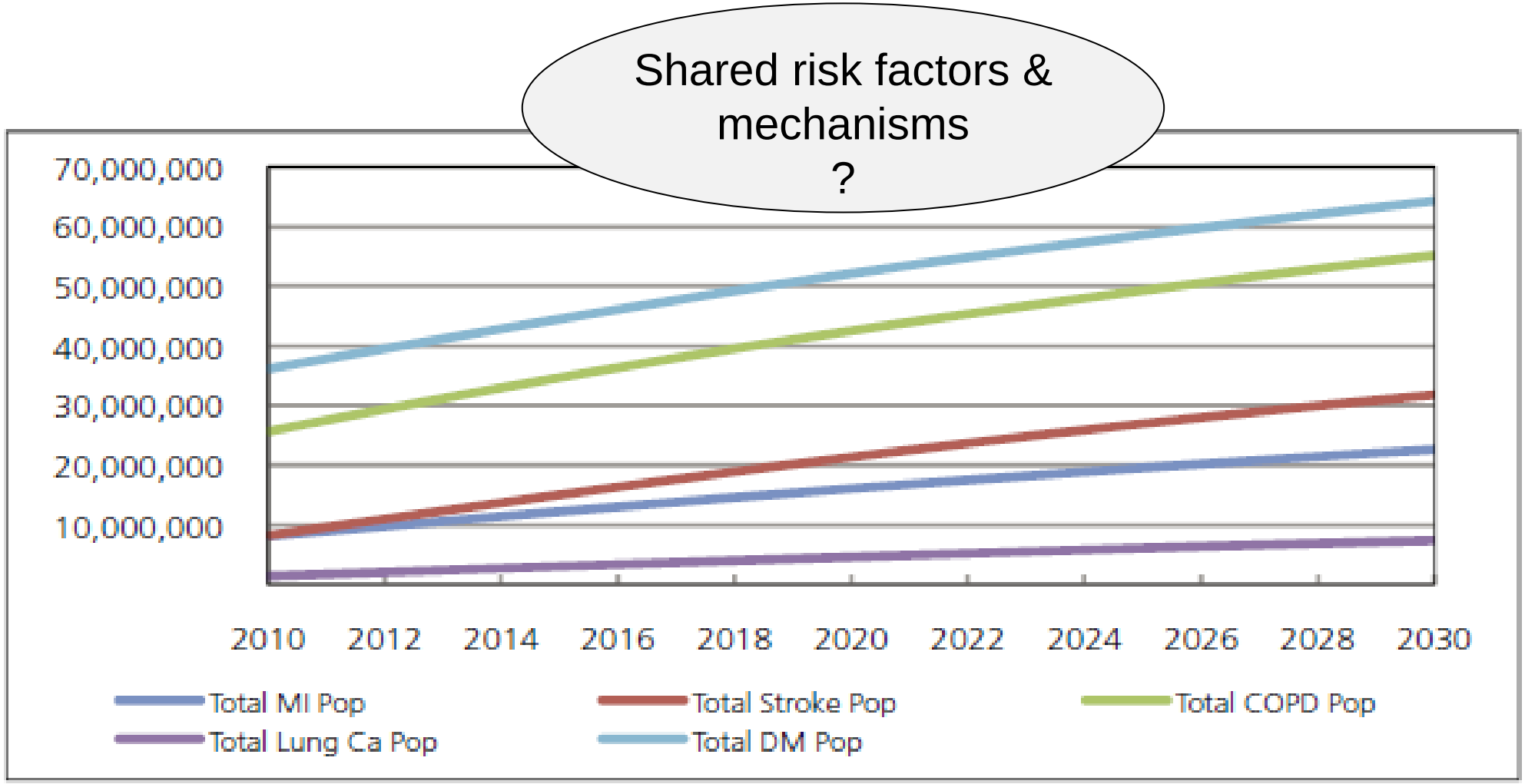
SAPALDIA studies in progress



Projected increase in NCDs cases, China, 40+

calling for efficient prevention strategies

World Bank Report, Toward a Health and Harmonious Life in China 2011



UK Biobank

a kingdom's worth of data and samples

Baker M Nature 2012

In the past few years, more than a half a million people aged 40-69 in the UK

- collectively peed into cups
- spat into tubes
- had needles stuck in their arms
- spent hours having their weight, blood pressure, memory, lung volume and grip strength measured and recorded and answering extensive questionnaires about their lifestyles

The Political Dimension of Population-Based Biobanks

- maintain and strengthen competitive research at all levels
  - well characterized biological specimens for basic, clinical, epidemiological and pharmaceutical research
  - advancement of novel molecular/bioinformatics technologies
- data for health and environmental politics

cohorts
and
biobanks
drive
where
funds
scientists
life science industry
go

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SAPALDIA-Team

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Scientific team at coordinating centers: M Adam (e/g), E Boes (g), PO Bridevaux (p), D Carballo (c), E Corradi (e), I Curjuric (e), J Dratva (e), A Di Pasquale (s), L Grize (s), D Keidel (s), S Kriemler (pa), A Kumar (g), M Imboden (g), N Maire (s), A Mehta (e), F Meier (e), H Phuleria (exp), E. Schaffner (s), GA Thun (g), A Ineichen (exp), M Ragettli (exp), M Ritter (exp), T Schikowski (e), G Stern (pd), M Tarantino (s), M Tsai (exp), M Wanner (pa).

(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