Fine Particulate Matter: Health Implications and Current Research

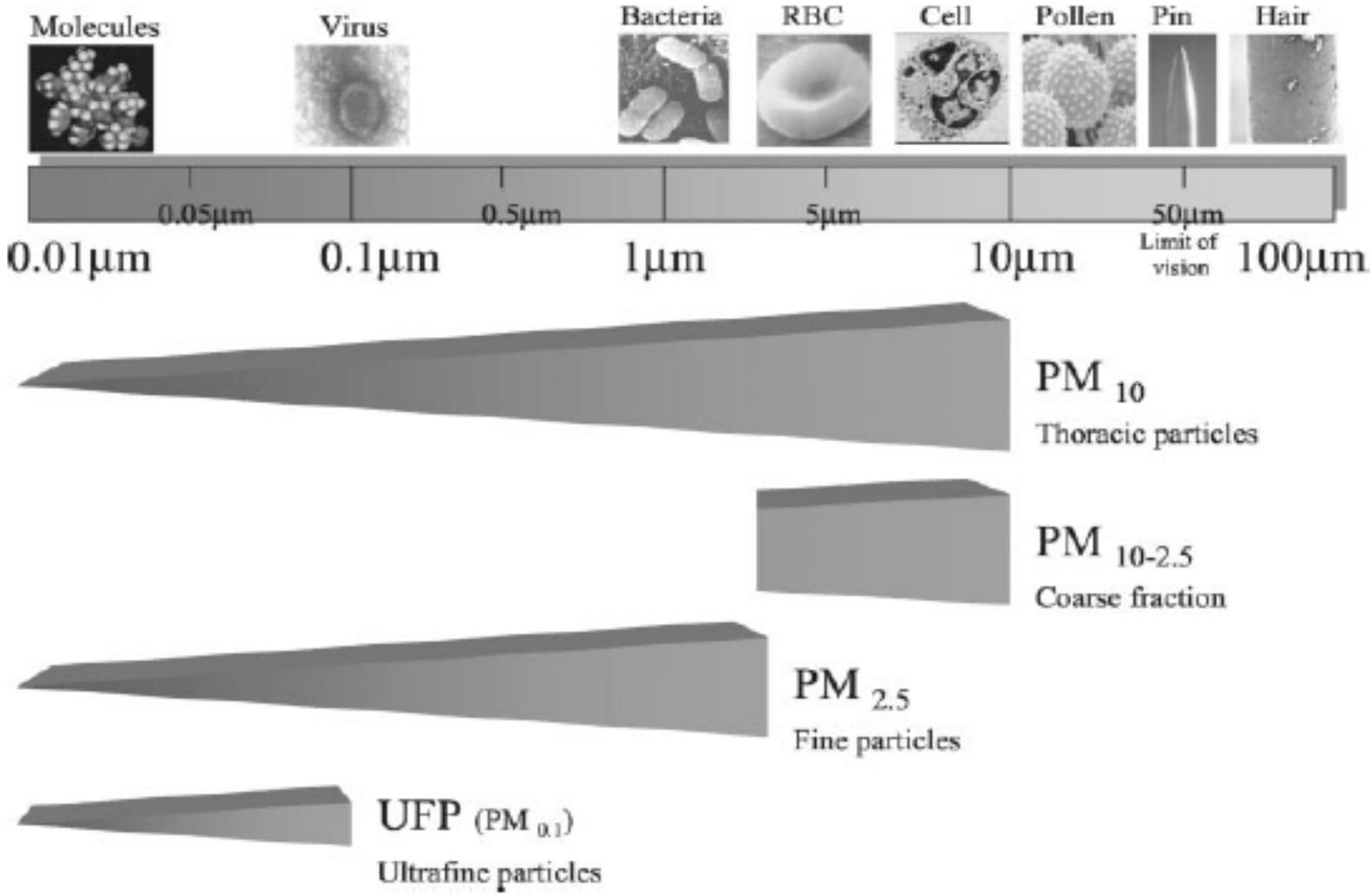
Chad Weldy, weldyc@uw.edu

U.S. National (Primary) Ambient Air Quality Standards (NAAQS)

- Mandated to be reviewed every 5 years as to the adequacy of the existent standard to protect human health,
- **Economic impact not to be involved!**

Pollutant	Unit	Averaging Time	Concentrations	Statistic
SO_2	ug/m^3 (PPM)	Annual, 24h	80 (0.03), 365 (0.14)	Annual Mean, Maximum
CO	ug/m^3 (PPM)	8h, 1h	10 (9), 40 (35)	Maximum, Maximum
O_3	ug/m^3 (PPM)	1h, 8h	235 (0.12) 157 (0.08)	Maximum, Maximum
NO_2	ug/m^3 (PPM)	Annual	100 (0.053)	Annual Mean
PM_{10}	ug/m^3	Annual, 24h	150, 50	Annual Mean, 24h Mean
Lead (Pb)	ug/m^3	3 months	1.5	Quarterly Average

What is fine particulate?



Brook R. Circulation 2004

London Fog Incident, December 5th-9th, 1952


Seattle Visibility 10/24/05 03:00:08 PM

Where do they come from?

- Emissions from Power Plants, Traffic, Wood Burning, other combustion processes
- Incomplete combustion can form particles and liquid dr of chemicals

$$2C_8H_{18} + 25O_2 \rightarrow 18H_20 + 16CO_2 + \textbf{energy}$$

(octane + oxygen → water + carbon dioxide + energy)

- Natural sources do make up a component of the ambient particulate matter, this is typically from mechanical erosion, but it is less toxic, and only a fraction of the particulate derived from mechanical erosion is $PM_{2.5}$, most is coarse $>PM_{10}$

Okay where does it go when you inhale it?

respiratory tract from a deposition perspective:

extrathoracic (nasopharyngeal)

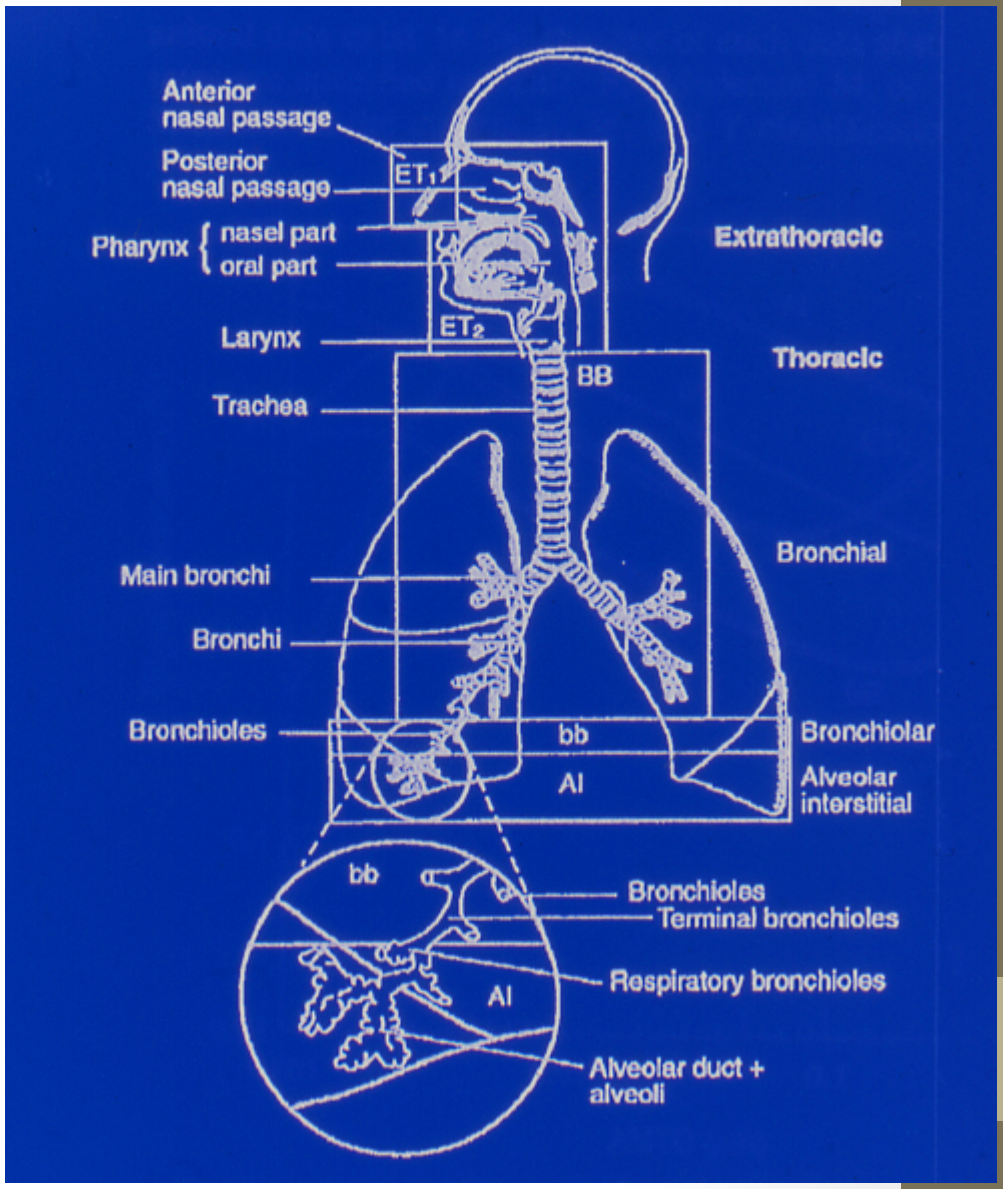
- nose
- mouth
- oropharynx
- larynx

tracheo-bronchial

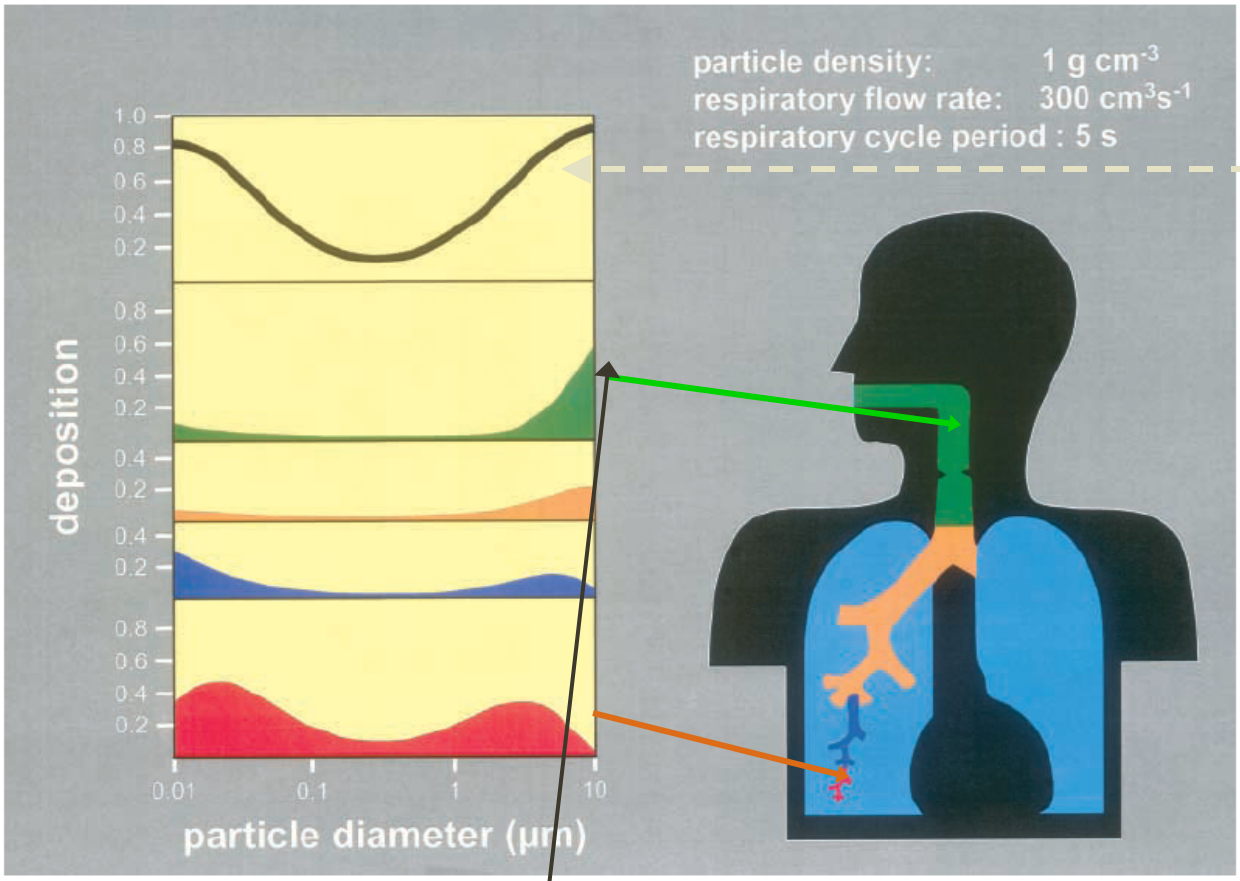
- trachea
- bronchi
- terminal bronchioles

alveolar (pulmonary)

- respiratory bronchioles
- alveolar ducts
- alveoli



Size of the particle determines where it goes in the lung!



total lung deposition

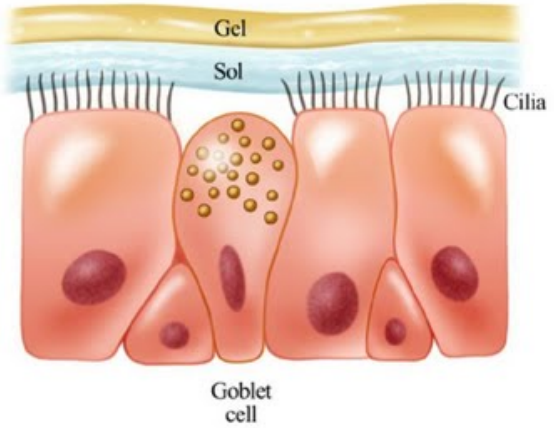
Figure 2. Total and regional deposition of unit-density spheres in the human respiratory tract predicted by the ICRP deposition model for oral inhalation at rest.

1. particles larger than 10 µm in diameter are largely not inhaled into the lungs.

2. particles in the largest and smallest parts of the inhalable range are deposited best, especially in the alveoli.

Heyder J. Proc Am Thorac Soc, 2004

Why is this important?

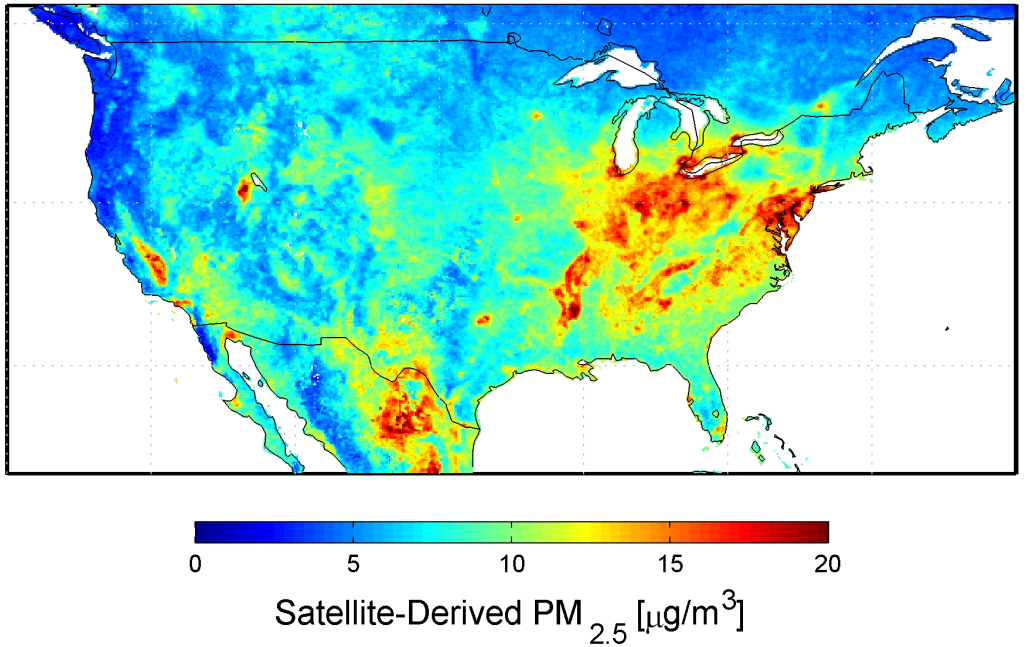


- Our respiratory tract has what is called a ‘mucociliary escalator’ that lines the larynx, trachea, and bronchi
- This action of ‘ciliary beats’, pushes a mucus layer, and everything else that is embedded in that mucus layer, up towards the back of the throat, which is eventually swallowed or coughed up
- Particles inhaled inhaled into the alveolar region of the lung do not come back up, instead they are able to interact with resident cells in the lung, such as the lung epithelium and alveolar macrophages

http://thesocietypages.org/socimages/

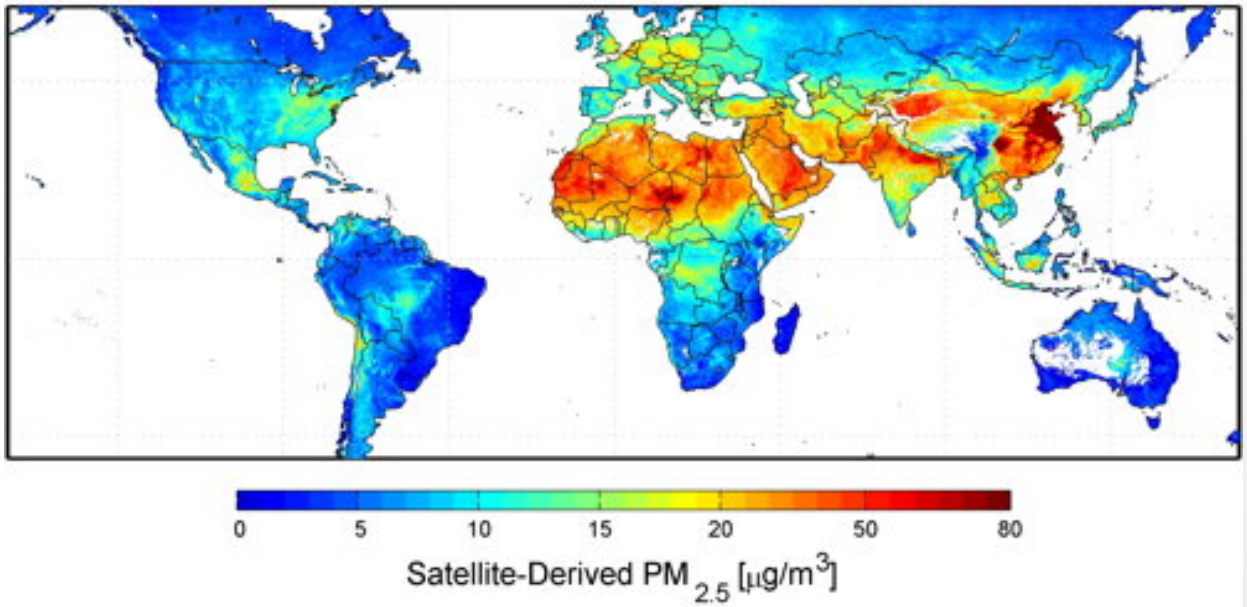
These are ‘snapshots’ in time, and do little to actually estimate an individual’s exposure.

But they are helpful to see the disparity in $PM_{2.5}$ levels across the country



Beijing and other cities in China are known to have some of the worst $PM_{2.5}$ levels in the world

Saharan Africa has extremely high levels, this is mostly due to natural sources

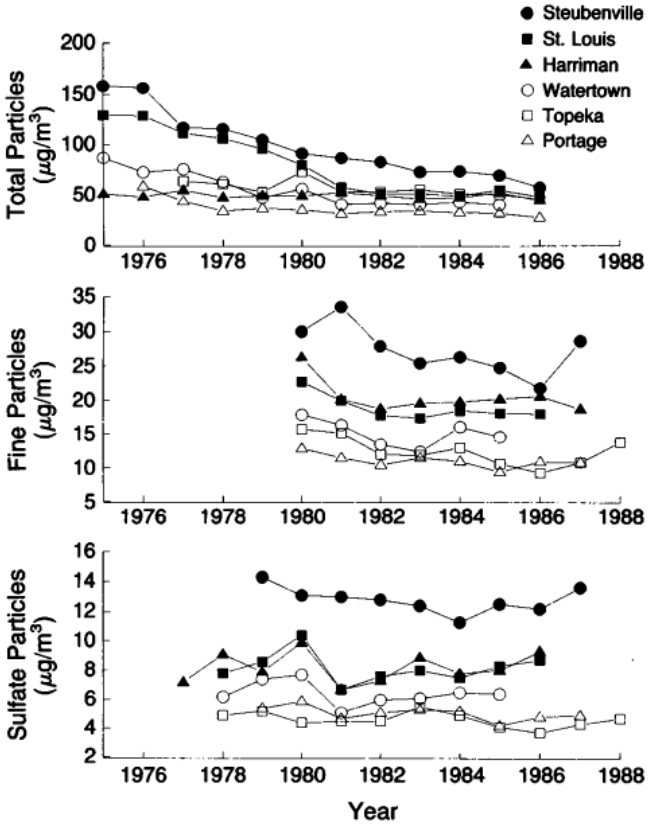


The New England
Journal of Medicine

Volume 329 DECEMBER 9, 1993 Number 24

AN ASSOCIATION BETWEEN AIR POLLUTION AND MORTALITY IN SIX U.S. CITIES

Douglas W. Dockery, Sc.D., C. Arden Pope III, Ph.D., Xiping Xu, M.D., Ph.D.,
John D. Spengler, Ph.D., James H. Ware, Ph.D., Martha E. Fay, M.P.H.,
Benjamin G. Ferris, Jr., M.D., and Frank E. Speizer, M.D.



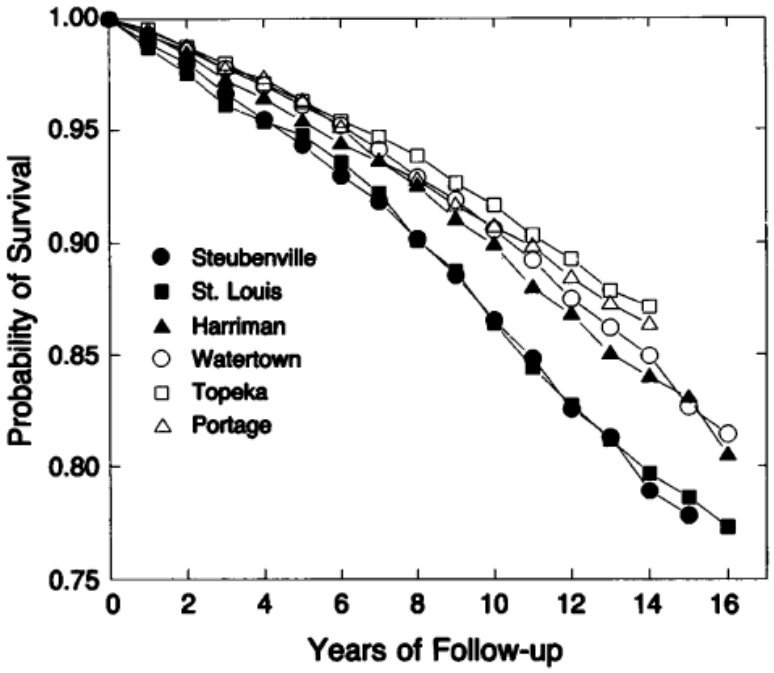
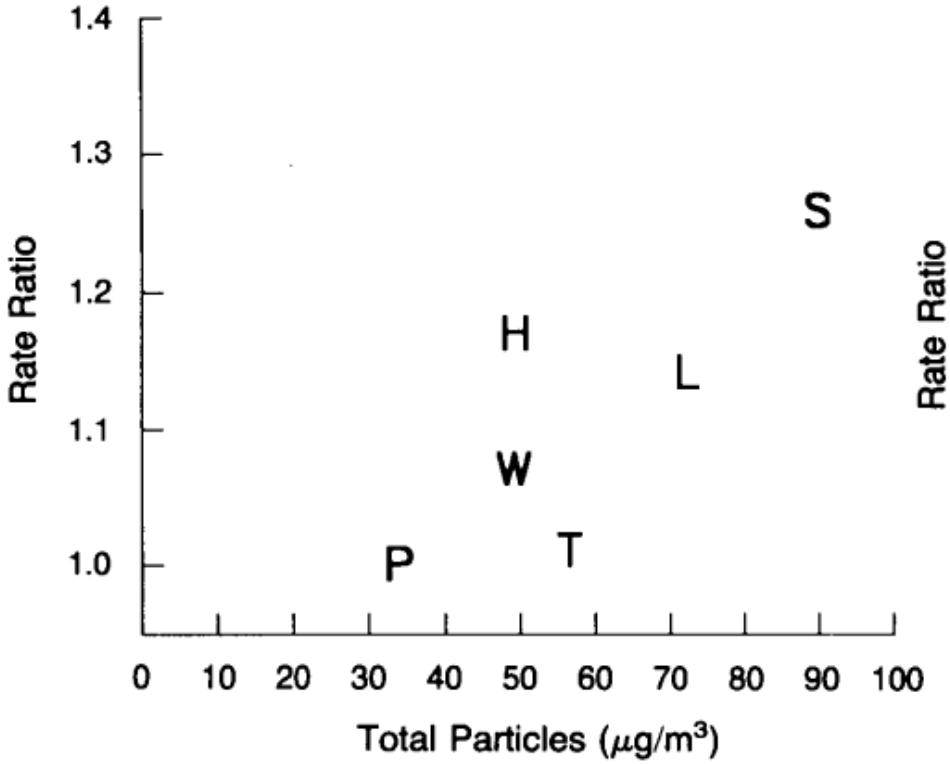
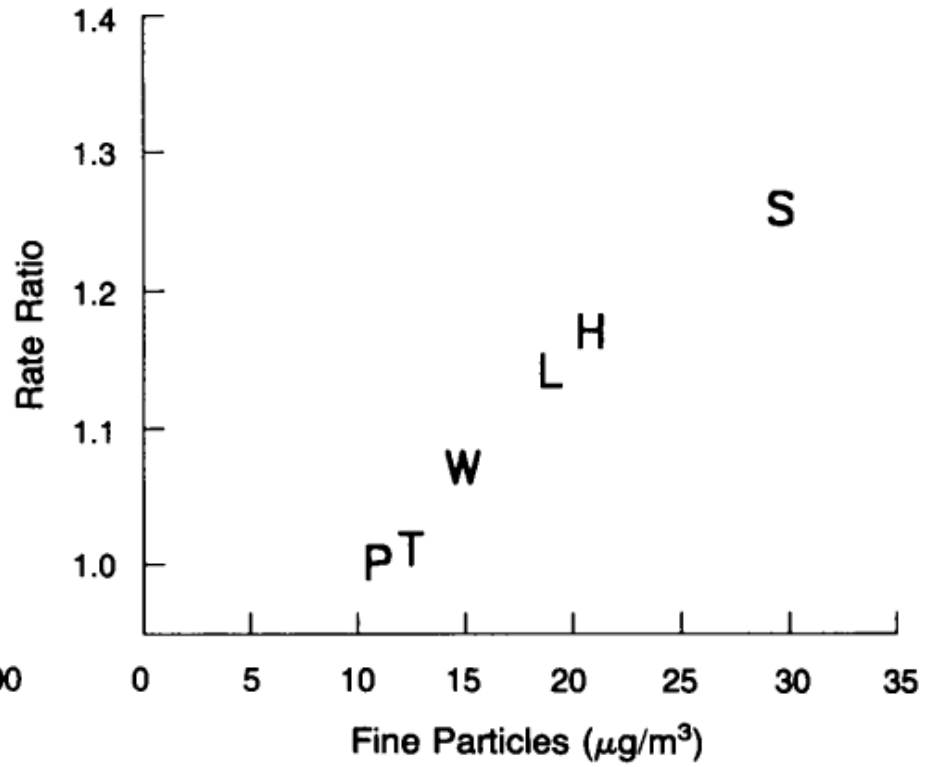


Figure 2. Crude Probability of Survival in the Six Cities, According to Years of Follow-up.

Fine particulate more associated with mortality



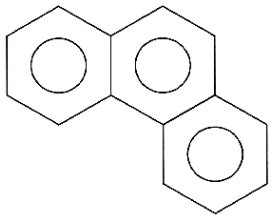


What is $PM_{2.5}$ made of?

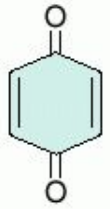
- Depends on what is combusted
- PM from Diesel Exhaust is largely carbonaceous, but often times metals are added for performance (e.g. lead, platinum, manganese) but importantly, has thousands of different organic chemicals on the particle's surface
- PM from natural sources (typically $PM_{2.5}$-PM_{10}) can have metals, components of bacterial growth, as well as oxides, chlorides, and sulfates
- $PM_{2.5}$ from coal can have metals (e.g. mercury, zinc, selenium)
- Overall, ambient $PM_{2.5}$ can have a lot of material in in, and can differ from one location to another

The surface of PM is important!

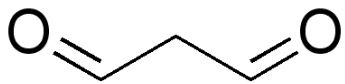
- It is becoming apparent that the surface of the particle is where there is toxic action
- Chemicals on the surface of the particle can include organic chemicals like polyaromatic hydrocarbons (PAHs), quinones, aldehydes, all of which are known toxicants, and highly reactive towards creating free radical oxygen species (ROS)
- ROS → Oxygen with an extra electron = Highly reactive!



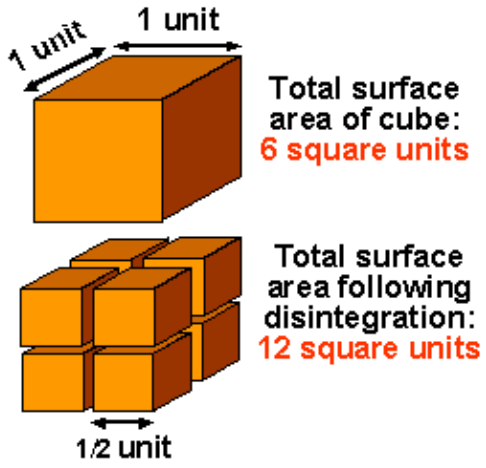
Phenanthrene
$C_{14}H_{10}$



p-Benzoquinone



PAHs **Quinones** **Aldehydes**



EPA and $PM_{2.5}$

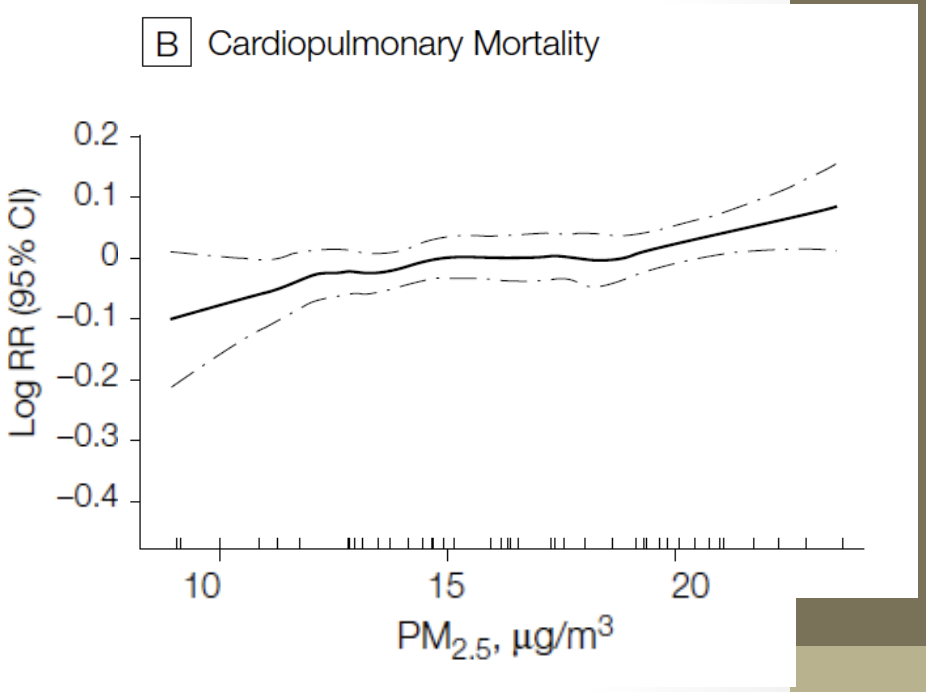
- Following landmark studies in the 1990's which observed increased risks of mortality from $PM_{2.5}$ inhalation, the EPA revised their NAAQS for PM to include $PM_{2.5}$

- Former NAAQS standard for PM was (PM_{10}) 50ug/m^3 annual mean, 150ug/m^3 24hr average
- New NAAQS removes the annual PM_{10} standard!
- $PM_{2.5}$ NAAQS was 15ug/m^3 annual mean, 65ug/m^3 24hr average
- As of last year, **new 24hr average is 50ug/m^3**

Epidemiology: a lifetime of air pollution exposure

- Pope and colleagues
- Mortality data from 500,000 individuals across the U.S. were associated to air pollution parameters

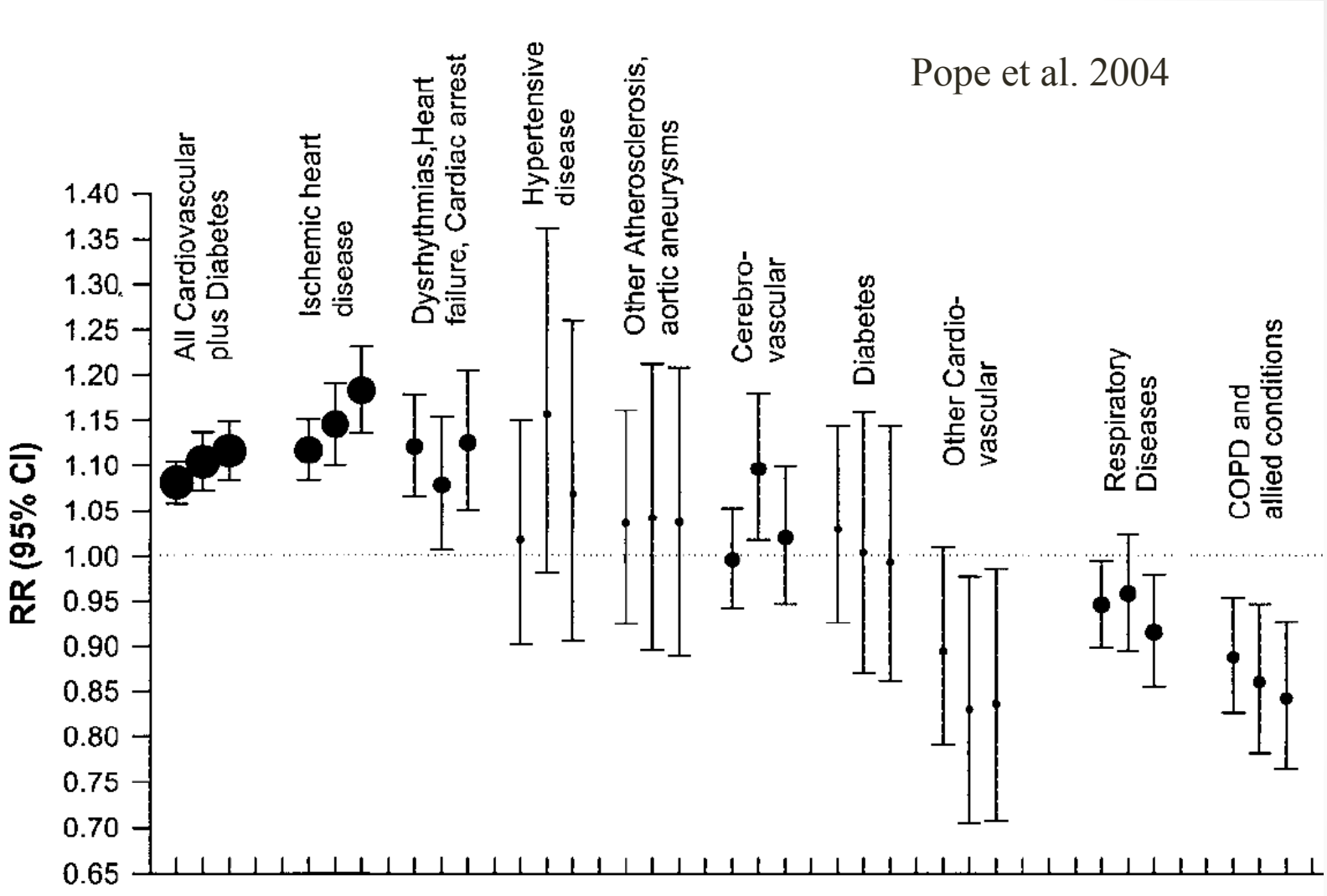
- Each 10ug/m^3 increase in $PM_{2.5}$ was associated with a 6% increase in risk of cardiopulmonary mortality



Pope et al. 2002

Stratifying cardiopulmonary mortality

- Of the 500,000 mortalities, more than half were ‘cardiopulmonary’,
- ~45% cardiovascular and 8% pulmonary
- Upon stratification of cardiovascular mortalities into specific groups, associations between $PM_{2.5}$ and cardiovascular mortality were more robust

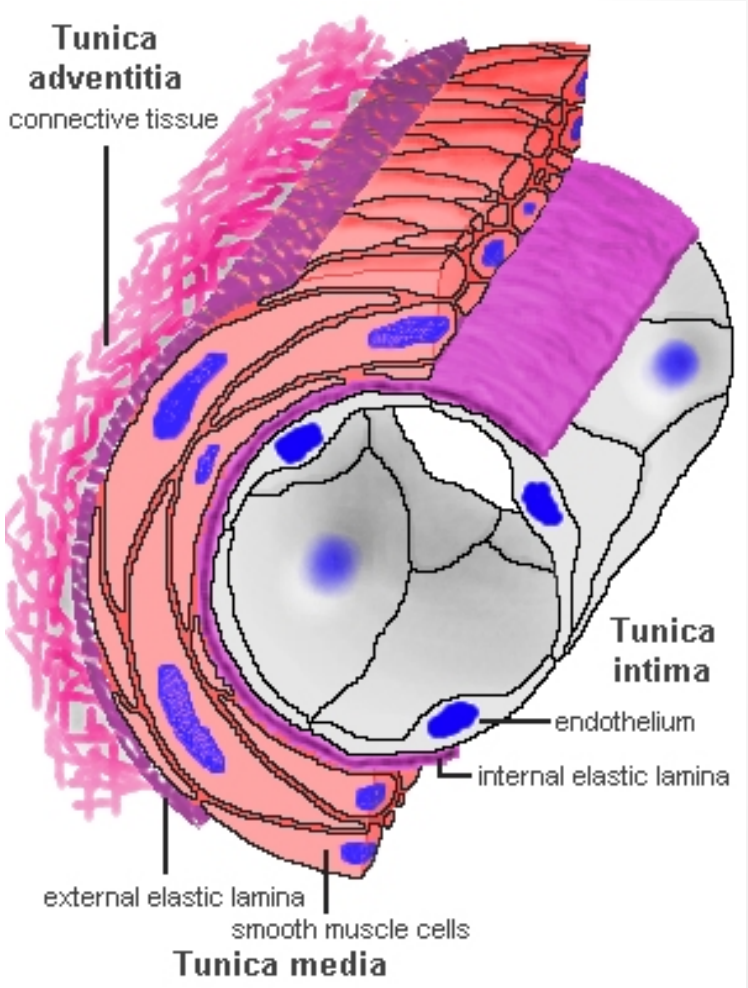


For every 10ug/m^3 increase in $PM_{2.5}$ there was an increase in mortality of:

12% 'All Cardiovascular', 18% 'Ischemic Heart Disease', 13%, 'Dysrhythmias, Heart failure, Cardiac Arrest'

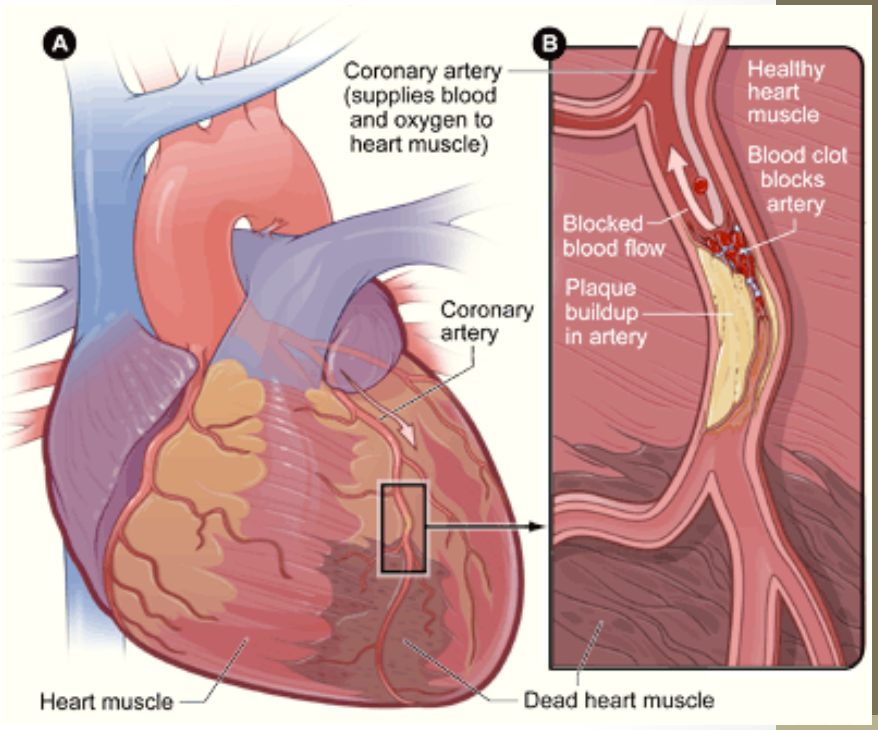
Vascular Reactivity

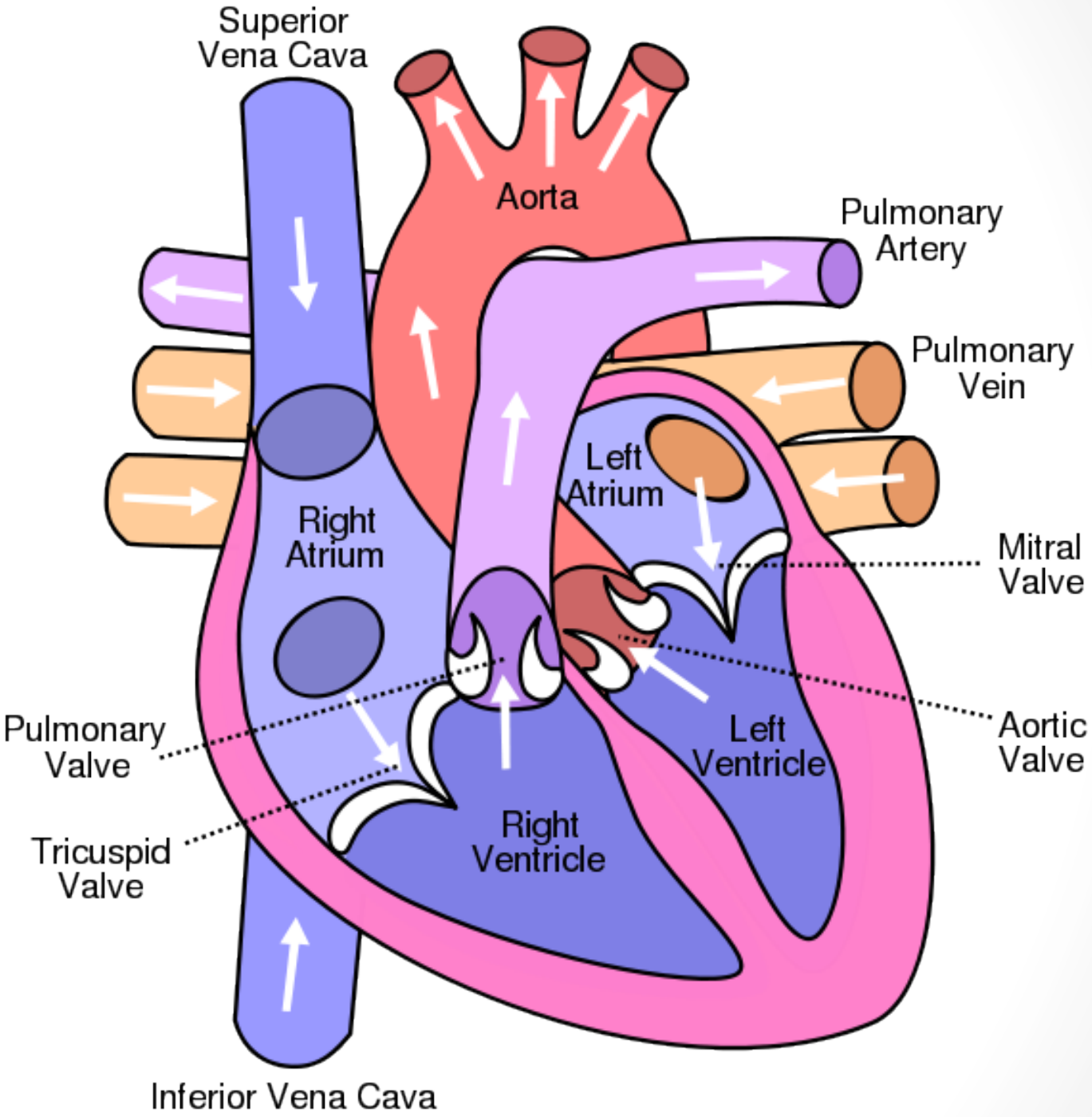
- Blood vessels dilate and contract
- Vascular tone: Balance between dilating and constricting factors
- Important determinant of acute cardiovascular events
  - Vasospasm
  - Compromised relaxation
  - Enhance contraction
  - Predisposition to thrombosis



Short term increases in $PM_{2.5}$

- Transient increases in $PM_{2.5}$ are associated with increased emergency room visits
- Many of these visits are due to acute myocardial infarction (MI)

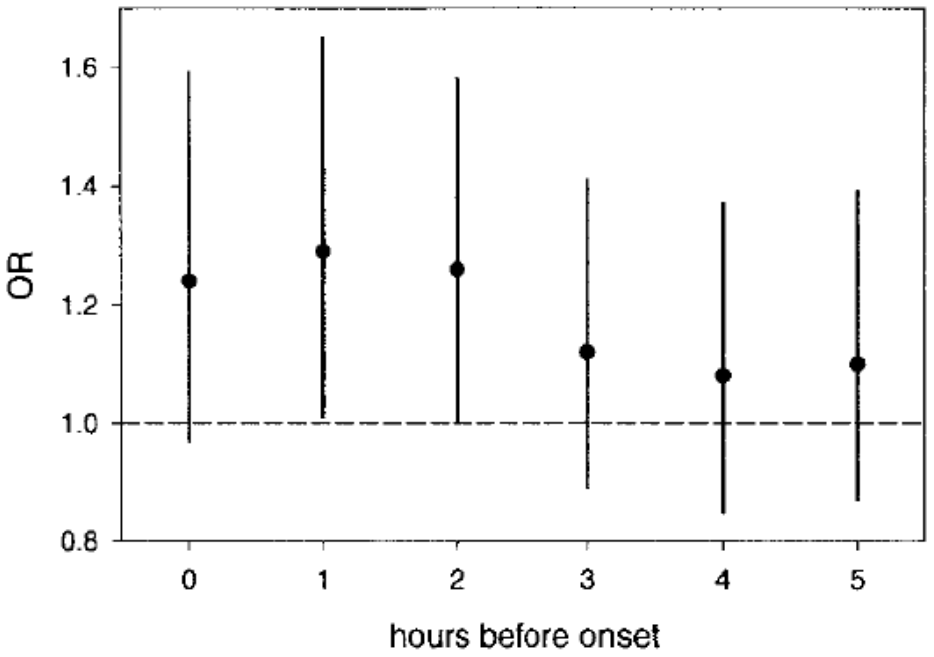



Superior
Vena Cava
Aorta
Pulmonary
Artery
Pulmonary
Vein
Left
Atrium
Right
Atrium
Mitral
Valve
Pulmonary
Valve
Aortic
Valve
Left
Ventricle
Right
Ventricle
Tricuspid
Valve
Inferior Vena Cava

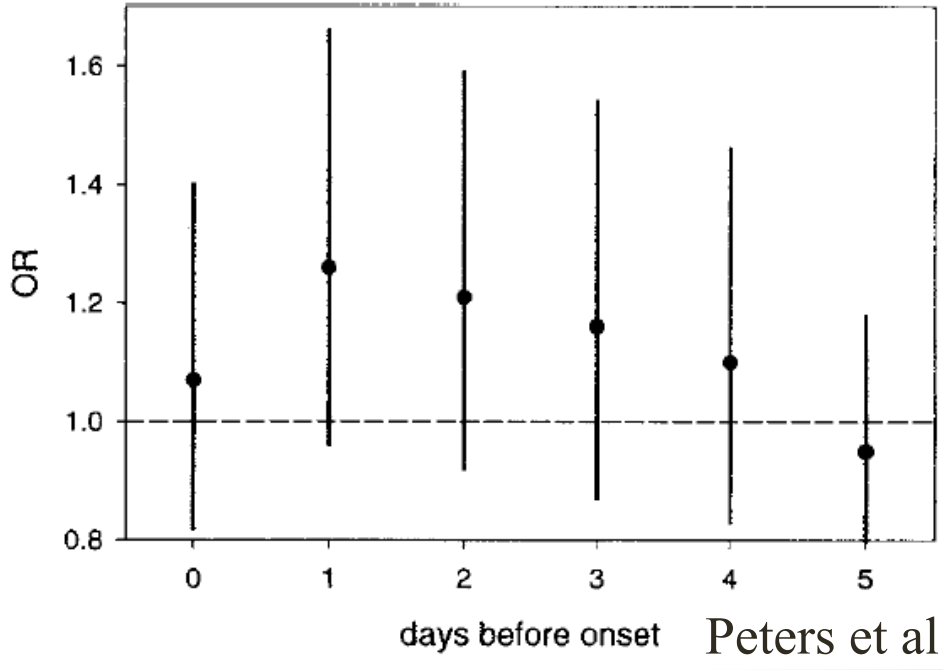
$PM_{2.5}$ and MI

- Peters and coworkers examined cases of MI and the $PM_{2.5}$ concentrations preceding the event
- A positive association between elevated $PM_{2.5}$ and MI was detected within 3 hours prior to symptom onset
- In addition, a delayed response was also observed where elevated $PM_{2.5}$ levels were associated with MI 24 and 48 hours before onset

For every 25ug/m^3 increase in $PM_{2.5}$, ORs for MI increase to ~1.3, 1 and 2 hours before onset



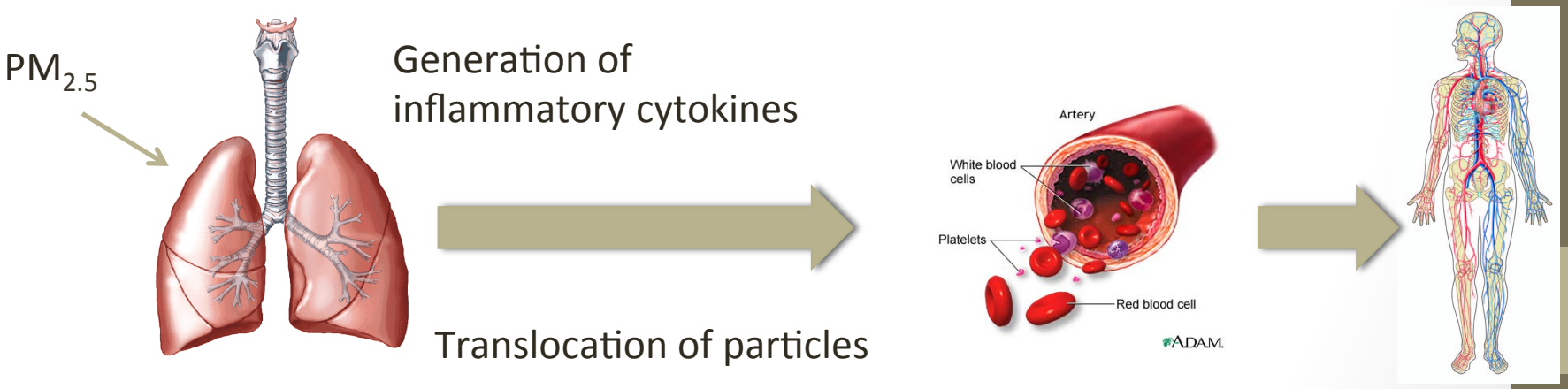
For every 20ug/m^3 increase in $PM_{2.5}$, ORs for MI increase to ~1.3, 1 and 2 days before onset



Peters et al. 2001

Short exposure, significant effects?

- How would the inhalation of $PM_{2.5}$ increase risk of MI within hours?
- Several hypotheses, but one central hypothesis revolves around the belief that $PM_{2.5}$ can induce endothelial dysfunction by inciting vascular oxidative stress



Limitations of epidemiology

- Although these reports provide excellent correlative data, there is little information to determine a cause of effect
- Without a controlled exposure and biological monitoring, it is difficult to determine these effects
- Several groups, including the University of Washington, have developed controlled $PM_{2.5}$ exposure systems to investigate these effects

Air Pollution and Cardiovascular Health

University of Washington

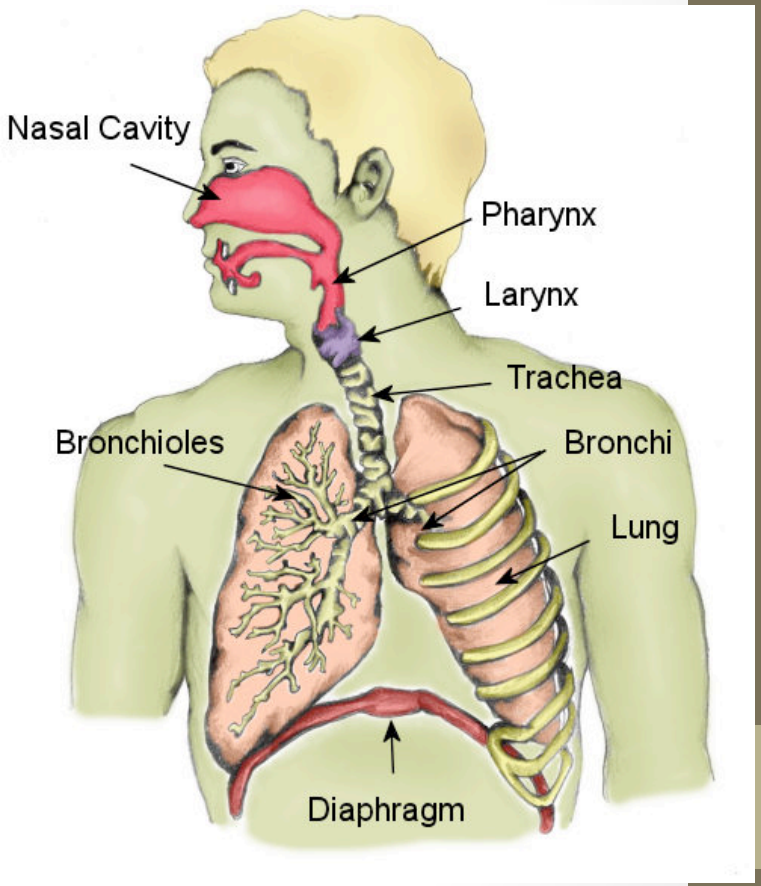
DISCOVER Center:

Cardiovascular Disease and Traffic-Related Air Pollution

- Epidemiology studies have provided substantial evidence that the inhalation of fine ambient particulate matter ($PM_{2.5}$) is associated with adverse cardiovascular outcome
- Although the correlation is well established, the specific effects and biological mechanism of effect have not been well characterized

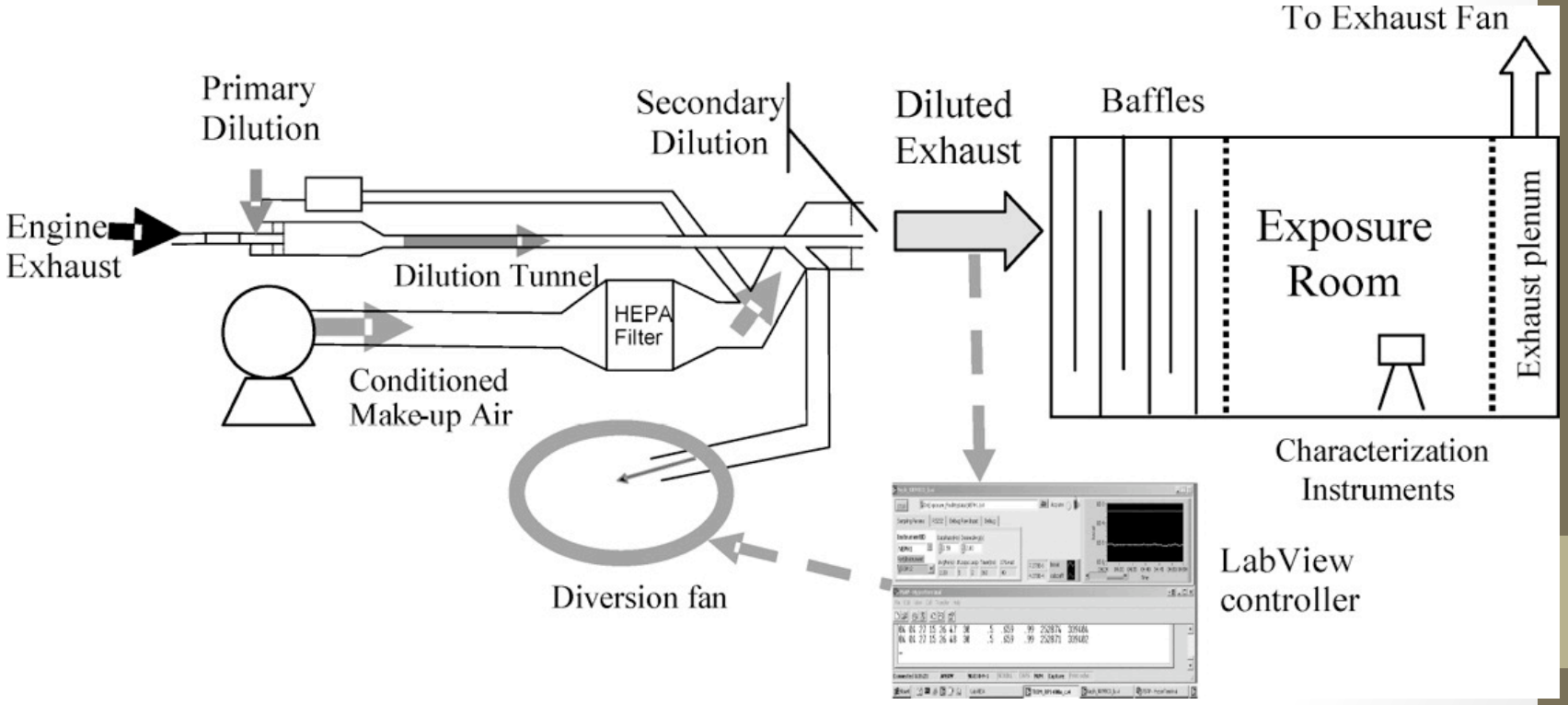
Diesel Exhaust (DE) is an important and relevant source of $PM_{2.5}$

- In many metropolitan regions, $PM_{2.5}$ is largely derived from diesel engines
- Due to its narrow aerodynamic diameter, when inhaled, DE can remain suspended in the airway and reach the deep lung
- DE particulate (DEP) is a highly carbonaceous material that can contain thousands of organic chemicals on its surface as well as metals that can participate in reactive oxygen species (ROS) generation



Controlled DE exposures

- Controlled generation of DE allows investigators to monitor and identify biological effects in humans and animals following short or long term exposures

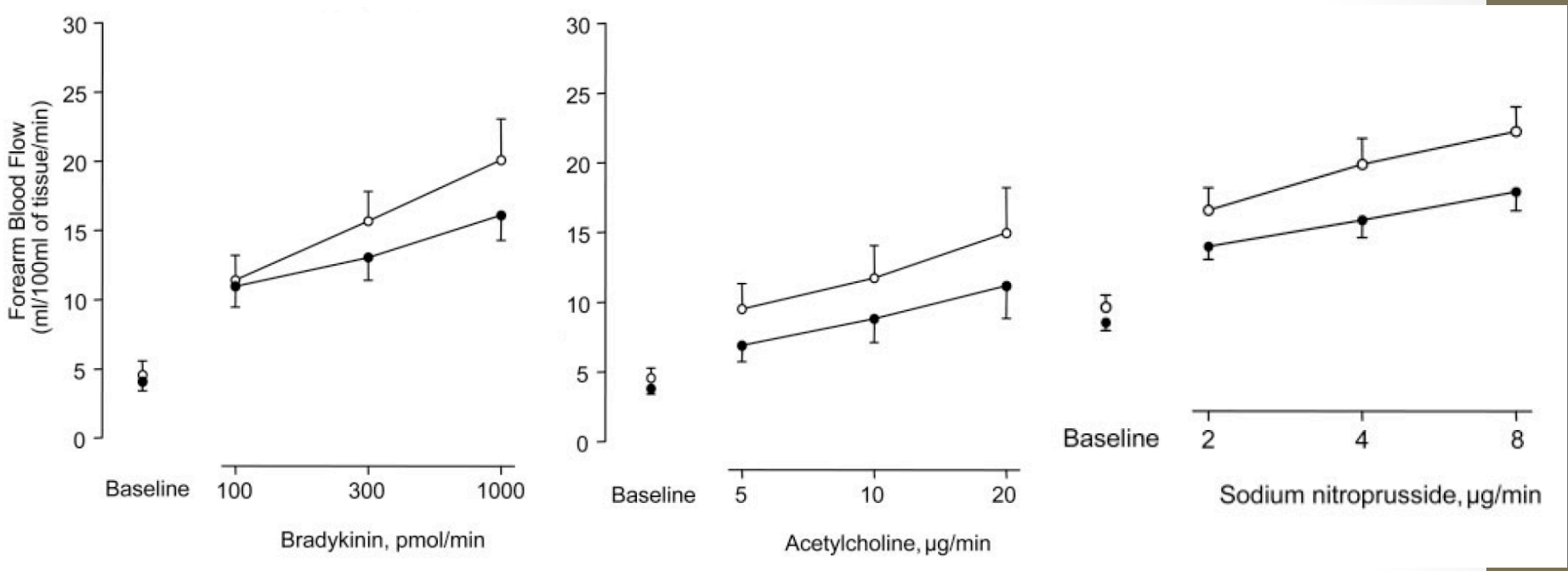


Gould et al. 2008

DE inhalation causes impairment in vascular reactivity

- By exposing healthy men to DE (300ug/m^3) for 1 hour with intermittent exercise, Mills and coworkers identified that DE caused impairment in vessel dilation, by measurement of forearm blood flow (FBF), following infusion of the vessel dilators, acetylcholine, bradykinin, and sodium nitroprusside
- Impairment in vessel dilation and reduction in FBF are significant effects as these can influence blood pressure and increase risk of MI

1 hr Diesel exhaust inhalation impairs vessel dilation for 24 hours after exposure

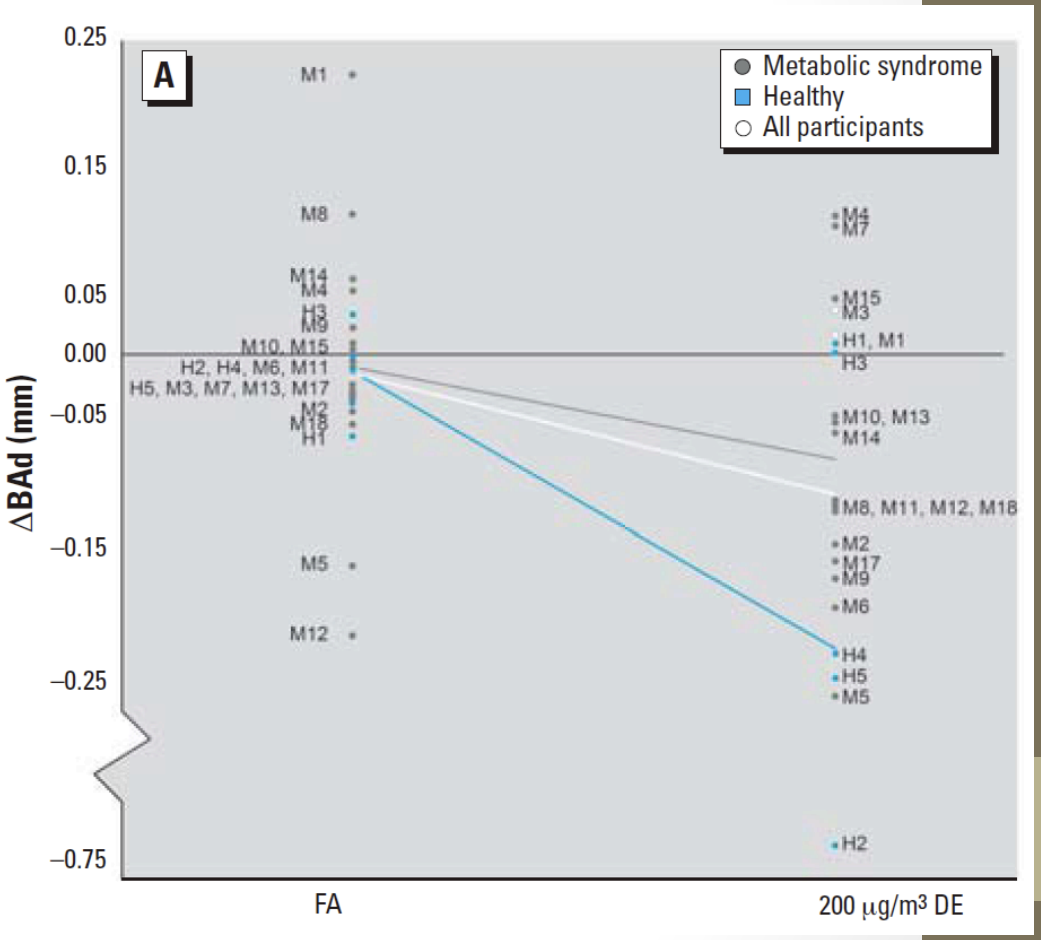


Mills et al. tested this effect 2-4 hours, 6-8 hours, and 24 hours after exposure

2 hour DE inhalation (200ug/m^3) causes acute vasoconstriction

Work done at the UW identified that a 2 hour exposure without exercise, caused an acute decrease an brachial artery diameter in healthy participants

This was an important finding indicating that short term exposure can impair vessel function in the absence of dilatory stimulation



Peretz et al. 2008

How does DE inhalation cause impairment in vessel function?

- Vascular tone = balance between vessel constriction and vessel dilation
- Changes in vascular tone can occur when the production of, or sensitivity to, vasoactive agents is altered
- Further investigations can be done with toxicology studies using mouse models

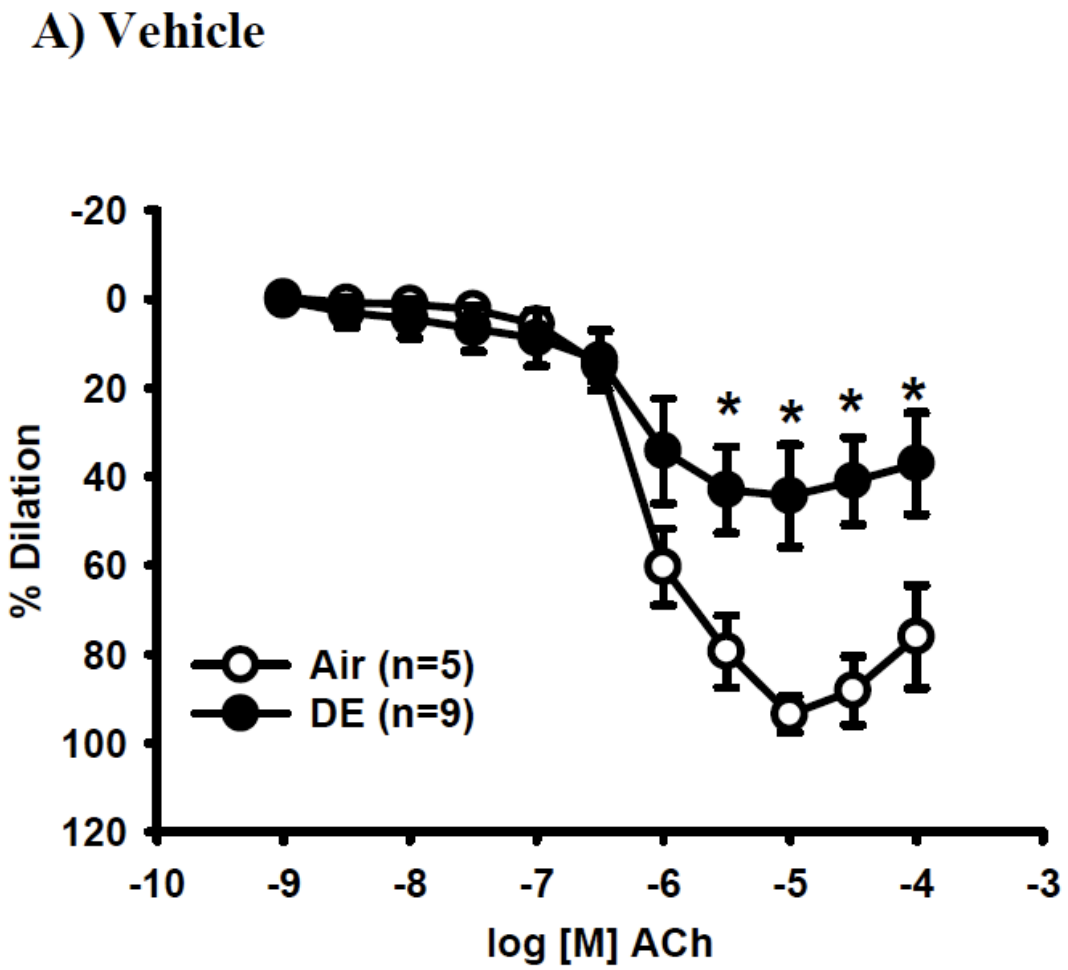
DE inhalation causes impairment in vessel dilation by impairing NO synthesis

Nitric Oxide (NO) is an important agent to dilate blood vessels

After a 5 hour DE exposure (300ug/m^3)

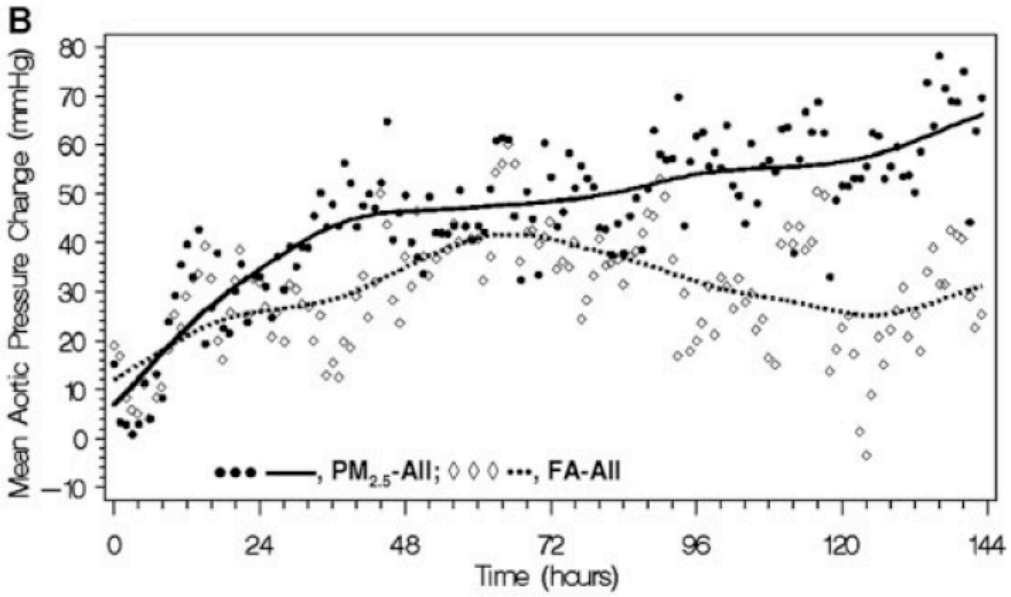
Compromised dilatory response to ACh in coronary arteries

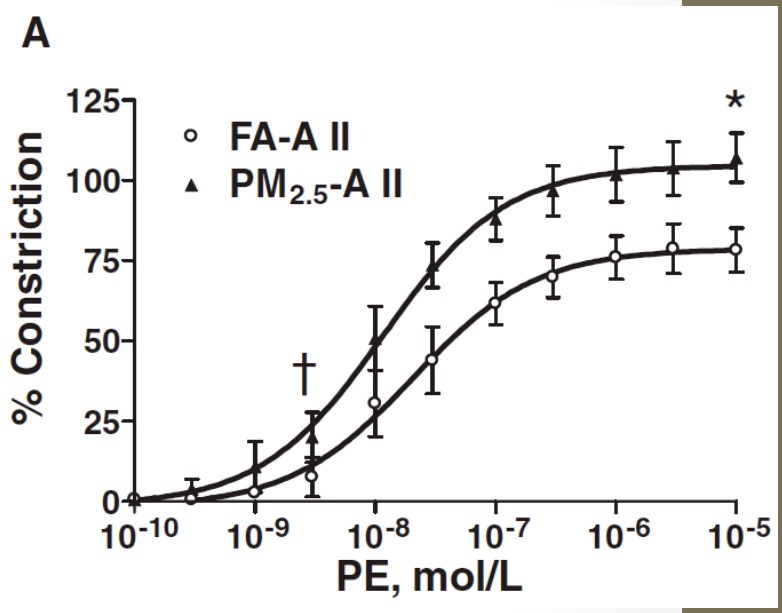
ACh stimulates dilation via eNOS activation



Cherng et al. 2010

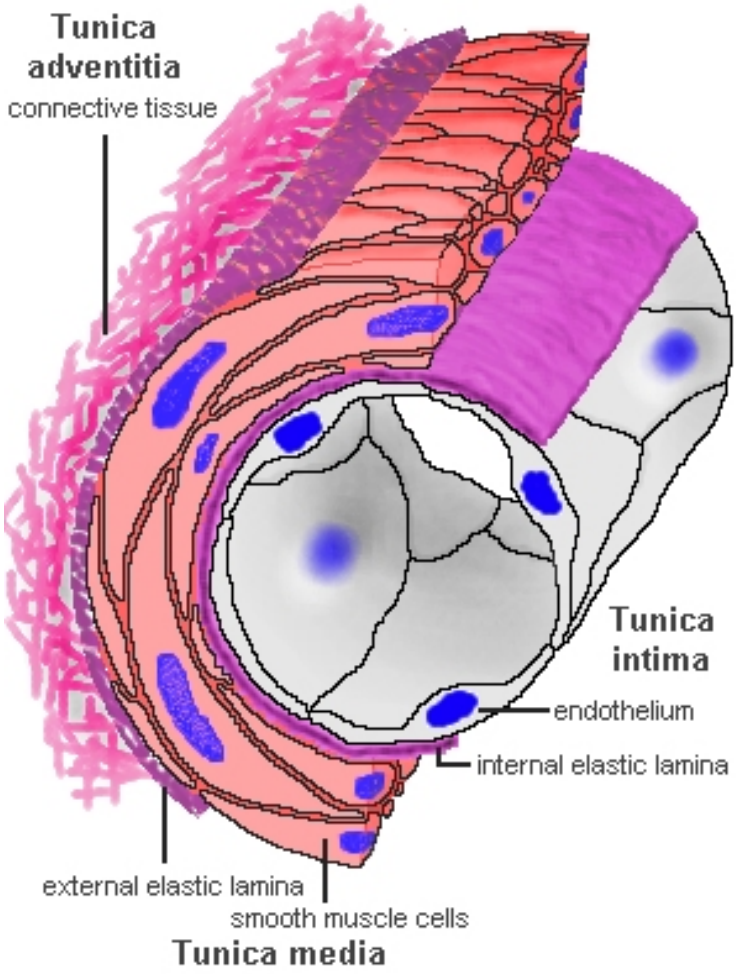
$PM_{2.5}$ inhalation increases sensitivity to vasoconstrictors

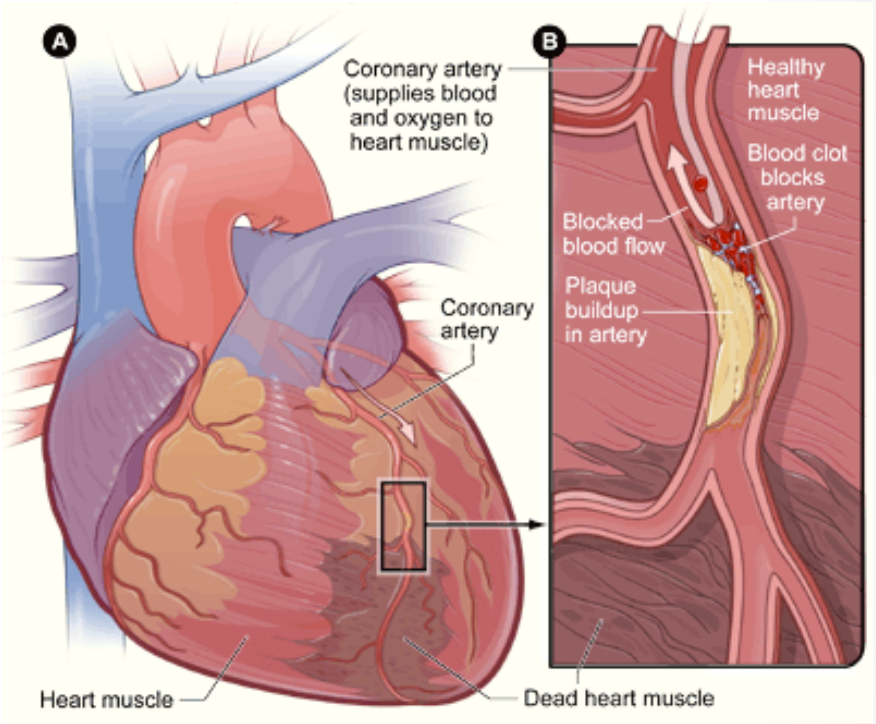


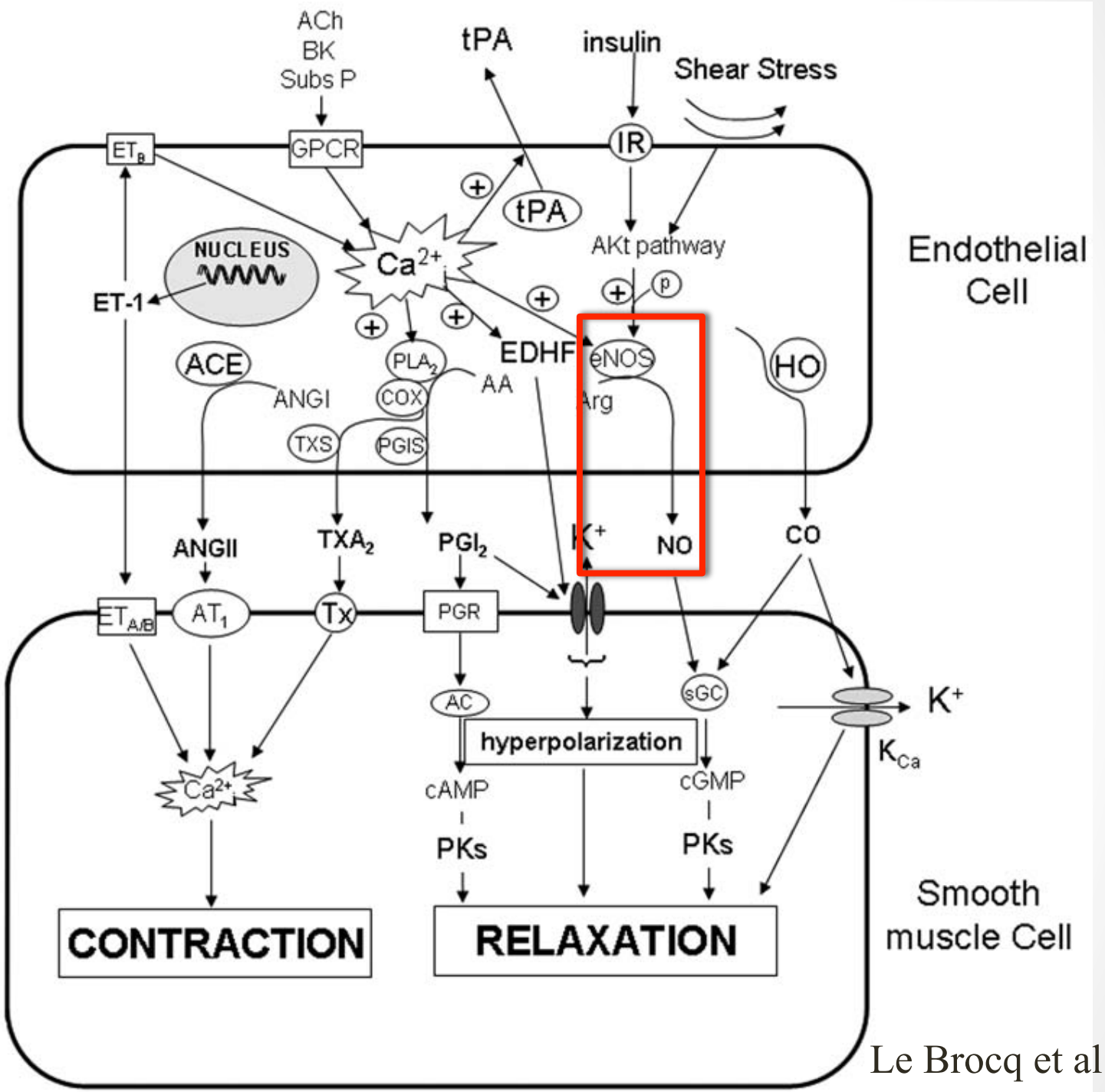


Sun et al. 2008

Why is this important?

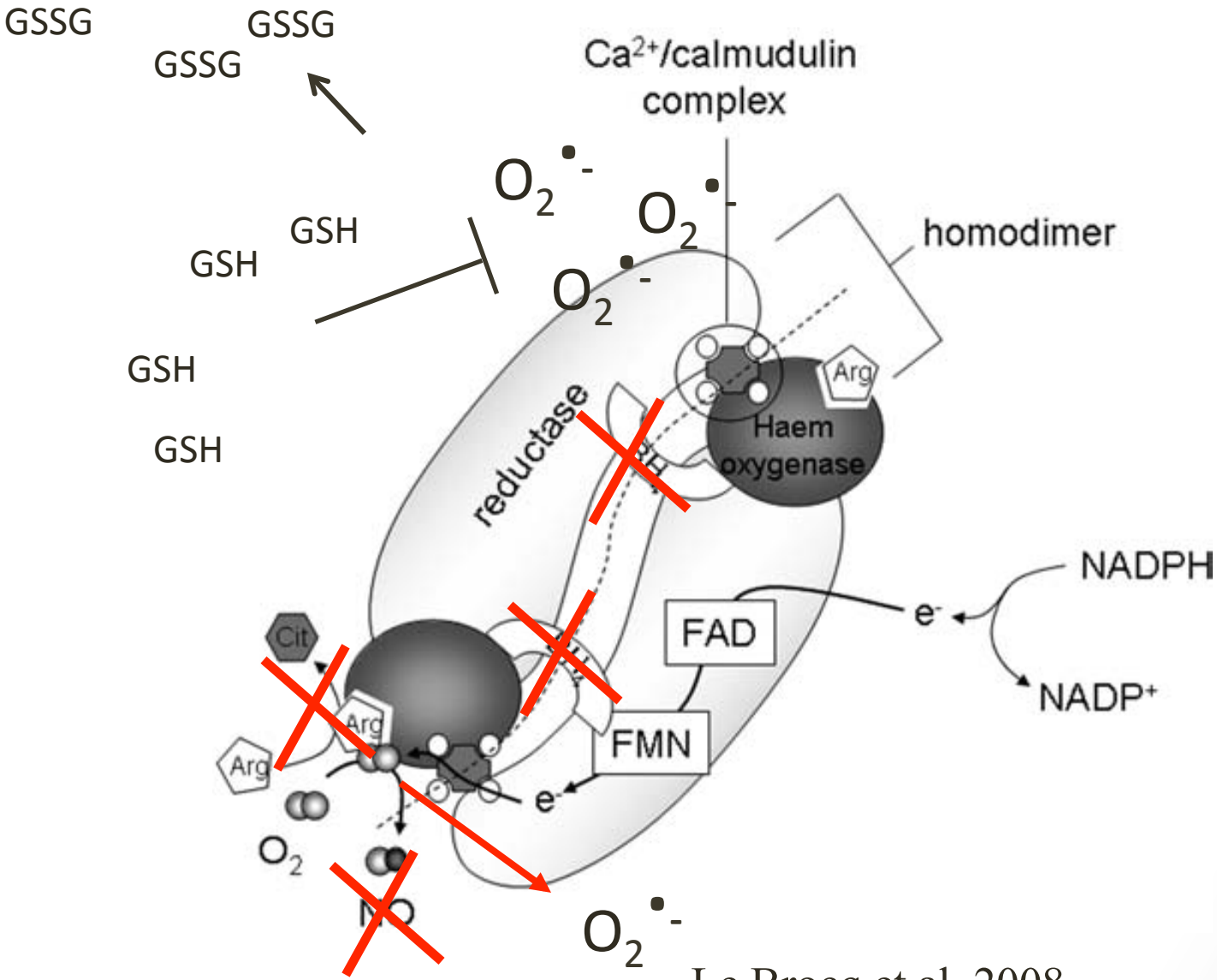






Le Brocq et al. 2008

eNOS is redox sensitive due to its cofactor, BH4



Le Brocq et al. 2008

Inhalation of DEP

↓

DEP uptake in macrophage and epithelium

↓

Lung and airway inflammation due to oxidative stress

↓

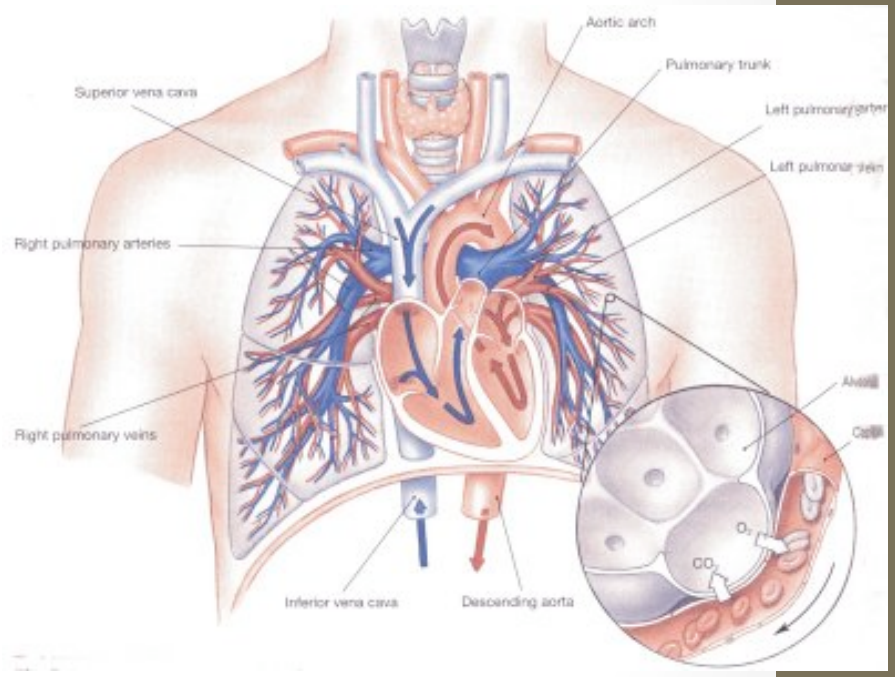
Proinflammatory cytokines enter systemic circulation

↓

Inflammatory cytokines cause vascular oxidative stress

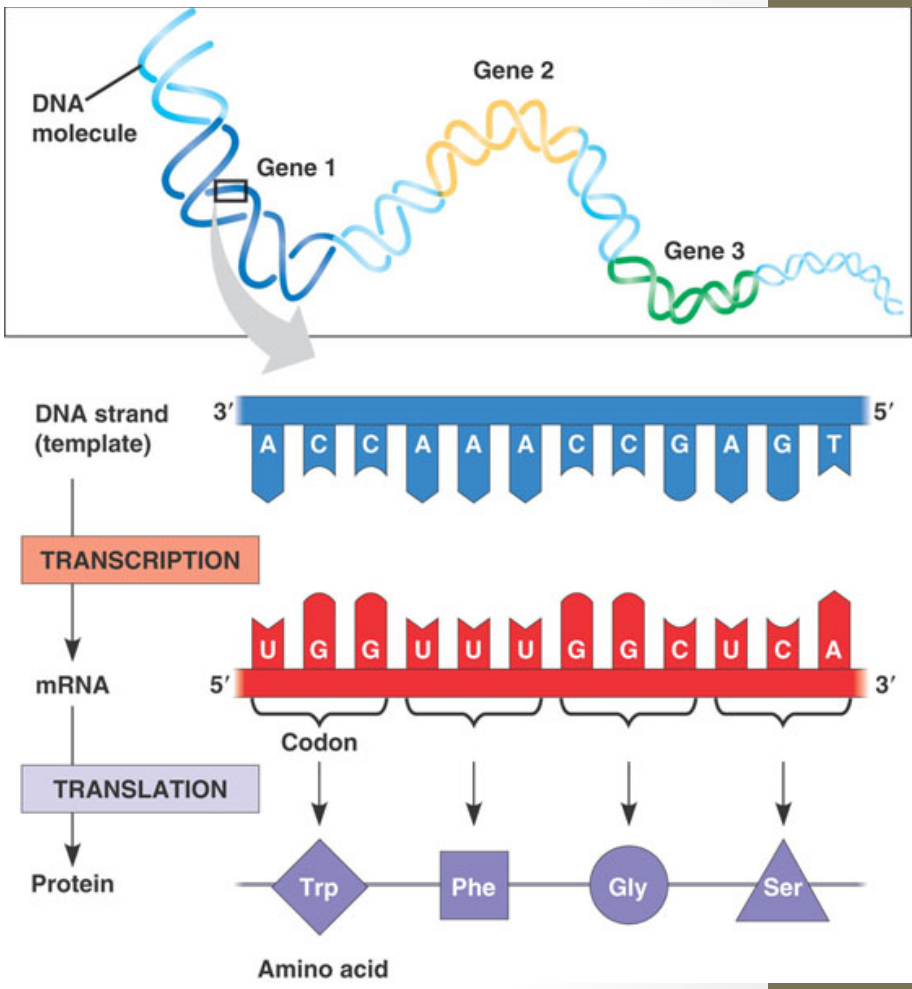
↓

Impairment in vascular function



Gene x Environment Interactions

- Our genes are not all the same! (obviously)
- Mutations in our genetic code are passed down to the next generation
- Often times those mutations are not necessarily overtly deleterious, but can change how well the gene is expressed
- These are called ‘polymorphisms’ when they are frequent (>1% of population has the mutation)
- Frequently these polymorphisms are highly frequent (>20%)

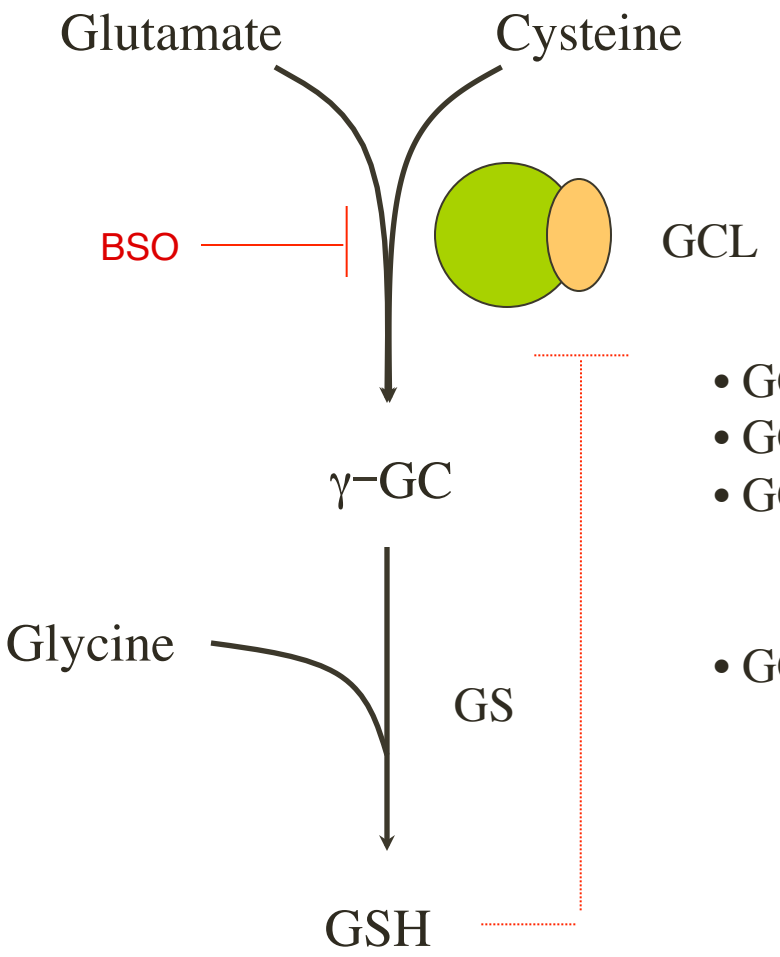


Predicting sensitive populations

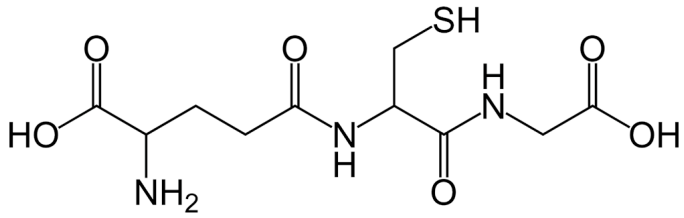
- If a genetic polymorphism increases the risk of an adverse health effect following exposure to an environmental contaminant, we want to know, and protect sensitive populations by altering regulations

- $PM_{2.5}$ is hypothesized to cause health effects by oxidative stress
- We have antioxidants defending our cells against oxidants
- There are known polymorphisms in important antioxidant genes,
- **Are these people more sensitive to DE inhalation?**

Glutathione (GSH) is a key intracellular antioxidant and may influence DE-mediated vascular effects



- GCLC possesses all catalytic activity
- GCLC is feedback inhibited by GSH
- GCLM: lowers the K_m for glutamate
  increases the K_i for GSH
  possesses no catalytic activity
- GCL is inhibited by buthionine sulfoximine (BSO)

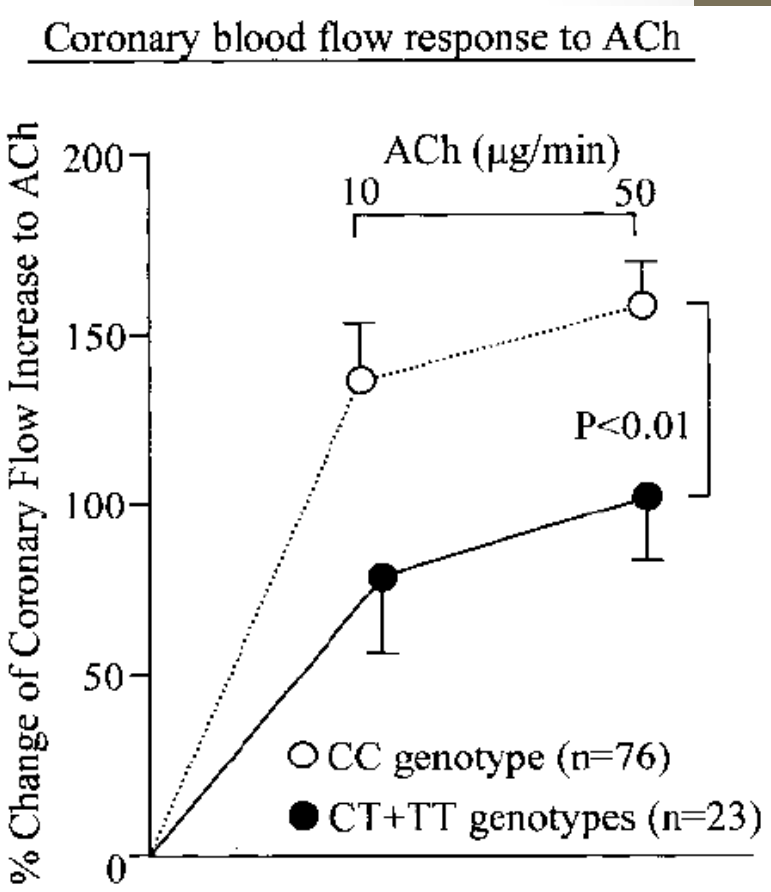


Gclm and *Gclc* are highly polymorphic, influence glutathione levels, vascular function, and risk of MI

TABLE 2. Genotype Frequencies of GCLM Promoter Polymorphisms in Control Subjects and Patients With MI

	Control Subjects (n=428)	Patients With MI (n=429)	OR (95% CI)	*P*
−588C/T and −23G/T, n (%)				
GCLM/TT-TT	2/428 (0.5)	16/429 (3.7)	...	...
GCLM/CT-GT	80/428 (18.7)	119/429 (27.8)	...	...
GCLM/CC-GG	346/428 (80.8)	294/429 (68.5)	...	...
−588T allele vs C allele	...	...	1.96 (1.41–2.65)	<0.001
−588TT and CT vs CC	...	...	1.94 (1.47–2.61)	<0.001
−588TT vs CT and CC	...	...	8.25 (1.89–36.11)	<0.001*

Data are presented as number of patients (%). CI indicates confidence interval; OR, odds ratio.
*Fisher's exact test.



Nakamura et al. 2002, 2003

Inhalation of DEP

↓

DEP uptake in macrophage and epithelium

↓

Lung and airway inflammation due to oxidative stress ⊣ GSH

↓

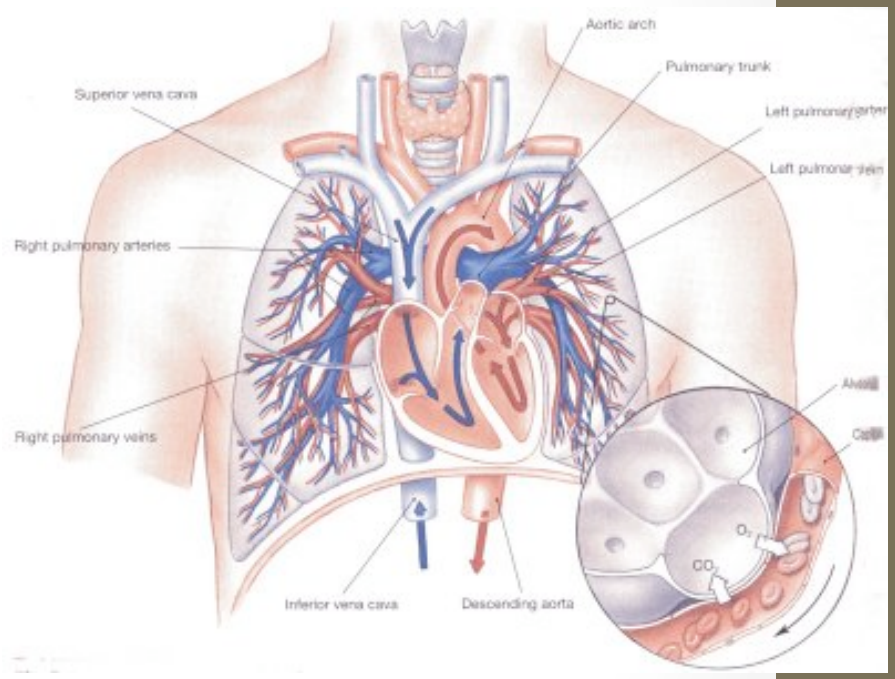
Proinflammatory cytokines enter systemic circulation

↓

Inflammatory cytokines cause vascular oxidative stress ⊣ GSH

↓

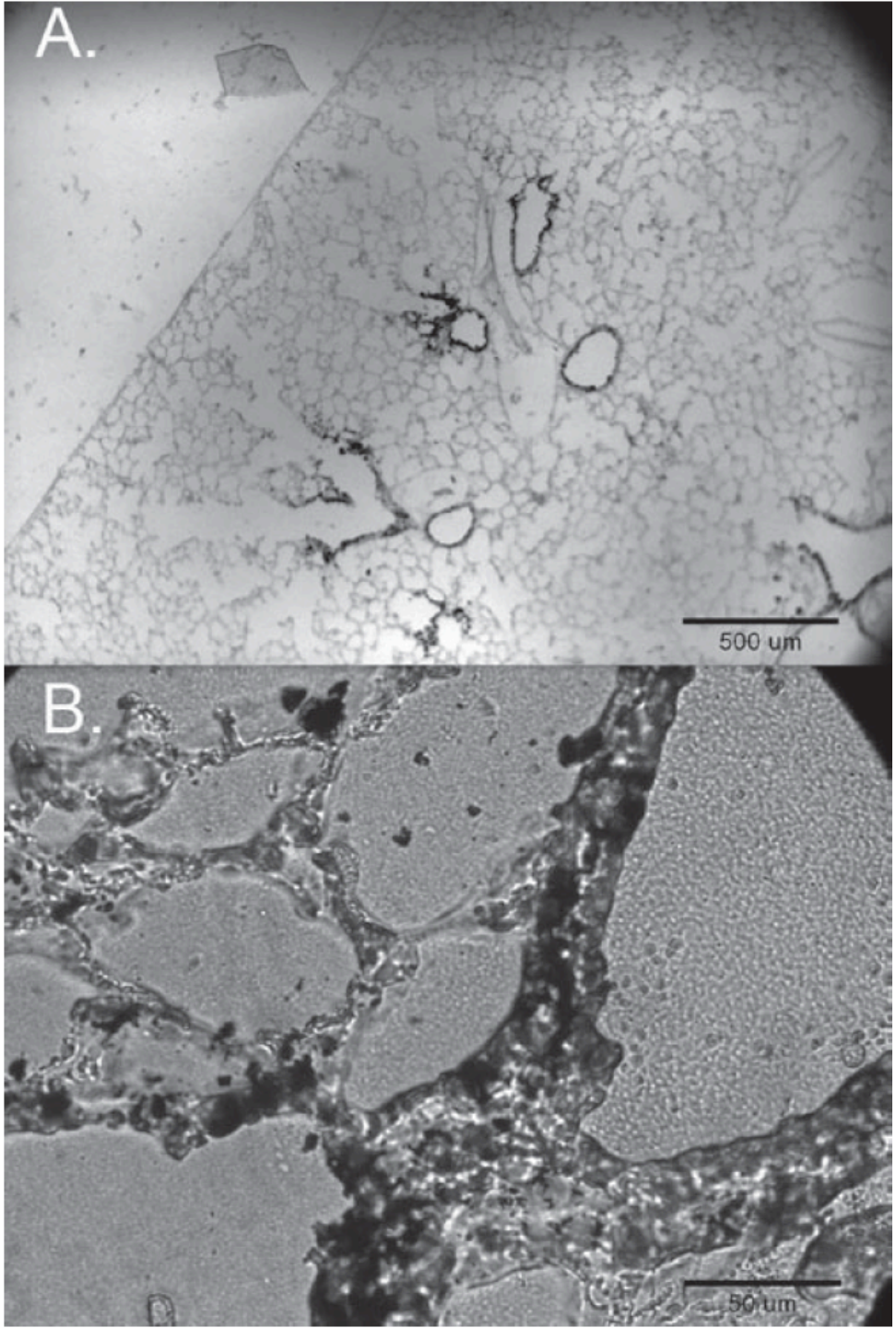
Impairment in vascular function



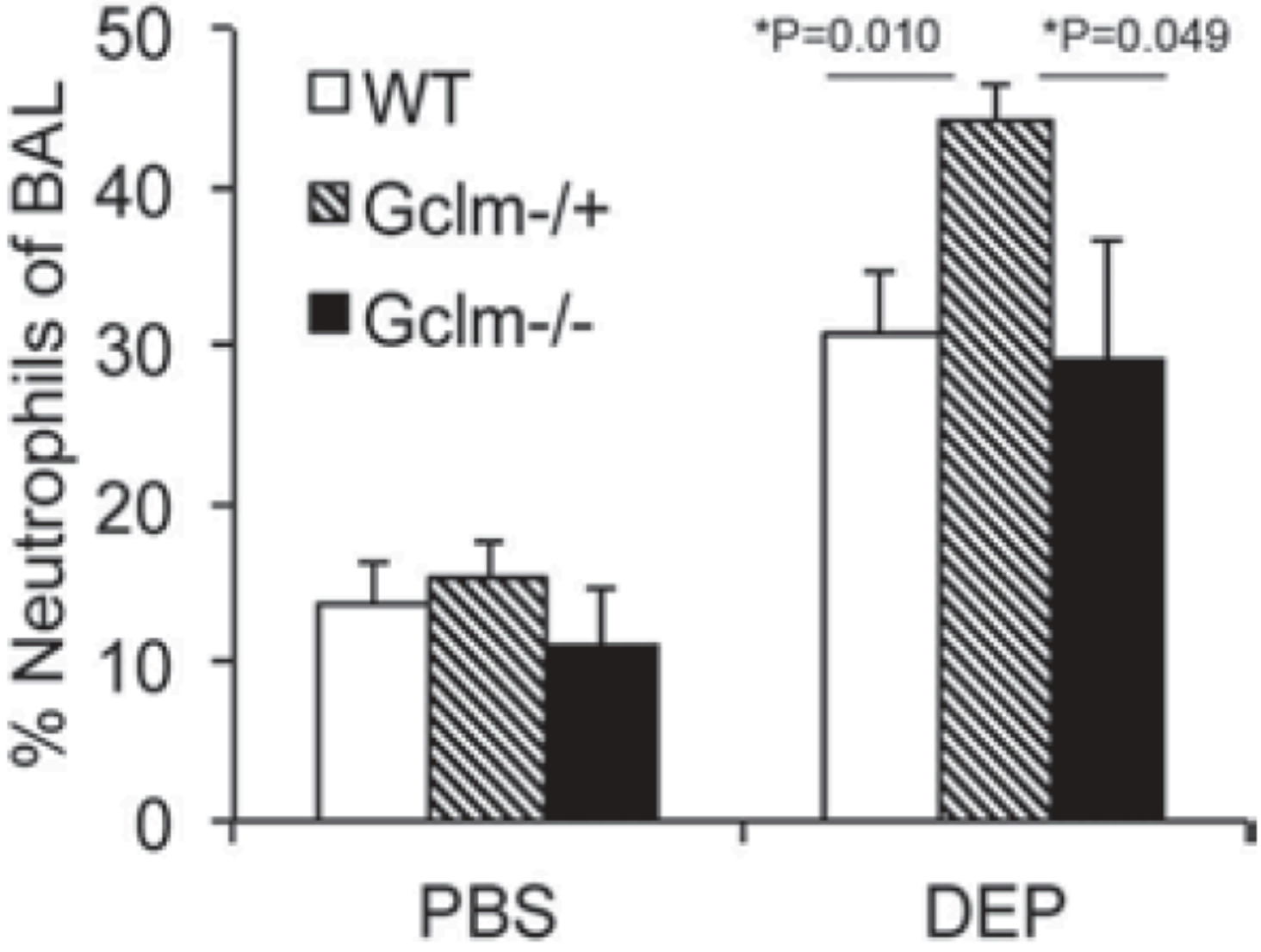
Gclm-KO mouse model

- By lacking the modifier subunit of GCL, these mice have a compromised ability to synthesize GSH
- Provides a model to investigate the role of GSH and oxidative stress in DE-induced vascular effects

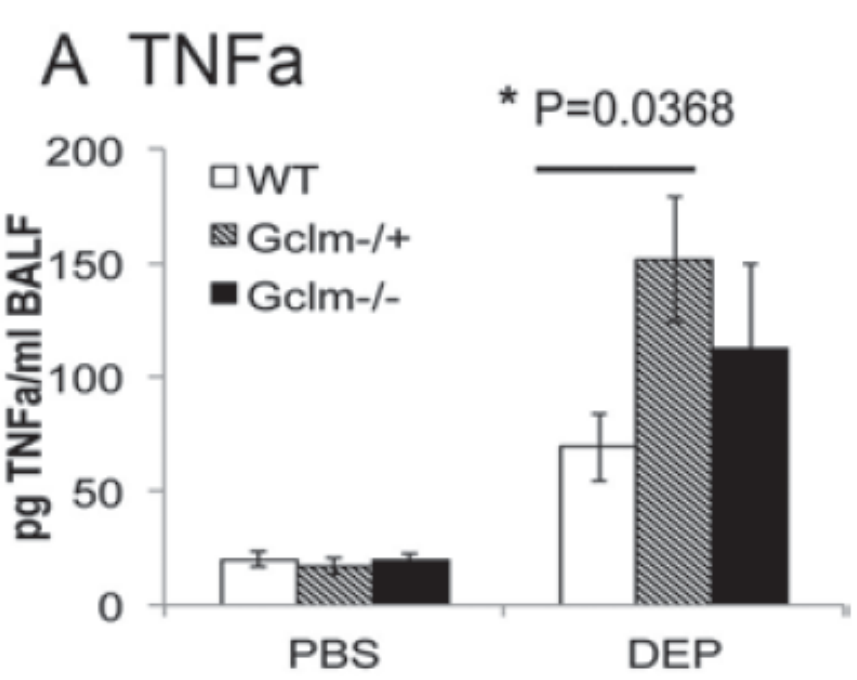
- 2 Questions
  - Are these mice more sensitive to DE-induced lung inflammation?
  - Are these mice more sensitive to DE-induced impairments in vascular reactivity?

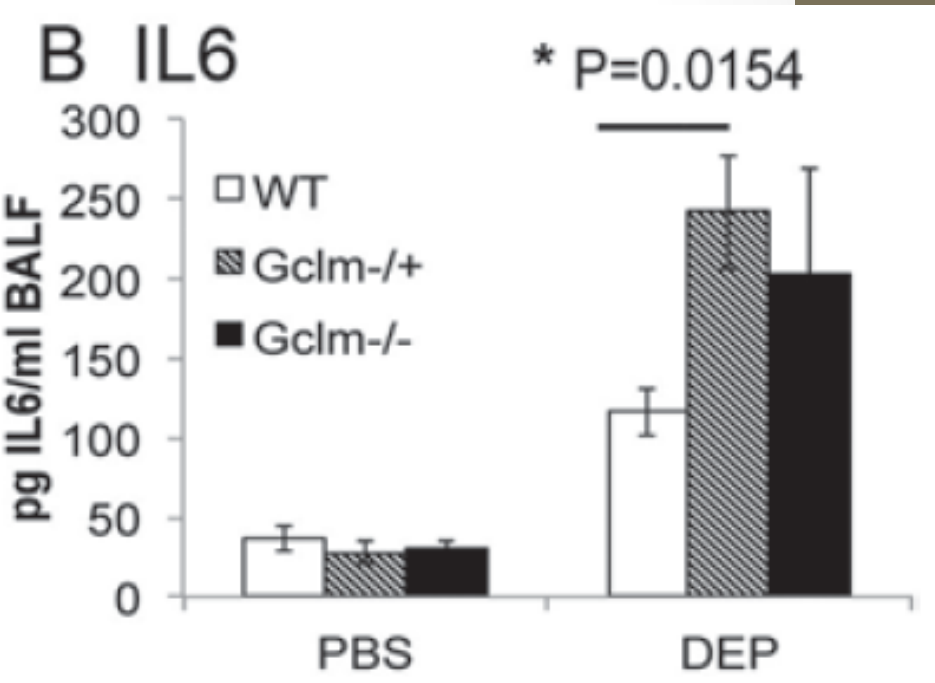

A.
500 um
B.
50 um

Gclm HT mice are more sensitive to neutrophil influx



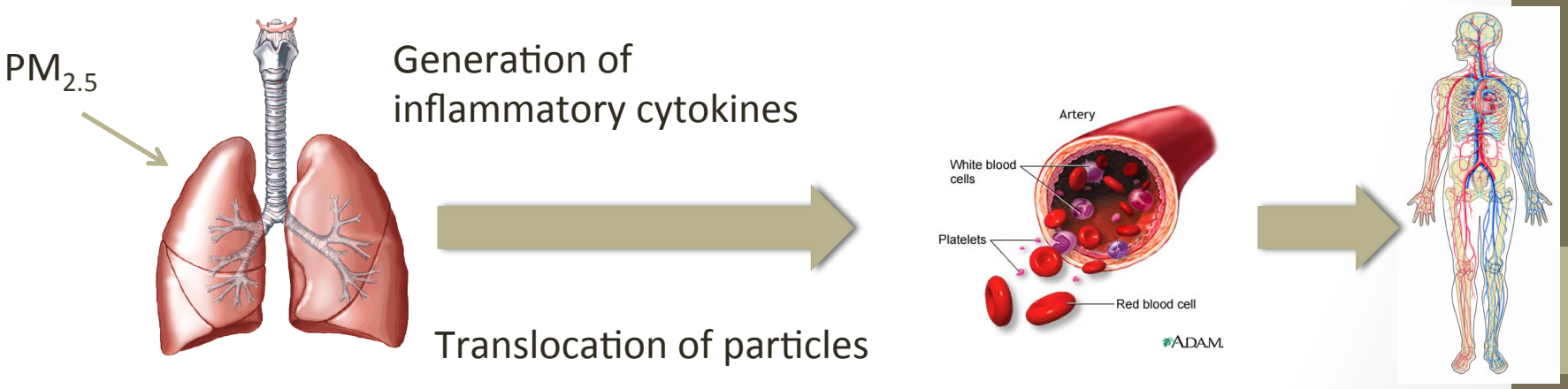
A greater amount of TNFa and IL6 is found in the lavage of *Gclm* HT mice



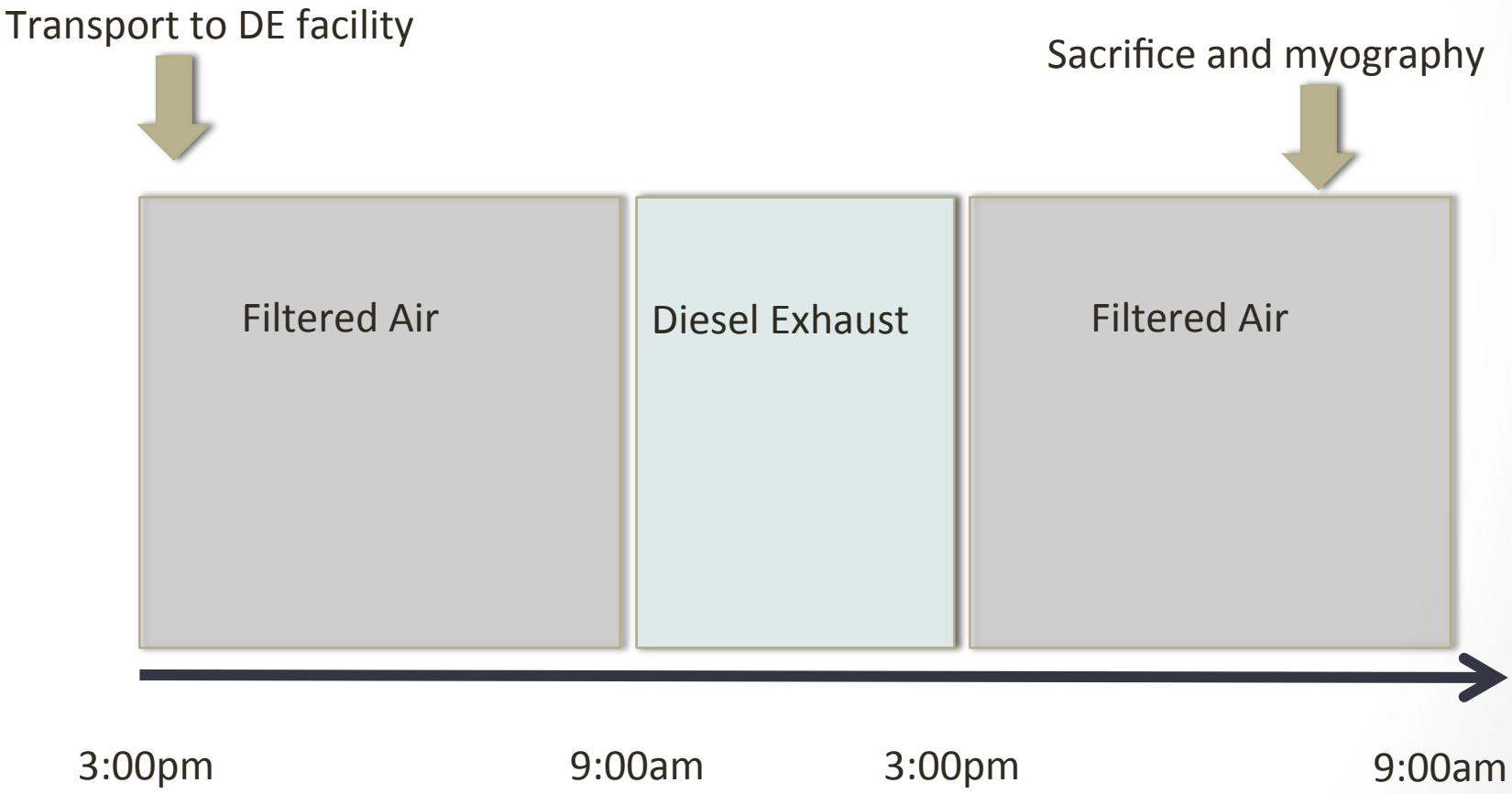


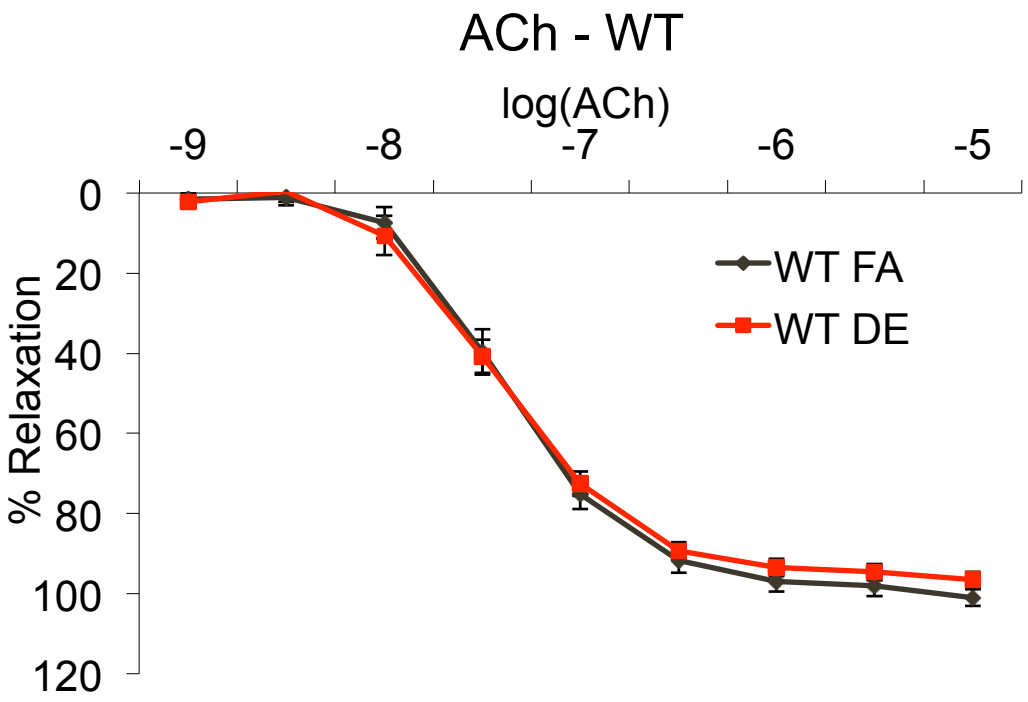
Gclm HT mice are more sensitive to lung inflammation

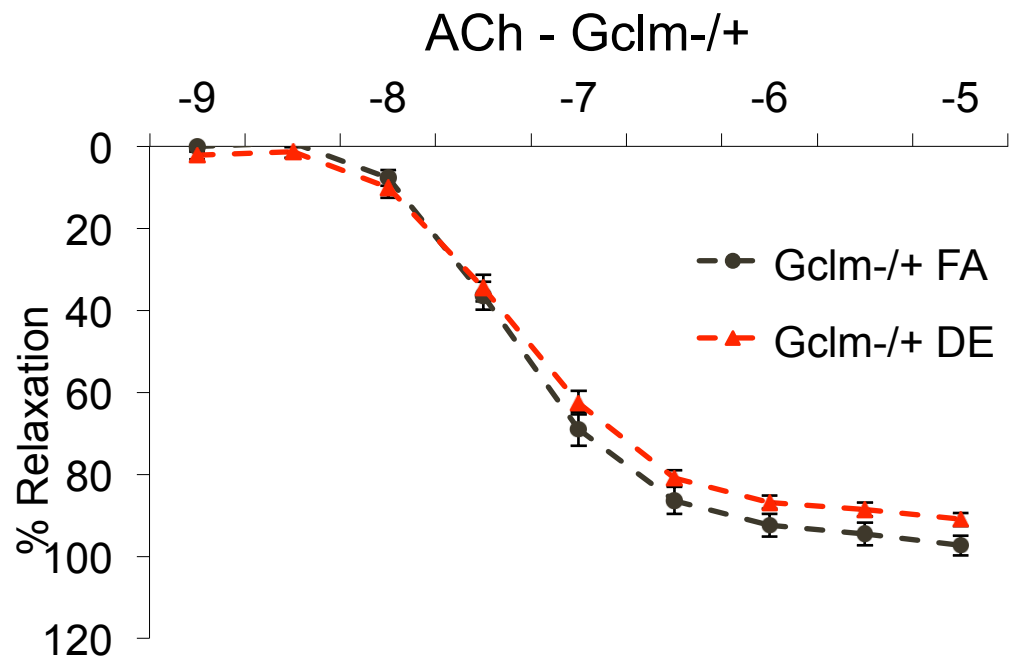
- Mice that are lacking 1 copy of the Gclm gene, have a glutathione content that is similar to the human polymorphism
- This suggests that humans with this polymorphism may also be more sensitive to lung inflammation
- This may mean more sensitive to changes in vascular reactivity

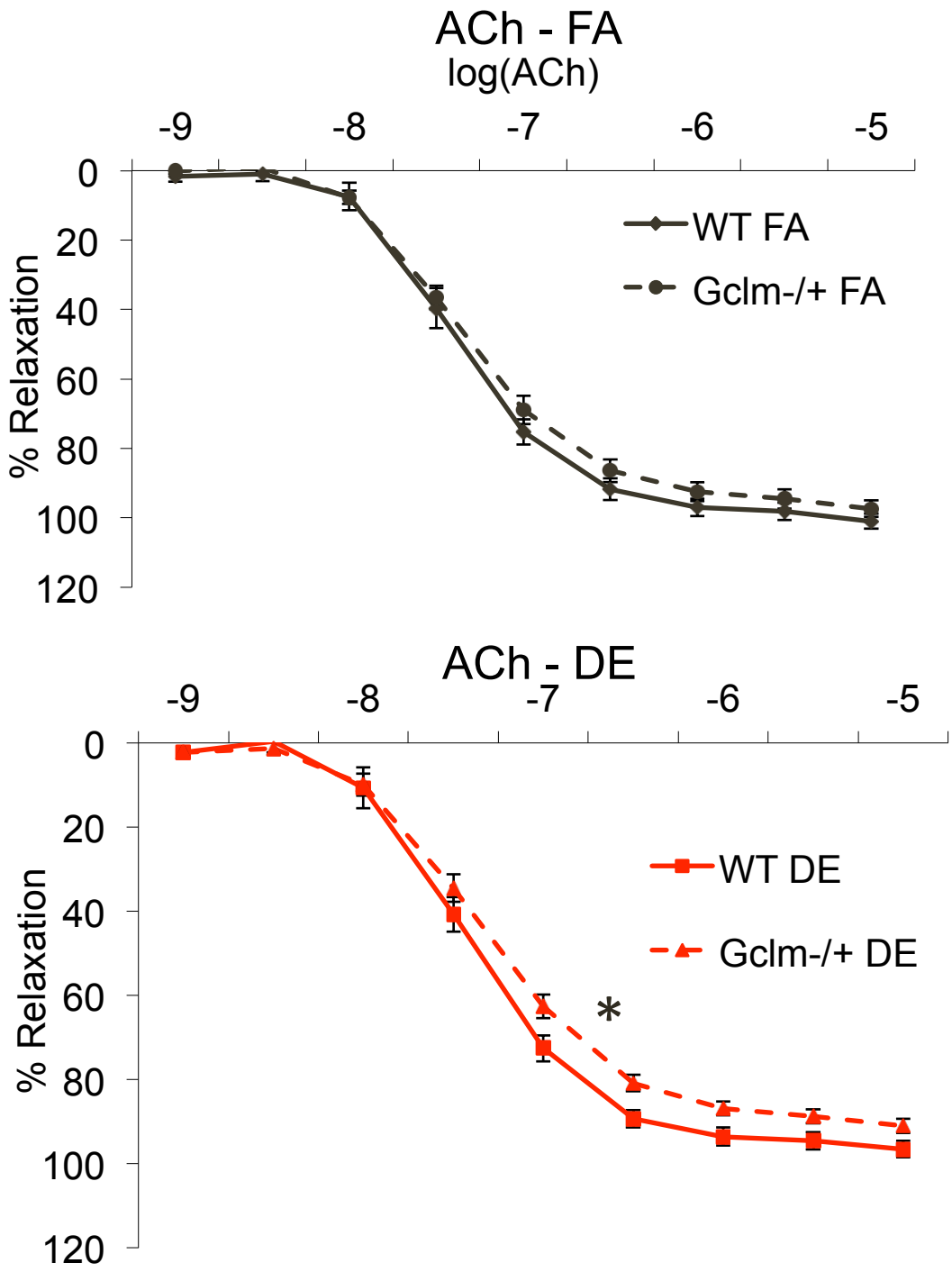


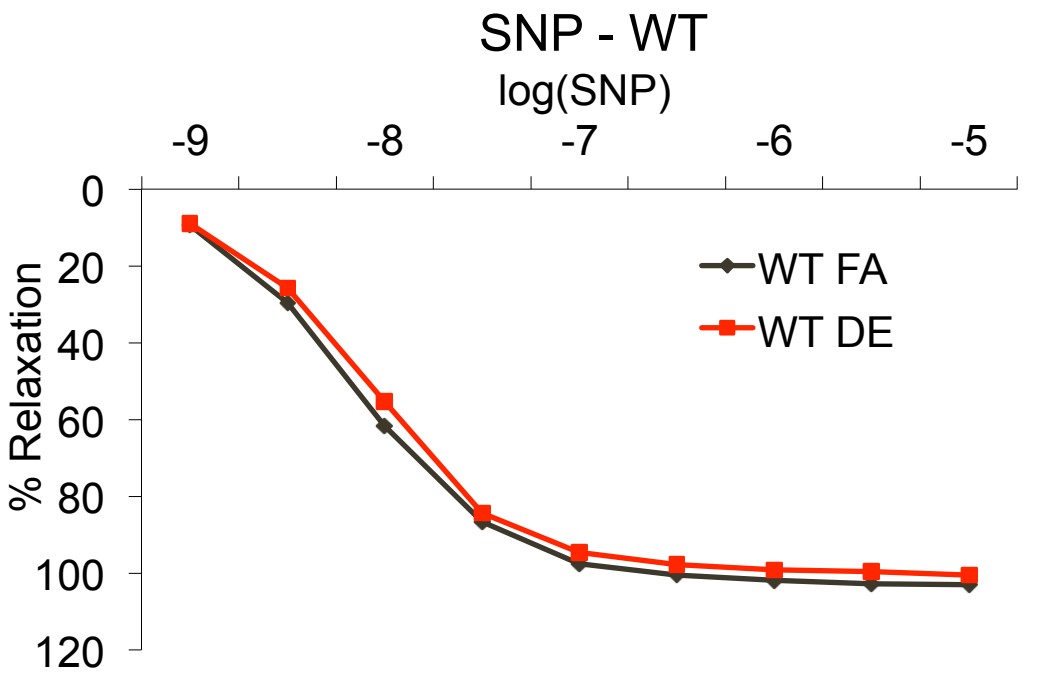
6hr DE inhalation, 300ug/m^3

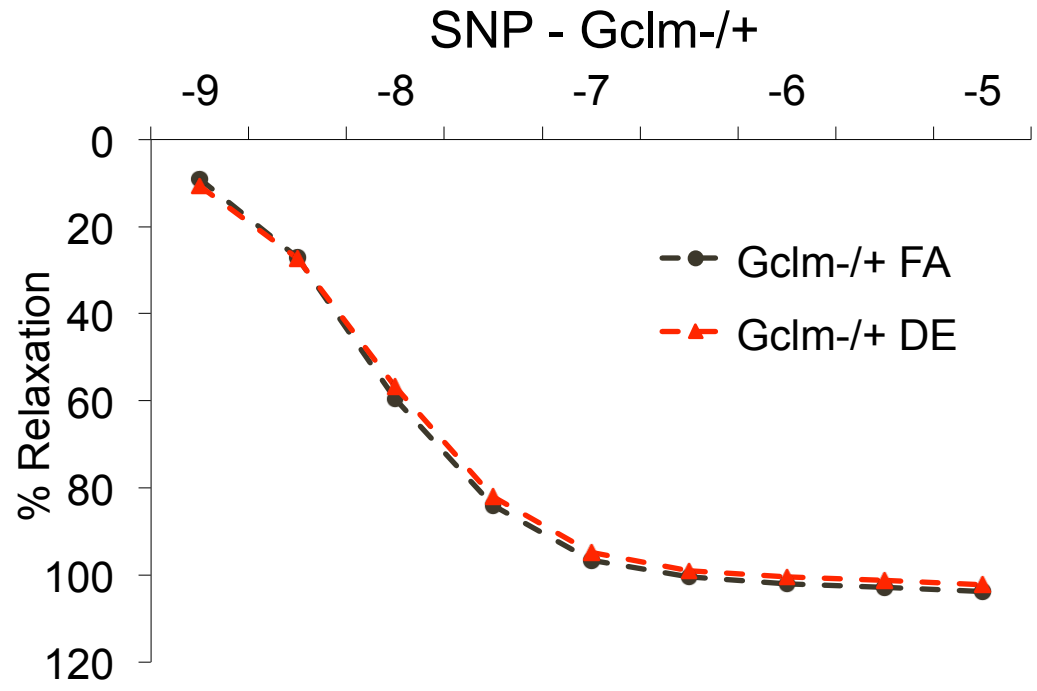


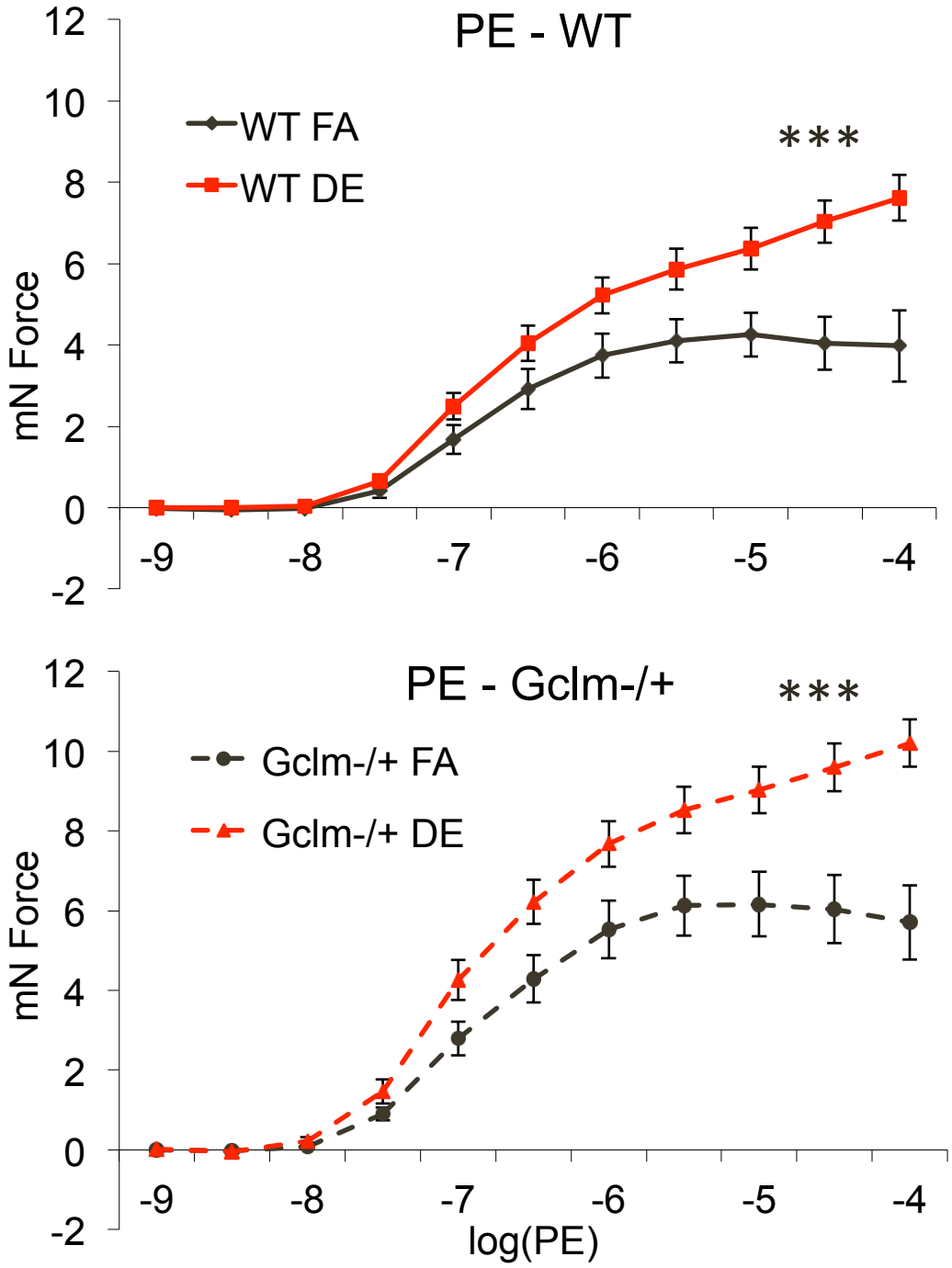

ACh - WT
log(ACh)
-9
-8
-7
-6
-5
0
20
40
60
80
100
120
% Relaxation
WT FA
WT DE

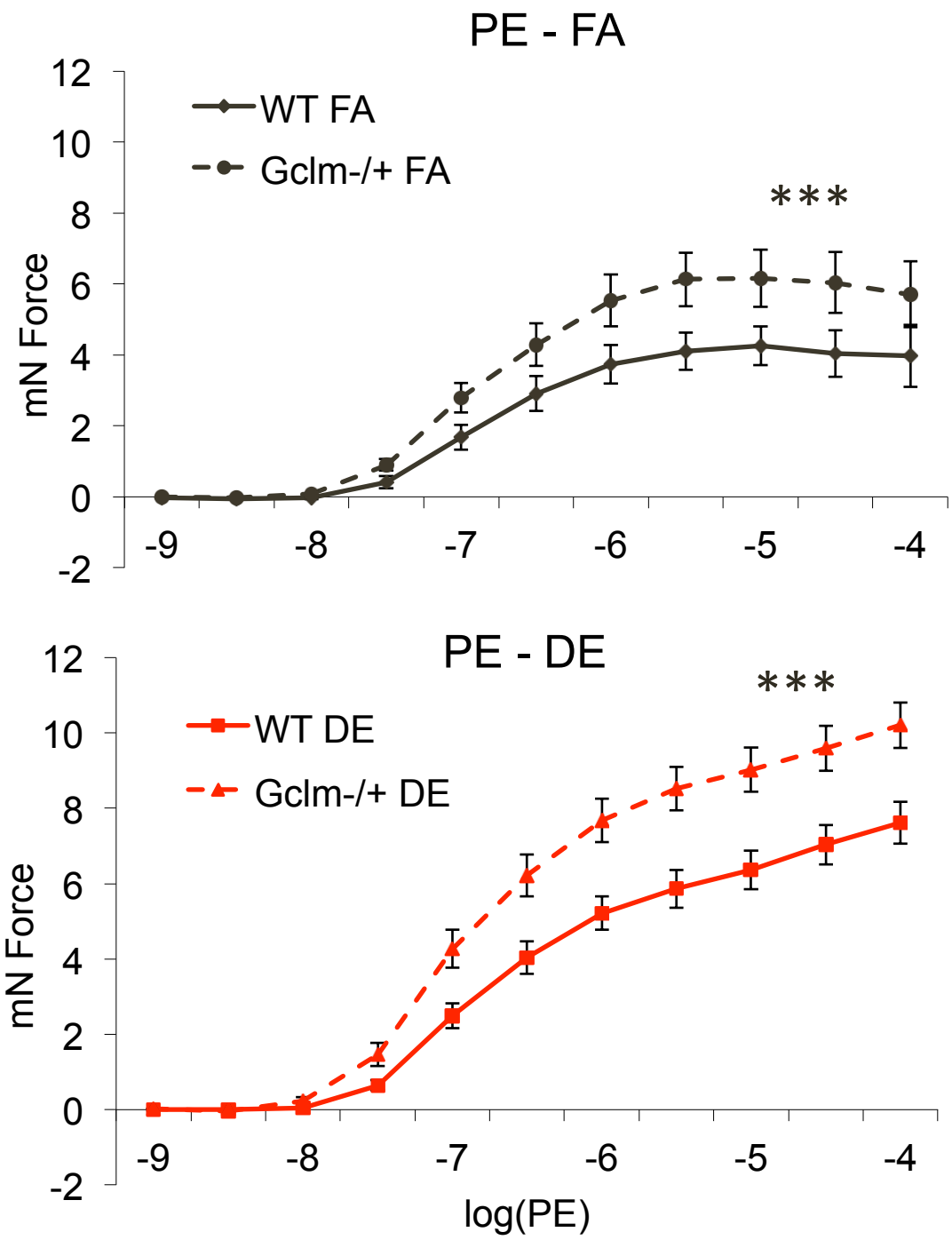

ACh - Gclm-/+
-9
-8
-7
-6
-5
0
20
40
60
80
100
120
% Relaxation
Gclm-/+ FA
Gclm-/+ DE


ACh - FA
log(ACh)
-9
-8
-7
-6
-5
0
20
40
60
80
100
120
% Relaxation
WT FA
Gclm-/+ FA
ACh - DE
-9
-8
-7
-6
-5
0
20
40
60
80
100
120
% Relaxation
WT DE
Gclm-/+ DE
*

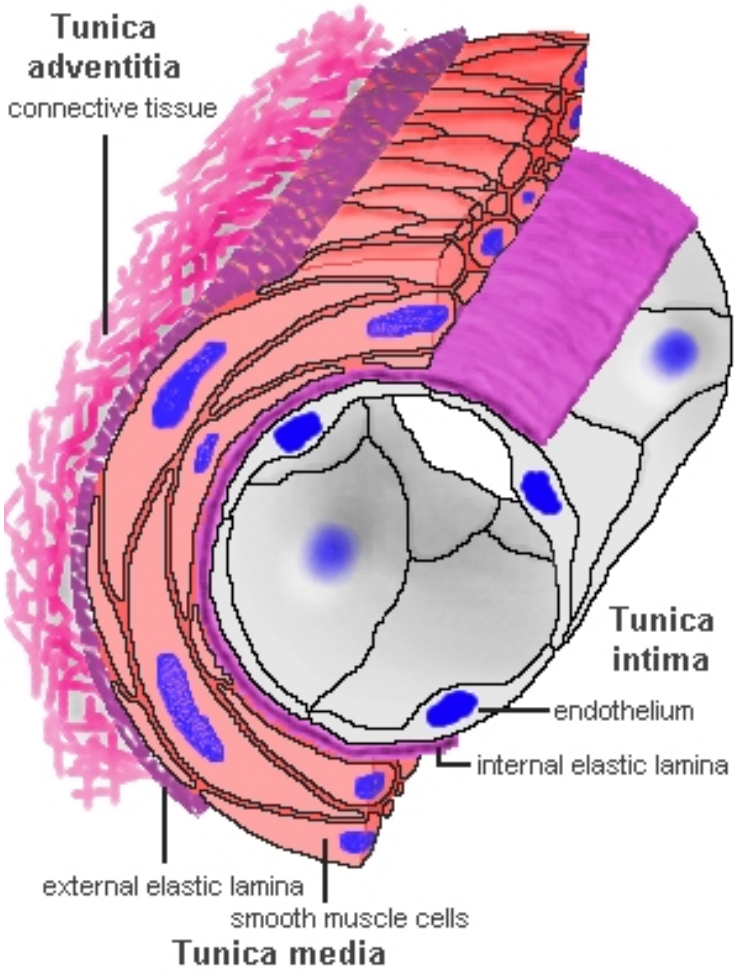

SNP - WT
log(SNP)
-9
-8
-7
-6
-5
0
20
40
60
80
100
120
% Relaxation
WT FA
WT DE

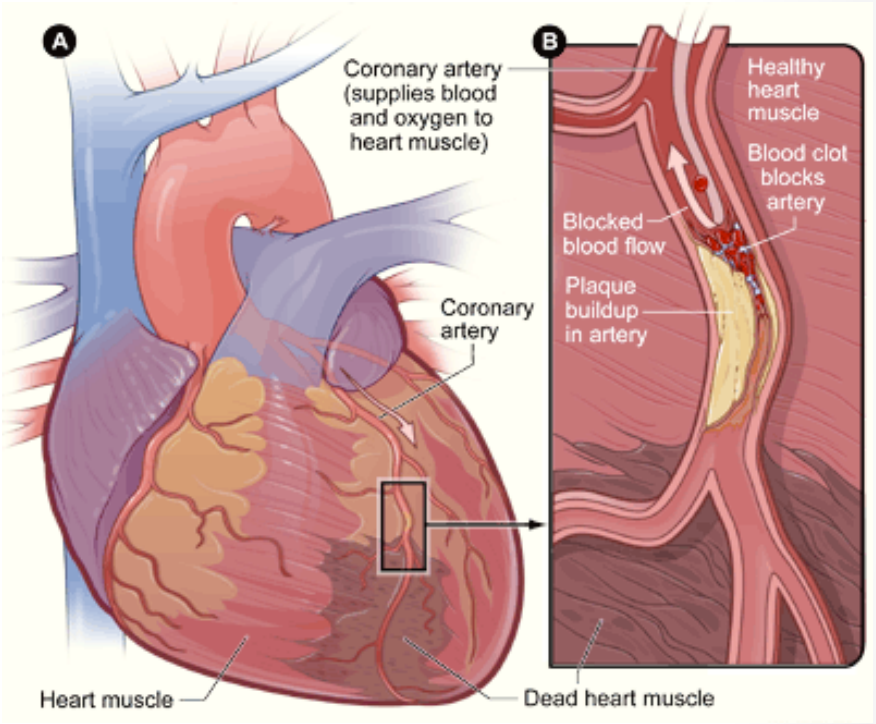

SNP - Gclm-/+
-9
-8
-7
-6
-5
0
20
40
60
80
100
120
% Relaxation
Gclm-/+ FA
Gclm-/+ DE


PE - WT
WT FA
WT DE
***
mN Force
12
10
8
6
4
2
0
-2
-9
-8
-7
-6
-5
-4
PE - Gclm-/+
Gclm-/+ FA
Gclm-/+ DE
***
mN Force
log(PE)


PE - FA
WT FA
Gclm-/+ FA
***
mN Force
12
10
8
6
4
2
0
-2
-9
-8
-7
-6
-5
-4
PE - DE
WT DE
Gclm-/+ DE
***
mN Force
log(PE)

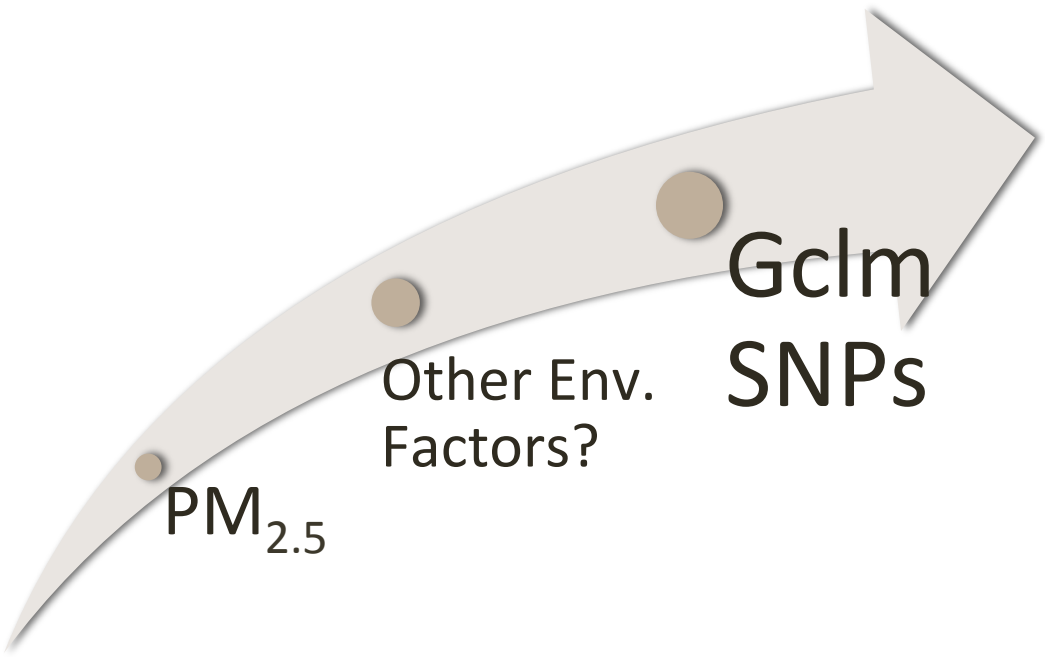
Why is this important?





Strong evidence for a *Gene x Environment* interaction

- We demonstrate that loss of only one copy of Gclm impairs ACh-mediated vessel relaxation and NO synthesis
- A short term DE inhalation dramatically enhances aortic contractile response to phenylephrine
- This enhanced contraction is exacerbated in Gclm-/+ mice

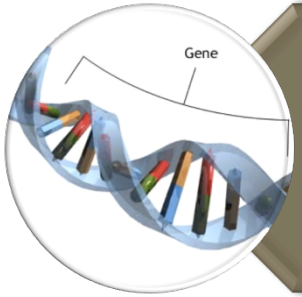


Vascular Oxidative Stress

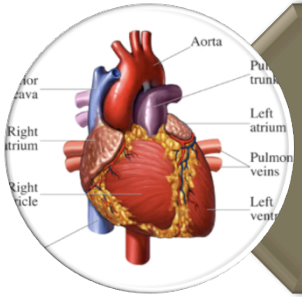
Vascular Reactivity

Risk of Acute MI

Translation and communication



Our genes influence our response to environmental factors



Gclm SNPs are frequent and may influence our biological response to $PM_{2.5}$

Regulatory policies need to take into account sensitive populations