Human Studies of Susceptibility

• What can we Learn?

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How does Susceptibility Arise?

• Genetics and Epigenetics
• Pre-existing disease and other phenotypes
  – Other may include age, gender etc
• Other stressors
  – Diet, other environmental exposures, psycho-social stress, personal SES, neighborhood characteristics
The Issue of Susceptibility

• Is a question of what the dose-response looks like (i.e. not the same for everyone)
• It is intimately connected to the question Thresholds in the population dose-response
Thresholds

• Toxicologic studies often find thresholds
• Studies are typically done on clonal animals or very inbred strains
  – ➔ no genetic diversity
• Typically done on healthy animals
  – ➔ no health diversity
• Typically done on animals born at same time, and adults
  – ➔ no age diversity
Human Populations

• Have diversity with respect to all of these, as well as many other factors that may modify the response to a toxin
• So if there is a threshold for a particular toxin in humans, we expect it to vary across people
• What are the implications of this?
If a Dose X will produce a response

any higher dose will also

Hence the dose-response curve is a cumulative probability distribution

\[ \text{Prob}(Y_i=1) = \text{prob}(T_i < X_i) \]
• Susceptibility due to many factors
  – age, genetics, pre-existing illness
• Central Limit Theorem
• Sum or Mean of many distributions tends to normal
• Suggest begins to look like cumulative Normal Curve
Histogram of $x_1$

Mean of 10 such Variables

<-- single very skewed variable

Histogram of $x_m$
The low dose end looks linear
That is probably why

- Although EPA has traditionally assumed a threshold for non-carcinogens
- Studies of lead, particles, and ozone have show linear dose-responses down to the lowest observed levels
- Such dose responses suggest heterogeneity in response
Dose-Response between Blood Lead and IQ in 7 Pooled Birth Cohorts

Log-linear model
5 knot spline
95% CI
Concentration-Response Relation between PM2.5 and Risk of Death on Followup: Six City Study
Particles and Deep Vein Thrombosis
Annual Decline In Lung Function Vs PM in Interval
Threshold?

- Bell, EHP 2006

Figure 3. Exposure–response curve for \( O_3 \) and mortality using the spline approach: percentage increase in daily nonaccidental mortality at various \( O_3 \) concentrations.
Implications of Linear D-R

• For Economic Analysis
Typically Assume

![Graph showing ambient concentrations and marginal costs.](image)

- Marginal Cost of Abatement
- Marginal Health Cost of Pollution

Ambient Concentrations ($\mu$g/m$^3$)
Linear Dose-Response $\rightarrow$ Much Lower Standard

Marginal Cost of Abatement

Marginal Health Cost of Pollution

$\$ \rightarrow C^*$

Ambient Concentrations ($\mu g/m^3$)
Identifying Susceptible Populations

• Because the population in Epidemiology includes the obese, diabetics, people with other chronic diseases
• People with genetic polymorphisms
• We can look to see if the effect of exposure is different in them
Example: Lead

• Lead-associated decrement in renal function greater in patients with:
  – pre-existing chronic kidney disease
  – Diabetes

• Association between increased patella lead and autonomic dysfunction (heart-rate variability) more pronounced in patients with metabolic syndrome
Air Pollution and Diabetes

• Air Pollution is associated with:
  – Increased myocardial infarction
  – Impaired endothelial function
  – Impaired autonomic function
  – Increased Inflammation and Oxidative Stress

• So is Diabetes
• First Results go back to 2001 for Mortality (in Montreal) (Goldberg et al) and Hospital Admissions (in multiple cities)(Zanobetti et al)

• Since that time similar results have been reported in Chicago, Boston, California, 9 Italian cities, and Shanghai for mortality

• Other studies in the US and Europe have also reported greater risks for CVD Admissions
Physiologic Studies Support these Results

• For Example, changes in autonomic control of the heart and other EKG abnormalities
  – E.g. Heart rate variability, QT interval, dispersion measures, ST segment etc
  – Widely associated with air pollution
  – Stronger effects of particles on HRV in diabetics and obese in Normative Aging Study
  – Stronger effects with Metabolic Syndrome in MESA
Biomarkers

- ICAM, VCAM, vWF Stronger in Diabetics (O’Neill)
- Madrigano saw interaction with obesity in NAS
- Alexeef saw interaction with Diabetes and long term exposure to BC on ICAM, VCAM
- PM increased vWF in Diabetics in ARIC
- Dubowski saw greater PM induced elevation of inflammatory markers in Diabetics in a panel study
If Diabetics are more Susceptible

• Because Diabetes already produces oxidative stress to the point that compensatory mechanisms are overwhelmed

• Other things that increase oxidative stress may also interact with air pollution
Which Brings us to Genes

• Candidate gene studies have not done well in genetic epidemiology
• Most gene-environment studies have taken a candidate gene or candidate pathway approach
• So we need to be cautious
The strongest message is

- Respiratory outcomes of air pollution interacting with genes related to oxidative defenses, particularly GST genes, but some others
Interaction with NQO1 for Asthma prevalence
% change in Fibrinogen per 1 IQR increase in black carbon

- Low oxidative stress score
- High oxidative stress score

MAx: x-days moving average

* $p_{interaction} < 0.05$

$p_{interaction} = 0.048$ for 4h
$p_{interaction} = 0.022$ for 24h
$p_{interaction} = 0.019$ for MA$_2$
$p_{interaction} = 0.031$ for MA$_3$
Effect of Particles on Heart Rate Variability by Genotype

Chahine, EHP 2007
**HMOX1** and **GST** variants modify attenuation of FEF25–75% decline due to PM10 reduction
Epigenetic factors can also modify responses to pollutants

Effect of particles on Fibrinogen levels by methylation status of F3
Social Factors
Decrease in Winter Temperature and MI Incidence by Individual and Area Factors: Worcester Heart Attack Study
COMBINED 4 CITY ESTIMATE OF EXCESS MORTALITY AT 30°C COMPARED TO MORTALITY AT 15°C, LAG 0

% mortality change

-5 - 0 - 5 - 10 - 15 - 20 - 25 -

TOTAL, > 65 YEARS OLD, < 65 YEARS OLD, IN HOSPITAL, OUT OF HOSPITAL, BLACK, WHITE, < HIGH SCHOOL, > HIGH SCHOOL, FEMALE, MALE
Figure 1  Effect modification by city characteristics in the 20 cities in the United States, between 1989 and 2000. AT, apparent temperature; PM$_{10}$, particulate matter of aero-diameter $\leqslant$ 10 $\mu$m. The two estimates and their 95% CI for each of the modifying factors represent the percentage increase in mortality for any 10 $\mu$g/m$^{3}$ of PM$_{10}$, for the 25th centile, and 75th centile of the modifier distribution across the 20 cities. For population density, the percentage increase in mortality per 10 $\mu$g/m$^{3}$ of PM$_{10}$ is presented for 1000 count/mile$^{2}$, and 3000 count/mile$^{2}$. 

Zeka et al, OEM 2006
Air Pollution and mortality
In 20 US Cities
Lead

• In rats, being raised in “enriched” environment mitigates lead-associated effects on spatial learning and normalizes gene expression in hippocampus (NMDA-R, BDNF)

• In humans:
  – children from lower strata of SEP express lead-associated cognitive deficit at lower biomarker levels
  – Impact of lead on children’s end-of-grade reading scores more pronounced at lower than upper tail of distribution (i.e., among children other risk factors for poor performance)
Psychosocial Sources of Variable Response

• In nonhuman primates, stress increases mobilization of lead from deep body stores (e.g., bone)

• In humans:
  – Among men, inverse association between bone lead level and cognition more pronounced among those self-reporting greater stress
  – In older adults, inverse association between bone lead and cognition greater among those living in neighborhoods with more psychosocial hazards
  – In children, higher cord blood lead level associated with greater total peripheral (vascular) resistance response to acute stress
Risks can also vary (and cluster) Geographically
Distribution of vulnerability to heat waves
What are the implications of such Heterogeneity?
A Simulation Study

• Take risk of MI by tertile of Income from Marmot analysis of Representative US sample
• Similarly Prevalence of Diabetes by tertile
• RR of MI for Diabetics from recent Danish Study
• Assume Diabetes doubles Particle risk, and so does some genetic profile
Figure 2. Annual mortality benefits and change in risk inequality for power plant control scenarios (A), along with distribution of risk for baseline conditions and selected control scenarios (B) (indicator = Atkinson index, $\varepsilon = 0.75$; pollutants = $SO_2$, $NO_2$, $PM_{2.5}$; baseline = PM-related mortality). Blue dots in A represent intermediate control scenarios, and letters represent defined scenarios listed in Table 1.