SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

Collaborative on Health and the Environment

A Fresh Look at Cardiovascular Disease

Environmental Risk Factors Across the Life Course

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Outline

- Introduction to Cardiovascular Disease (CVD) and Risk Factors
- Frameworks for understanding Environmental Risk in Cardiovascular Disease
  - Developmental Origins of Disease
  - Ecological Model
  - Life Course Model
- Current Literature on Environmental Exposures
  - Epigenetics
  - Cigarette Smoke
  - Air Pollution
  - Metals
- At-risk Populations and CVD
- Policy development/continuation

Cardiovascular Disease - A Brief Overview

- Stroke
- Atrial Fibrillation
- Sudden Cardiac Arrest
- Atherosclerosis
- Coronary Heart Disease
- Heart Failure
- Valvular, venous, and aortic diseases
- Peripheral Artery Disease

Cardiovascular Disease - A Brief Overview

- Atherosclerosis
- Coronary Heart Disease
- Peripheral Artery Disease

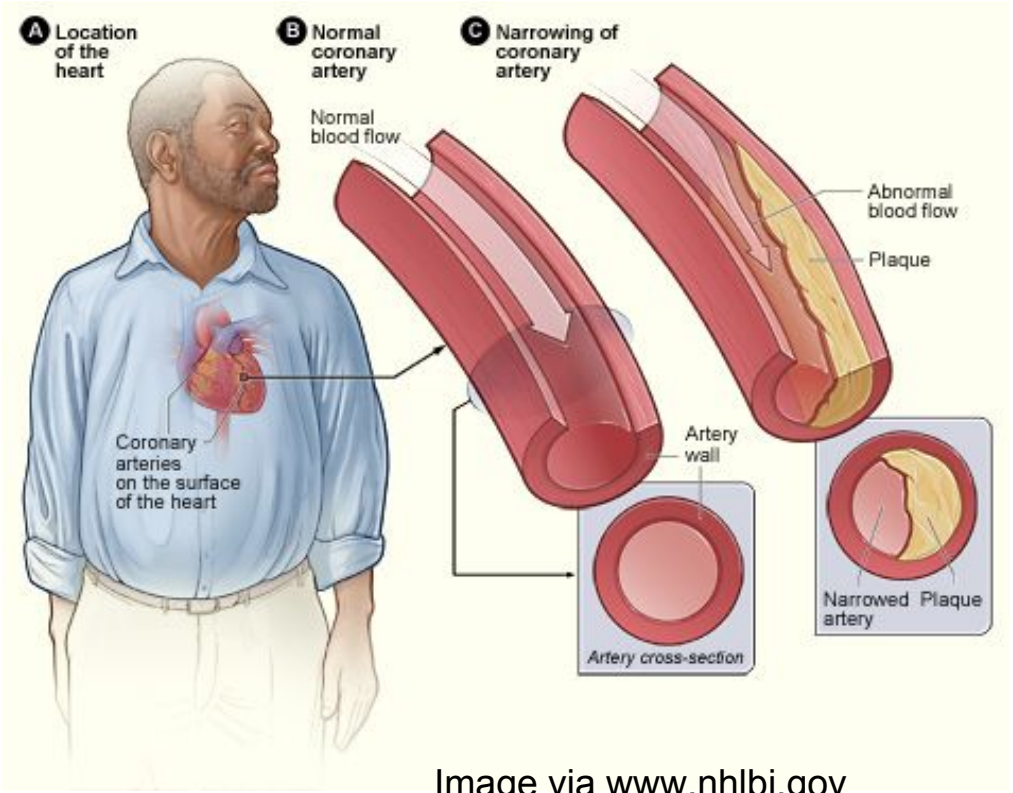


Image via www.nhlbi.gov

Cardiovascular Disease - A Brief Overview

- Stroke

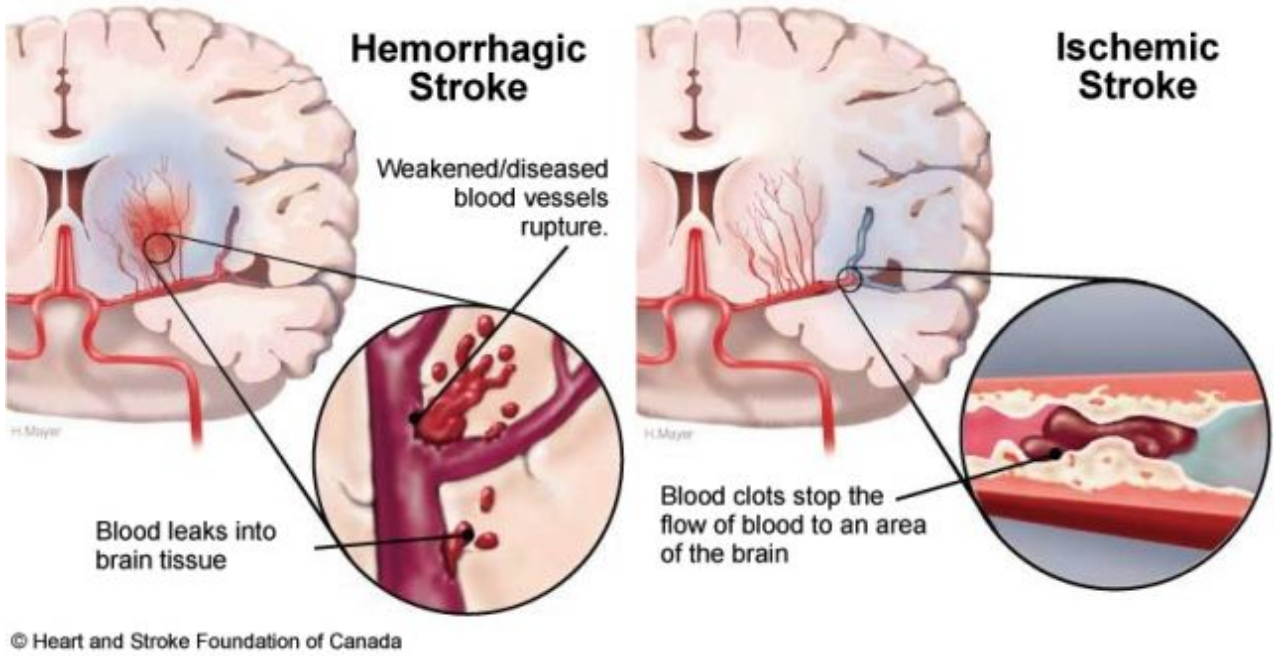


Image via http://www.heartandstroke.ca/

Cardiovascular Disease - A Brief Overview

- Heart Failure

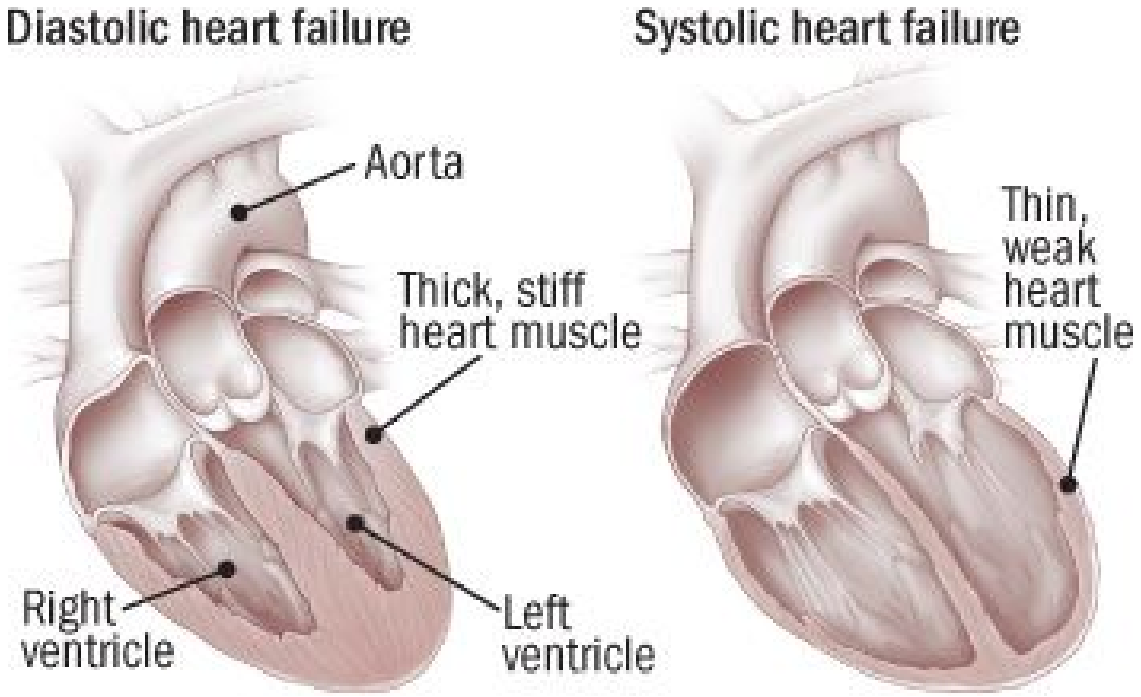
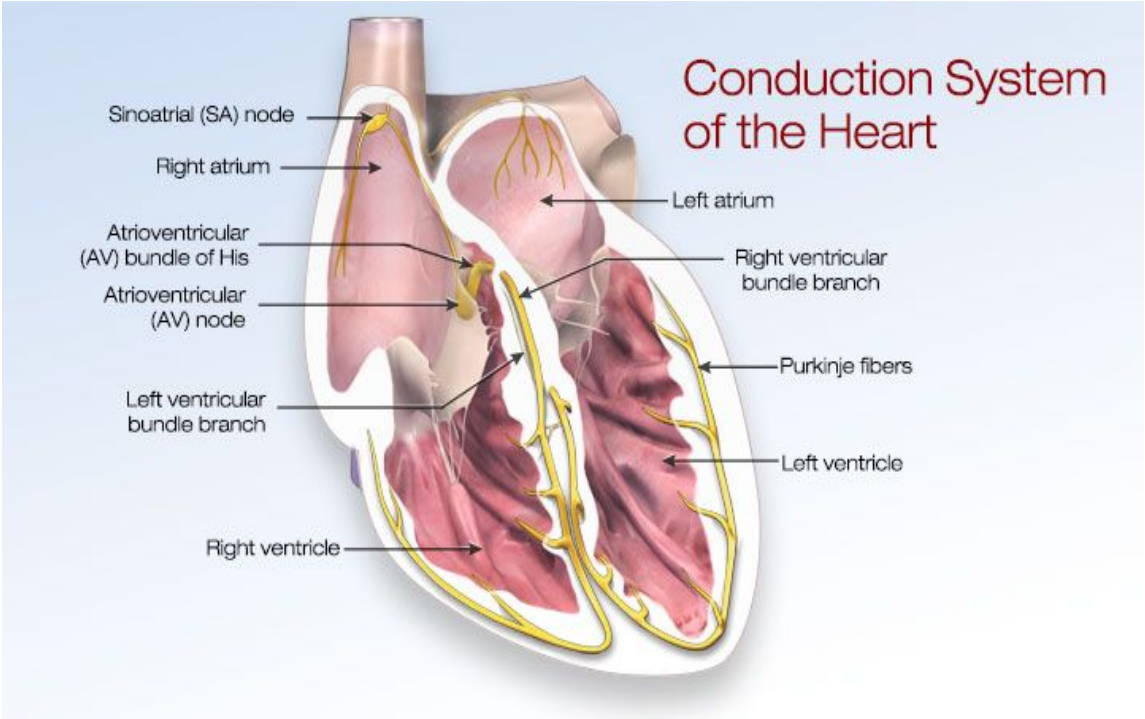


Image via www.health.harvard.edu

Cardiovascular Disease - A Brief Overview

- Sudden Cardiac Arrest
- Atrial Fibrillation
- Valvular, venous, and aortic diseases



Cardiovascular Disease - A Brief Overview

- Leading cause of death in U.S.
- Risk increases with increasing age

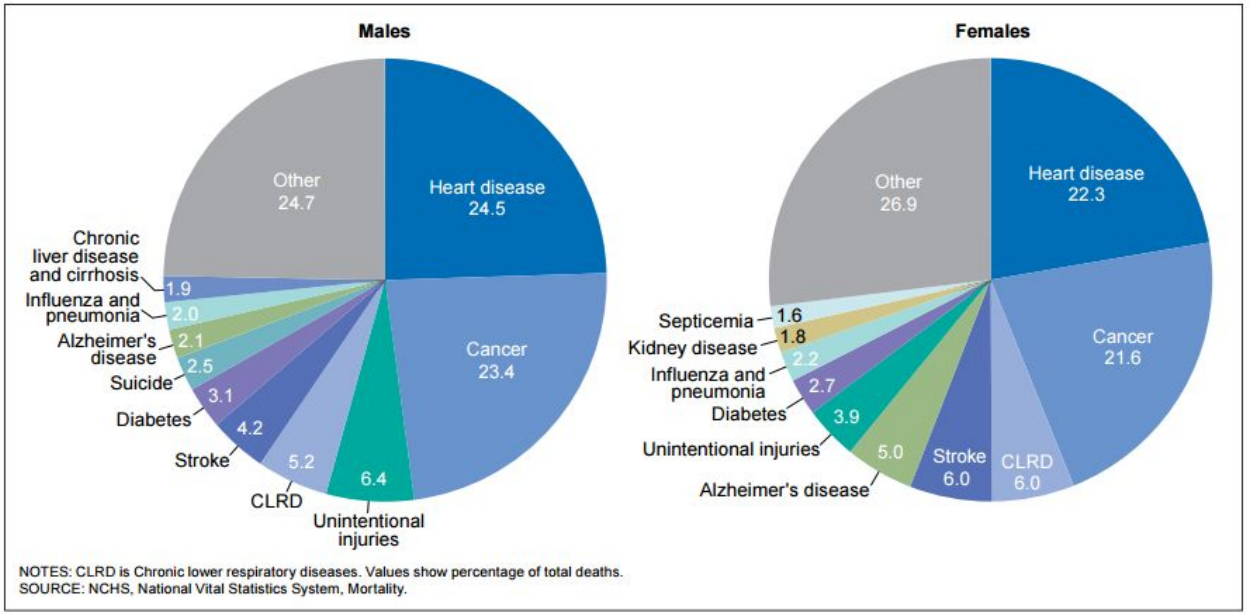
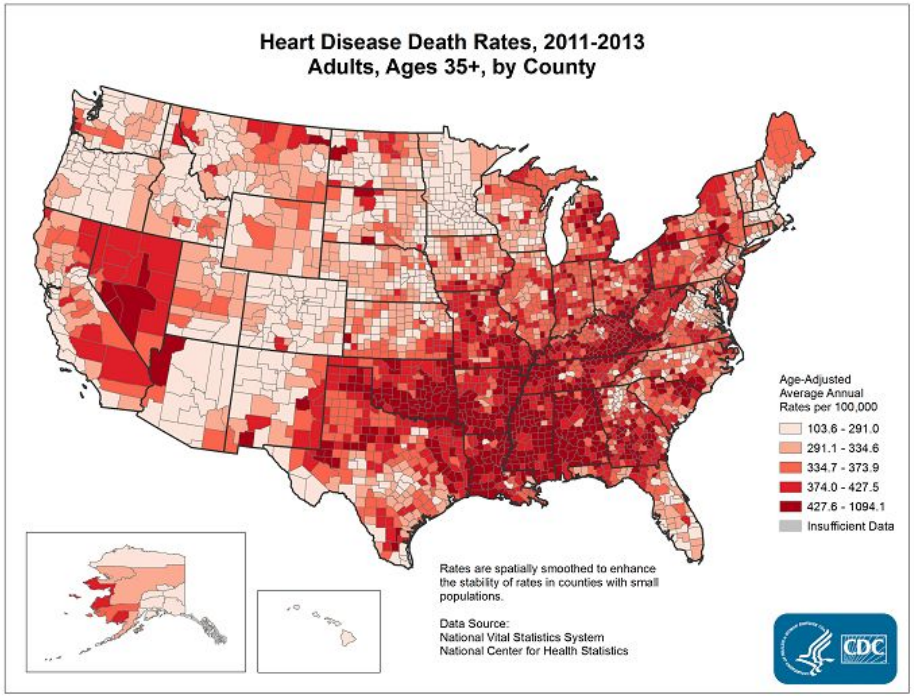
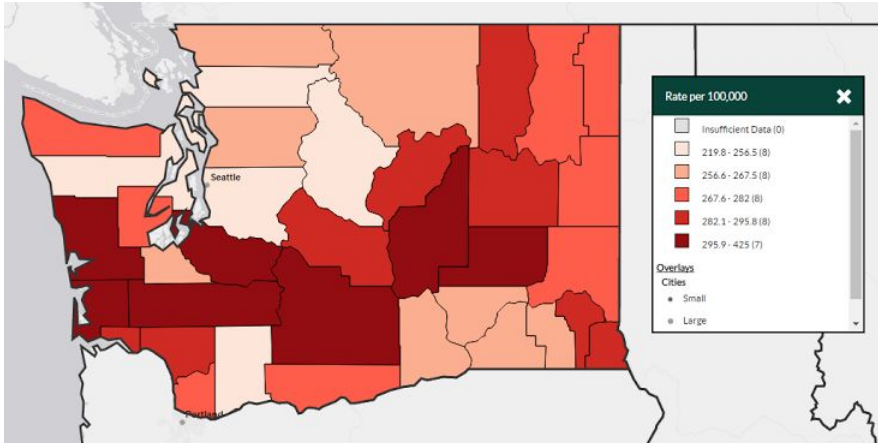


Figure 1. Percent distribution of the 10 leading causes of death, by sex: United States, 2014

2014 National Vital Statistics Reports
Centers for Disease Control and Prevention

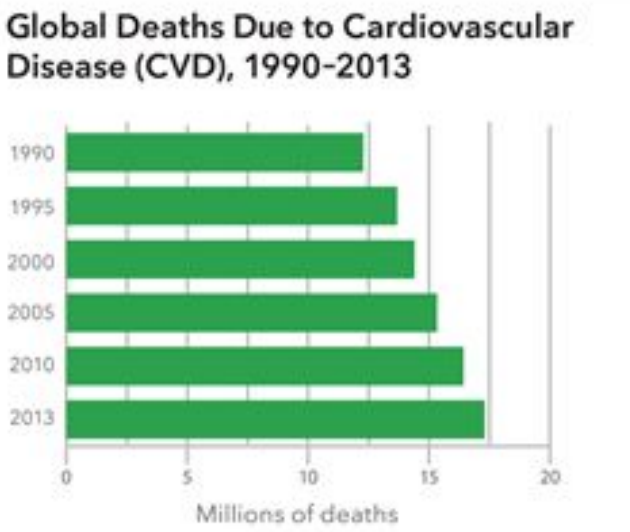
Cardiovascular Disease - A Brief Overview





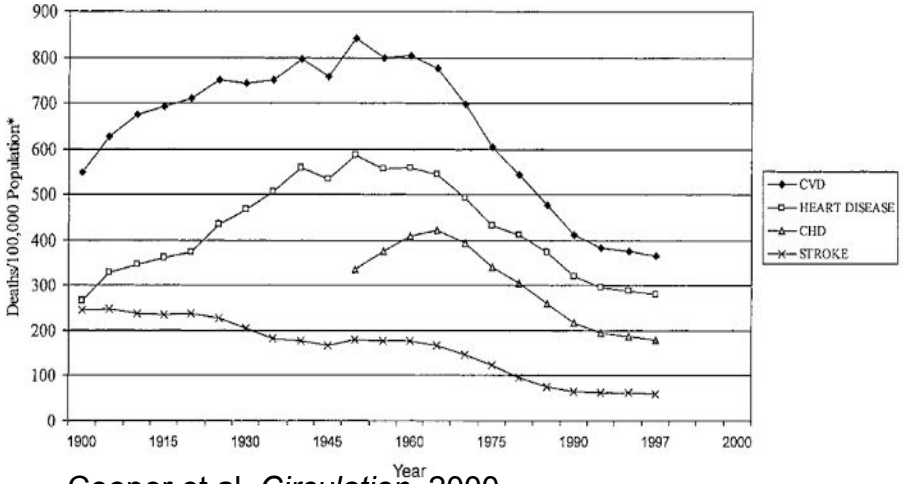
CVD Trends - Worldwide

- ~ 17 Million Deaths Per Year
- As communicable diseases decrease, the impact of cardiovascular disease increases.
- Obesity and CVD risk factors increasing worldwide



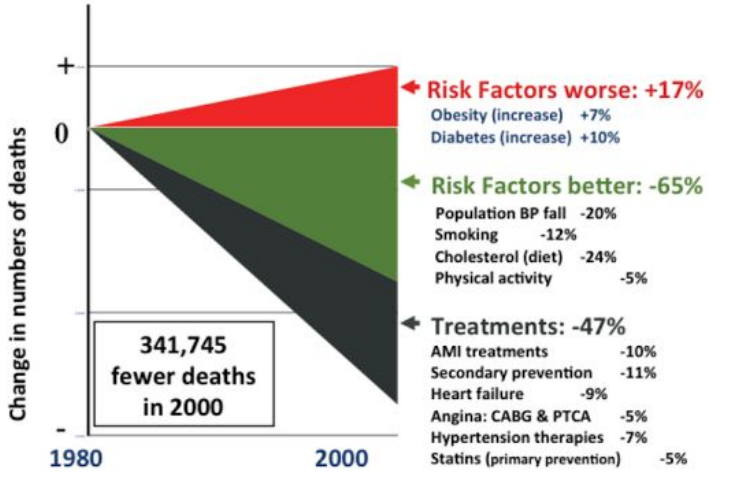
Cardiovascular Disease Trends - US

- Significant decrease in rate of all CVD deaths since ~1960
- Treatment of CVD risk factors has increased substantially



Cooper et al. *Circulation*, 2000

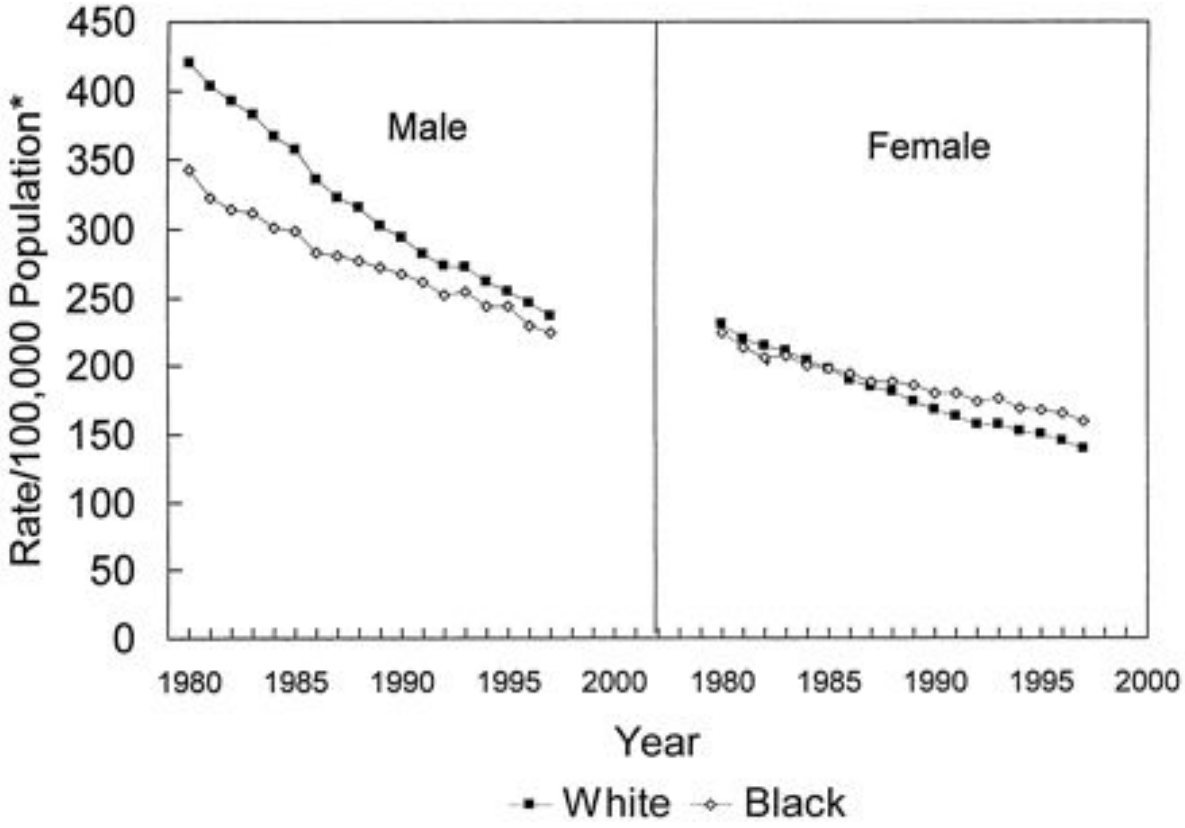
Figure 2.2: Major Shifts in Population Risks and Expanded Treatment of CHD, 1980-2000 (based Ford, 2007)



Explaining the fall in coronary heart disease deaths, IMPACT Model, United States, 1980-2000.

Cardiovascular Disease Trends - US

- Significant decrease in all C
- Treatment of CVD risk facto substantially
- **Trends differ by sex and ethnicity**



Cooper et al. *Circulation*. 2000

Cardiovascular Disease - Risk Factors

- Physical Inactivity
- Obesity
- Nutrition
- Genetics
- High Blood Pressure
- Metabolic Syndrome

http://www.runnersworld.com/newswire/is-exercising-in-polluted-areas-worth-the-risk

Traditional Cardiovascular Disease Framework

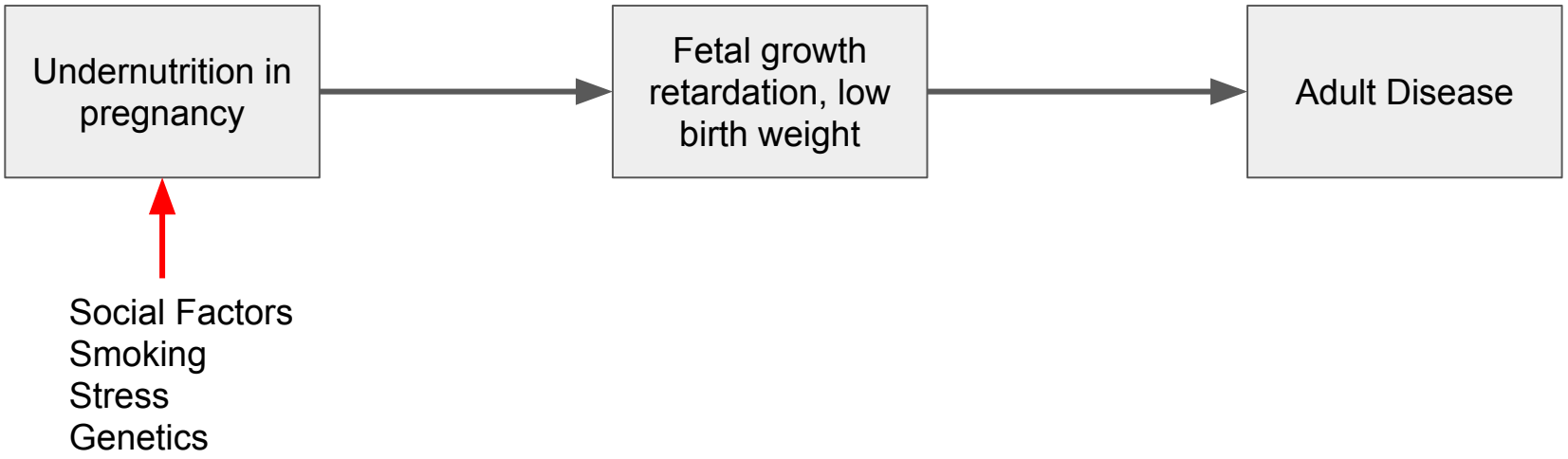
- E
- T

Table 1.3: WHO's "Best Buys" in NCD Prevention: Population- and Individual-Level Interventions with Known Cost-Effectiveness (WHO, 2011)

The population level	Protecting people from tobacco smoke and banning smoking in public places
	Warning about the dangers of tobacco use
	Enforcing bans on tobacco advertising, promotion and sponsorship
	Raising taxes on tobacco
	Restricting access to retailed alcohol
	Enforcing bans on alcohol advertising
	Raising taxes on alcohol
	Reducing salt intake and salt content of food
	Replacing trans-fat in food with polyunsaturated fat
	Promoting public awareness about diet and physical activity, including through mass media
The individual, health-care level	Counseling and multidrug therapy ("a regimen of aspirin, statin, and blood pressure-lowering agents...in people at high cardiovascular risk"), including glycemic control for diabetes for people ≥ 30 years old with a 10-year risk of fatal or nonfatal cardiovascular events ≥ 30%
	Aspirin therapy for acute myocardial infarction

Our Cardiovascular Disease Framework

- Developmental Origins of Health and Disease
- Barker Hypothesis



Langley-Evans, *Proc Nutr Soc,* 2006

Epigenetics (Gene x Environment Interaction)

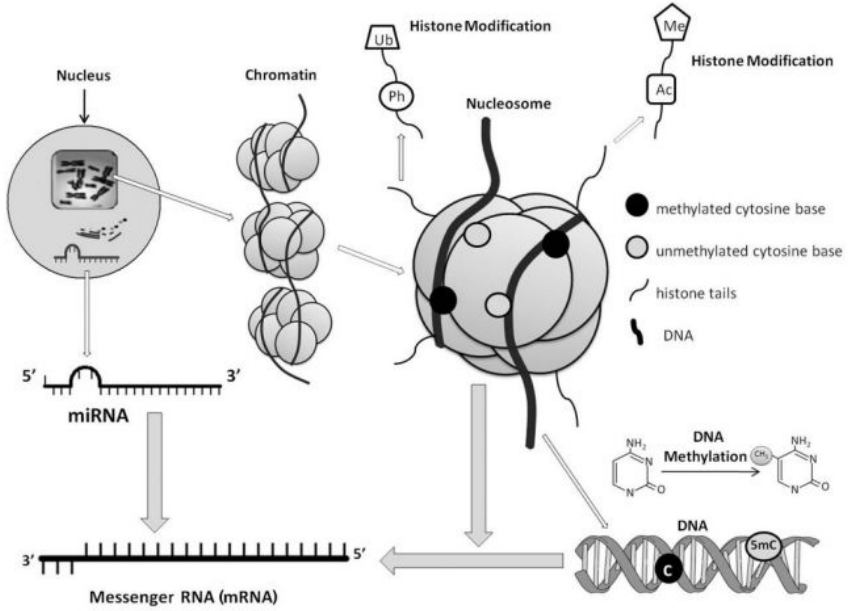


Figure 1 Transcriptional regulation at the epigenetic level. Epigenetic mechanisms, including DNA methylation, histone modifications and miRNAs, regulate chromatin compaction and gene expression. DNA methylation at CpG sites usually suppresses gene expression. Histones are globular proteins that undergo posttranslational modifications, such as Ac, methylation and phosphorylation, thus influencing chromatin structure and gene expression. Active genes are usually characterized by low DNA methylation and highly acetylated chromatin configuration that allow access to transcription factors. miRNAs are a set of small, non-protein-coding RNAs that negatively regulate expression of target genes at the posttranscriptional level by binding to 3′-untranslated regions of target mRNAs

Epigenetics

- Understanding risk is important for CVD prevention
- Much risk is yet unexplained
- Critical for understanding how childhood exposure affects risk.

- Dutch Famine Study
- Altered DNA Methylation in Heart Failure patients
- $PM_{2.5}$ exposure and DNA Methylation
  - Pollution Exposure associated with decreased LINE-1 Methylation
  - Lower LINE-1 methylation associated with CVD endpoints

Epigenetics

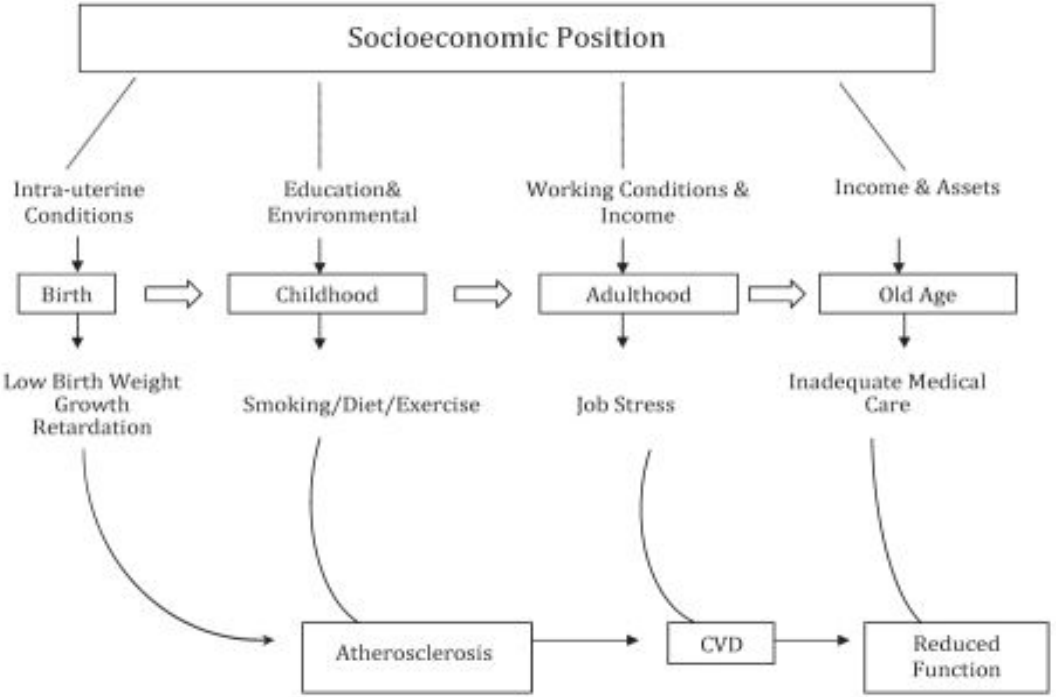
MicroRNAs in response to different environmental exposures and relation to cardiovascular disease

Exposure	miRNA/miRNA regulatory gene	Change/Effect of	Target/Function	CVD relevance	References
PM, carbon black	Dicer polymorphism rs13078	Minor allele A	miRNA biogenesis	Correlated with higher serum sICAM-1 and sVCAM-1 levels	(26)
	GEMIN 4 polymorphism rs1062923	Minor allele C	miRNA biogenesis	Higher sVCAM-1 levels	
Air pollution, metal pollutants	miR 222	Increased in peripheral blood	cKit, p57 (Kip2)	Induce vascular smooth muscle cell growth, angiogenesis (27); reduction in eNOS, vasoconstriction (25)	(24)
	miR 21		Phosphatase PTEN, PI3 Kinase pathway	Prevents cardiomyocyte apoptosis in MI (28)	
Aluminum	miR 146a	Increased, in vitro experimental model	NF-kappa B dependent, oxidoreductive pathway, ErbB pathway	Cardiomyocyte apoptosis cardiac hypertrophy (29)	(30)
Bisphenol A	miR 146a	Increased in placental cells			(31)
Alcohol	miR199a	Increased in liver sinusoidal endothelial cells	Hypoxia Inducible Factor HIF-1 α, Sirtuin 1.	Prevents hypoxia injury	(32)

Baccarelli, *Curr Opin Clin Nutr Metab Care*. 2012

Our Cardiovascular Disease Framework

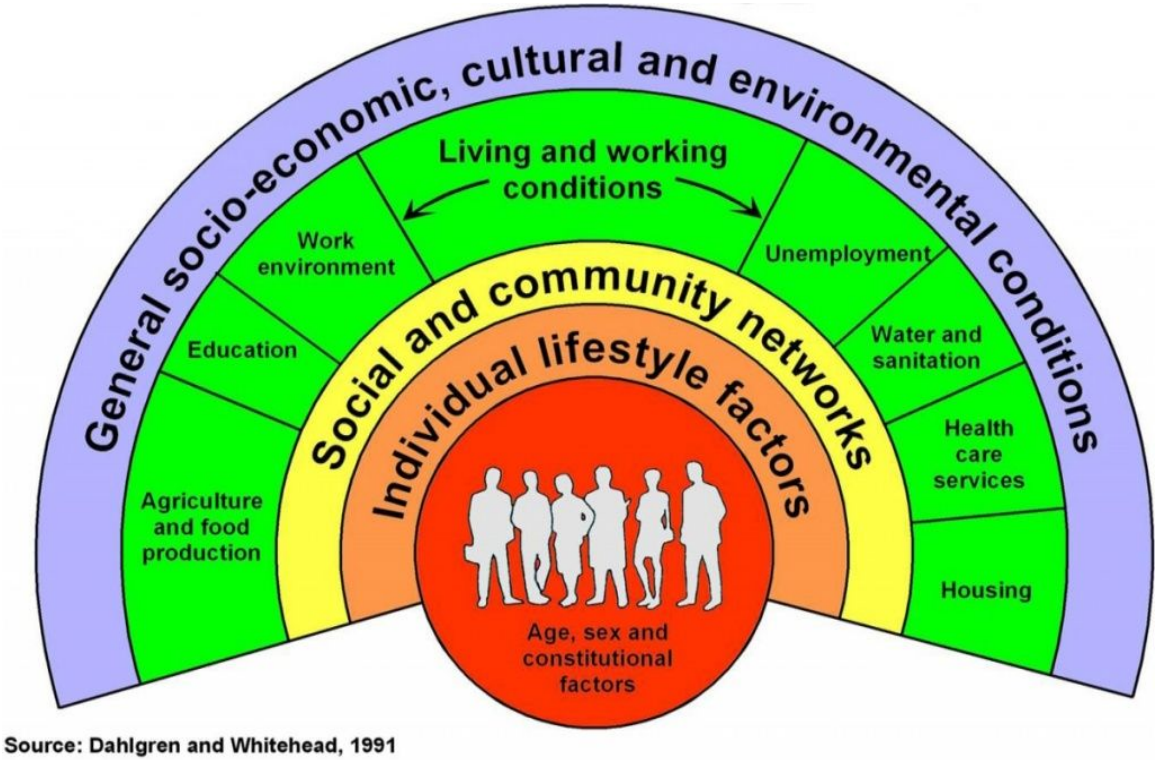
- Life Course Model



Berkman LF, Kawachi I, editors. Social Epidemiology. New York: Oxford University Press; 2000.

Our Cardiovascular Disease Framework

- Ecological Model



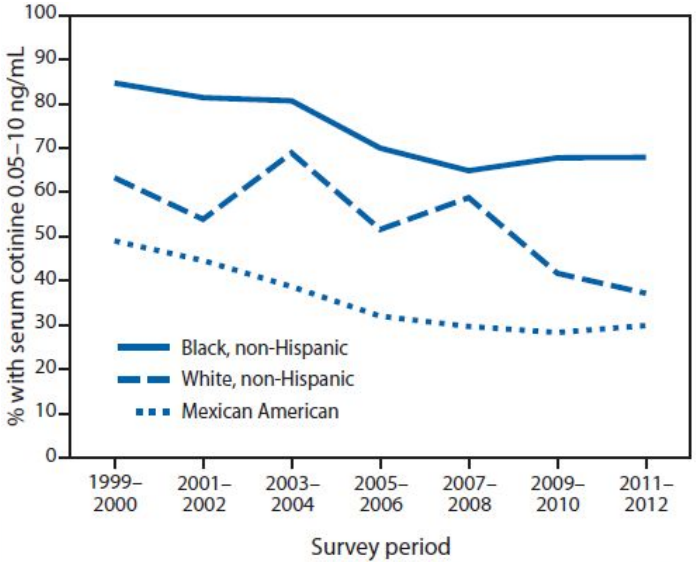
Our Cardiovascular Disease Framework

Environmental Factors in Cardiovascular Disease

- Smoking
- Pollution
- Metals
- Bisphenol a

Smoking

- Secondhand Smoke (SHS)
- Associated with
  - Heart Disease (20-40% increase)
  - Stroke (~25% increase)



Homa et al. *MMWR Morb Mortal Wkly Rep*. 2015

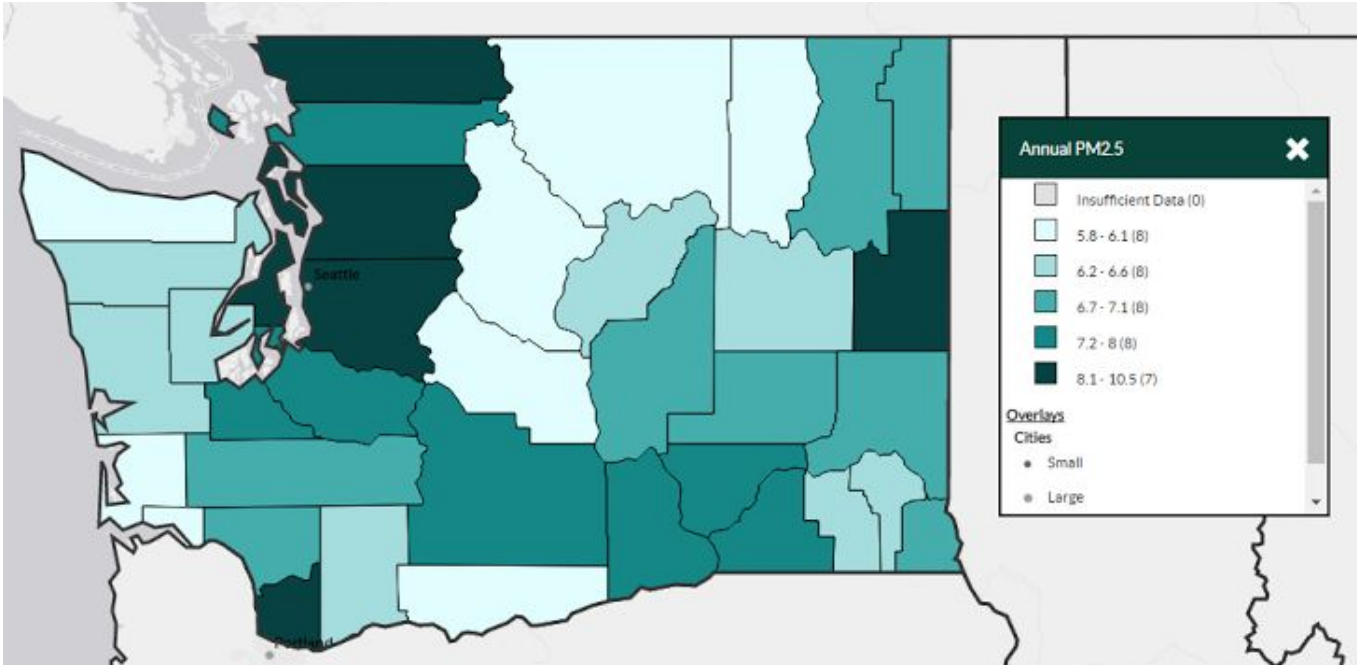
- ~34,000 deaths from heart disease/year
- Children
  - Increase in blood pressure
  - Blacks at higher risk of exposure (~68%) compared to whites (~37%)
- Disparities by race and income

Air Pollution

- Ozone (O_3)
  - Not emitted, forms in atmosphere from reactions between hydrocarbons and nitrogen oxides (NO_x).
  - NO_x emitted by vehicle exhaust, industrial emissions, chemical solvents, and plants/soils.
- Fine Particulate Matter ($PM_{2.5}$)
  - Heterogenous mixture of different particles
  - Emitted by
    - Gas and Diesel fuels
    - Dust
    - Burning of fuel for the home, construction, etc.

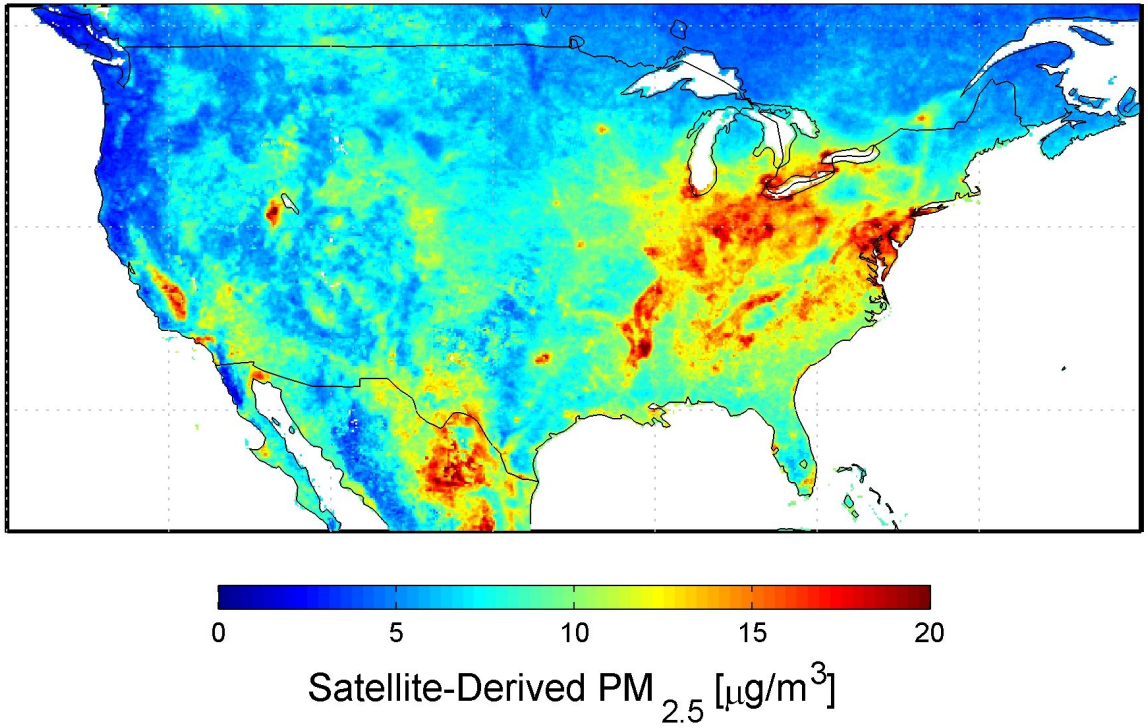
Air Pollution

Washington State



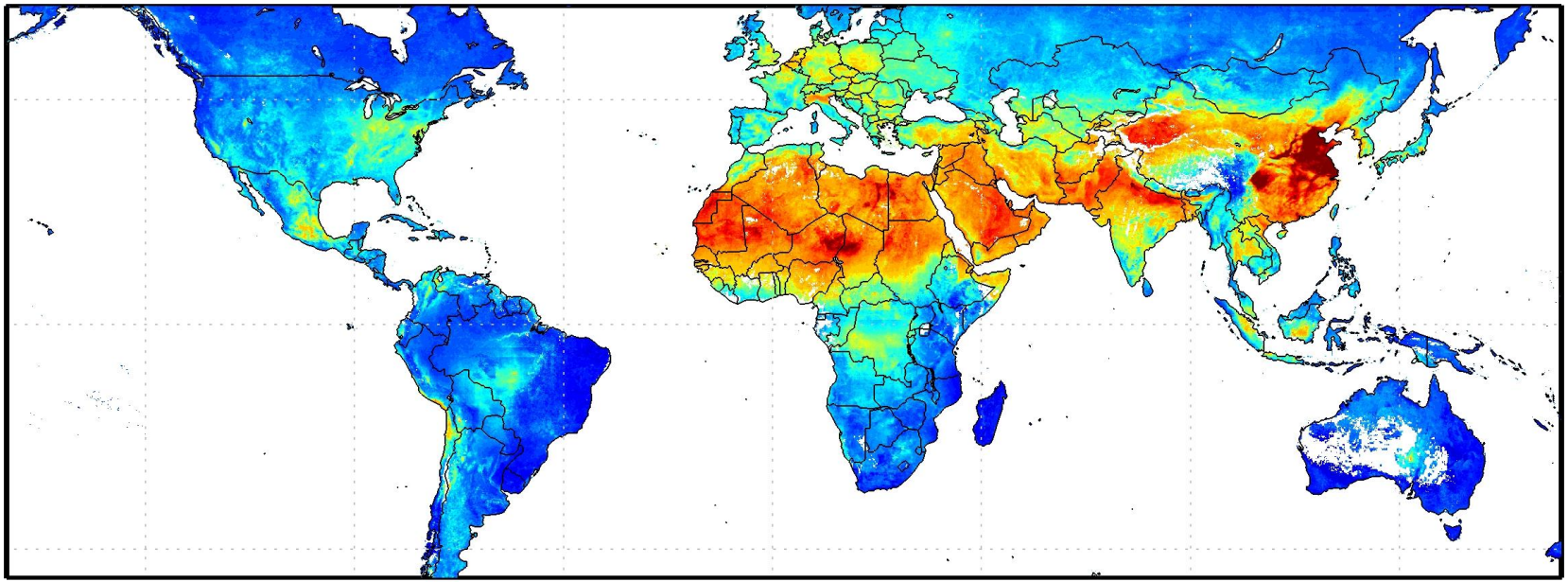
Interactive Atlas of Heart Disease and Stroke (nccd.cdc.gov/dhdspatlas)

Air Pollution



https://www.nasa.gov/topics/earth/features/health-sapping.html

Air Pollution



https://www.nasa.gov/topics/earth/features/health-sapping.html

Pollution - Cardiovascular Effects

- Cohort Studies
  - Harvard Six Cities Study
  - ACS Study
  - Women's Health Initiative
  - **MESA Air**

- Natural Experiments
  - Copper Smelter Strike
  - 1990 Dublin Coal Ban

- Associated with premature birth and low birth weight.
- Chronic exposure associated with increased blood pressure in children (Mexico City)
- Long-term exposure to PM_{10} leads to worse metabolic insulin sensitivity among children.

Pollution - Cardiovascular Effects

- Relatively Rapid response in CVD mortality when exposed to high $PM_{2.5}$ concentrations
- Risk increase is substantial at low $PM_{2.5}$ levels

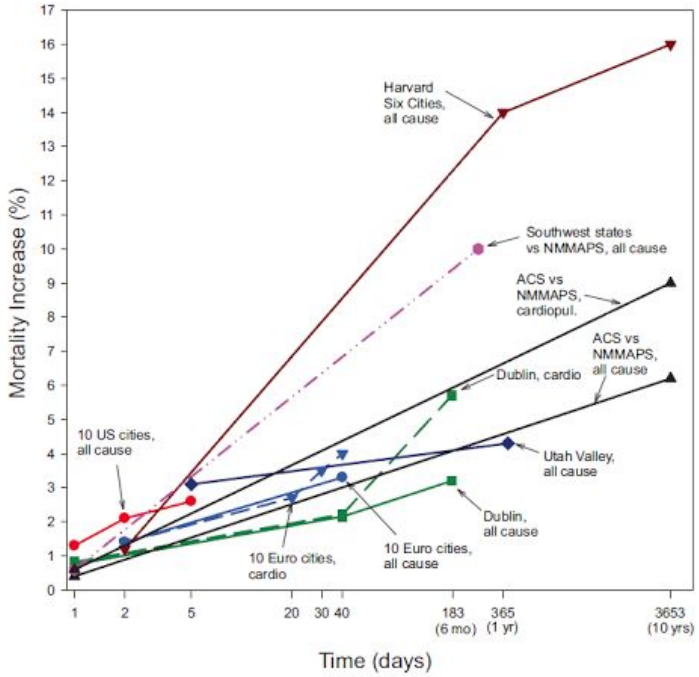
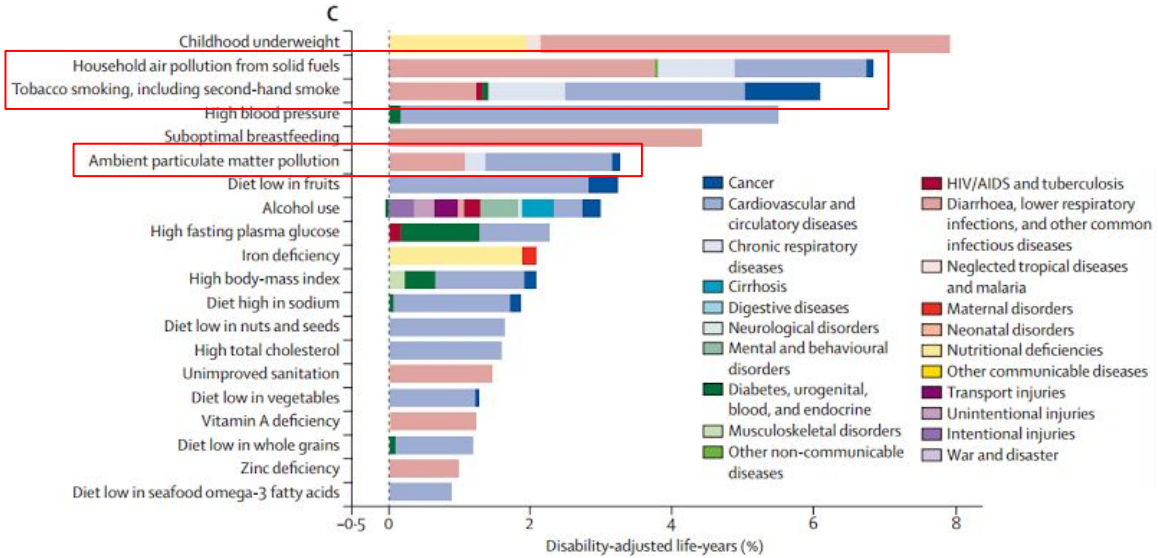


Figure 2. Comparison of estimates of percent change in mortality risk associated with an increment of 10 $\mu g/m^3$ in $PM_{2.5}$ or 20 $\mu g/m^3$ of PM_{10} or British Smoke (BS) for different time scales of exposure (log scale of approximate number of days, updated and adapted from Pope[281a]). Euro indicates European; cardio, cardiovascular disease; and cardiopul, cardiopulmonary.

Pollution - Worldwide Impact

- Major contributor to worldwide CVD burden

Figure 1: Burden of disease attributable to 20 leading risk factors in 1990, expressed as a percentage of global disability-adjusted life-years
For men (A), women (B), and both sexes (C).



Pollution - Cardiovascular Disease Mechanisms

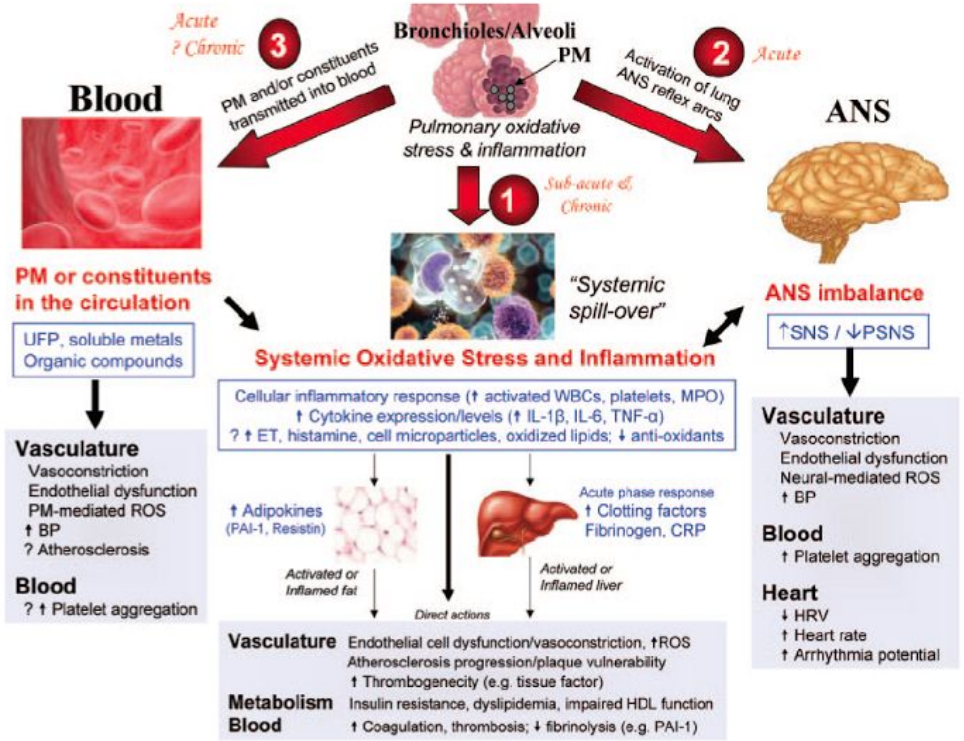


Figure 3. Biological pathways linking PM exposure with CVDs. The 3 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating cardiovascular events are shown. MPO indicates myeloperoxidase; PAI, plasminogen activator inhibitor; PSNS, parasympathetic nervous system; SNS, sympathetic nervous system; and WBCs, white blood cells. A question mark (?) indicates a pathway/mechanism with weak or mixed evidence or a mechanism of likely yet primarily theoretical existence based on the literature.

Brook et al. *Circ*. 2010

Metals - Cadmium

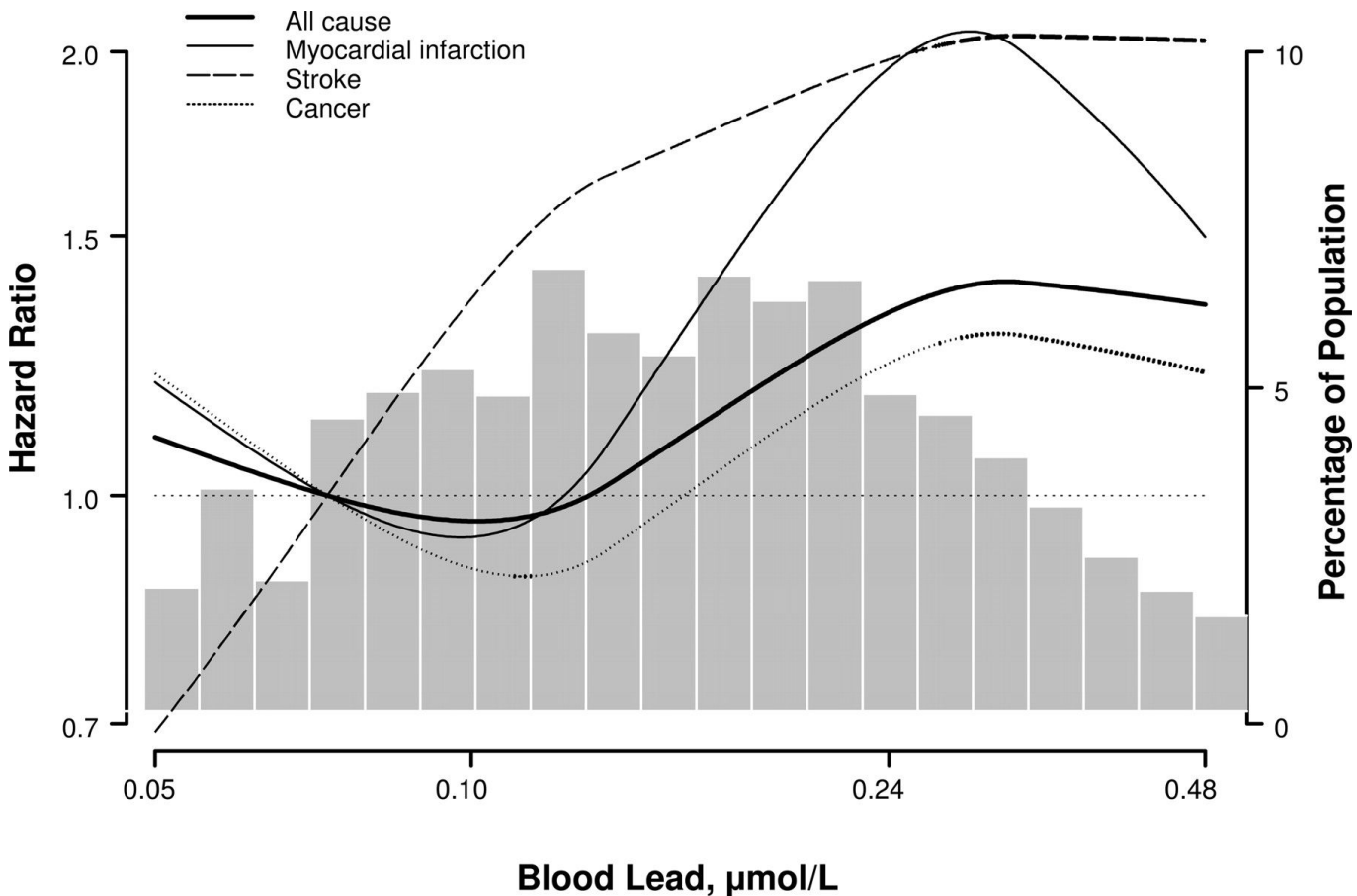
- Exposure from:
  - Tobacco Smoke
  - Contaminated water or soil near metal mines
    - Food exposure
  - Fuel combustion
- Absorption greatest in children
- Cardiovascular Disease
  - CVD mortality and blood cadmium
  - 50% increase in blood cadmium associated with 35% greater odds of prevalent stroke
  - Cadmium responsible for much of smoking risk

Metals - Lead

- Toxic heavy metal. Found in:
  - Plumbing
  - Gasoline additive
  - House paint
  - Batteries
- Absorbed into blood
- Stored in bones
  - Can remain for decades
- Risk of lead poisoning higher outside of U.S.

- High Blood Lead Levels Associated with:
  - Coronary Artery Disease
  - Stroke
  - Arrhythmias
  - Peripheral Arterial Disease
  - High Blood Pressure

Metals - Lead



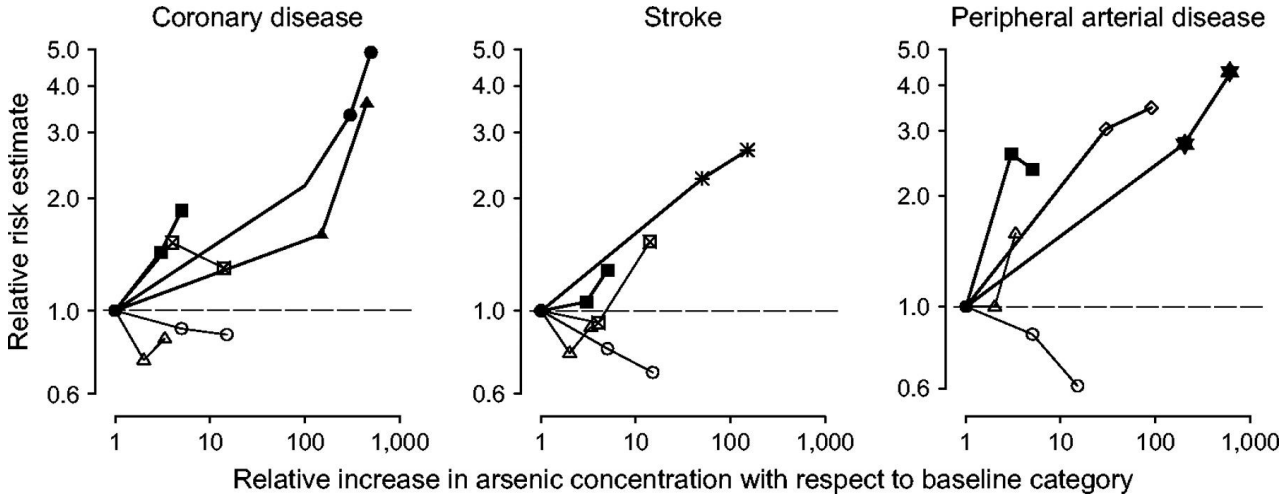
Menke et al.
Circulation. 2006

Metals - Arsenic

- Highly toxic metalloid
- Sources
  - Found naturally in soil
  - Released during mining
  - Used in pesticides
  - Found in pressure-treated woods
- > 100,000,000 worldwide chronically exposed to unsafe arsenic levels
  - Taiwan
  - Bangladesh
  -

Metals - Arsenic

- Cardiovascular Effects
  - Coronary disease
  - Stroke
  - Peripheral Arterial Disease
- Children
  - Thickening of arteries, signs of myocardial infarction



Navas-Acien et al. *Am J Epidemiol*

Metals - Arsenic

- Cardiovascular Effects
  - Coronary disease
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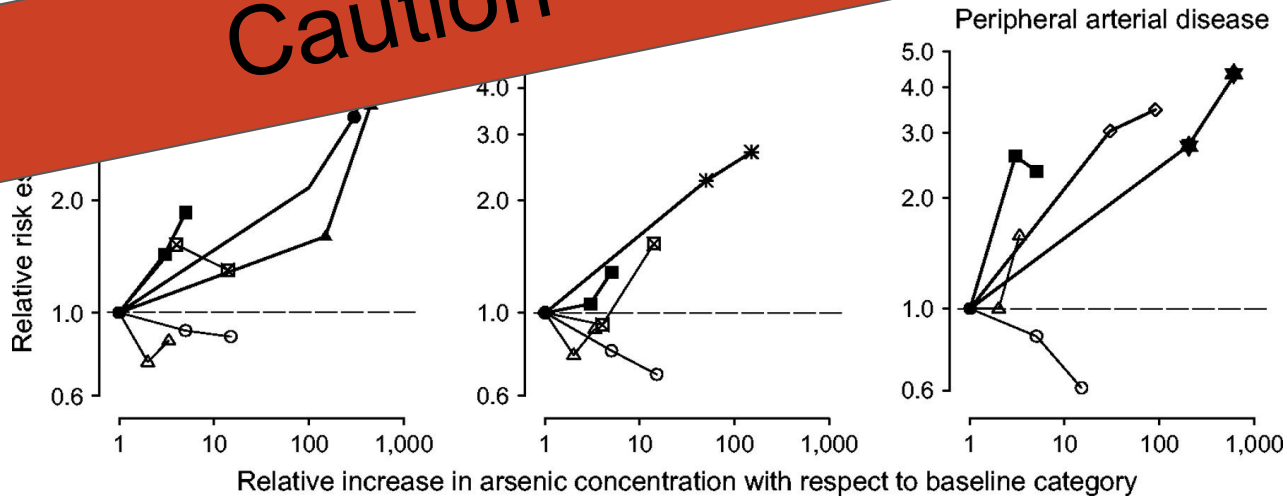
  - Thickenin… …s of

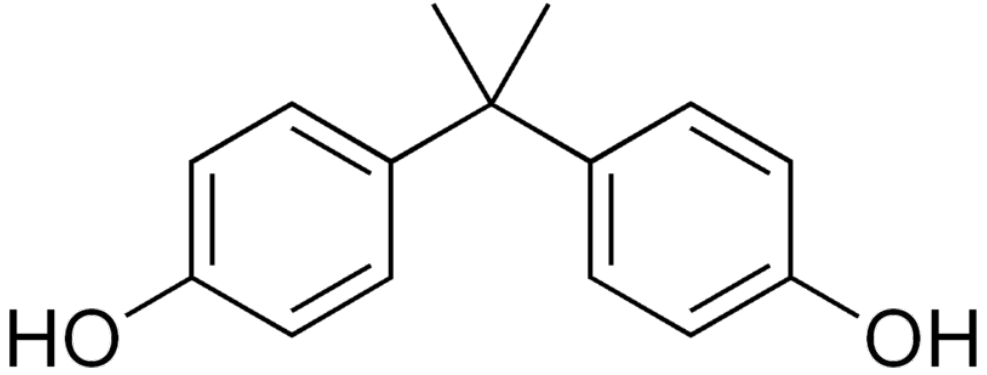
Caution



Navas-Acien et al. *Am J Epidemiol*

Bisphenol A

- Found in plastic containers
- Detectable levels in the urine of 93% of people (per CDC)
- In NHANES
  - Associated with:
    - Heart Attack
    - Coronary Artery Disease
    - Arrhythmias
- Likely a contributing factor in CVD



BPA FREE

BPA Free

NO PHTHALATES NO BISPHENOL-A NON-TOXIC PLASTIC
BPA FREE

Stress

- Job Stress
- Short-term stresses
- Perceived discrimination
  - In children 10-15, perceived discrimination associated with C-reactive protein, elevated blood pressure
- Stress fosters poor health decisions

Goosby et al. *Am J Hum Biol.* 2015

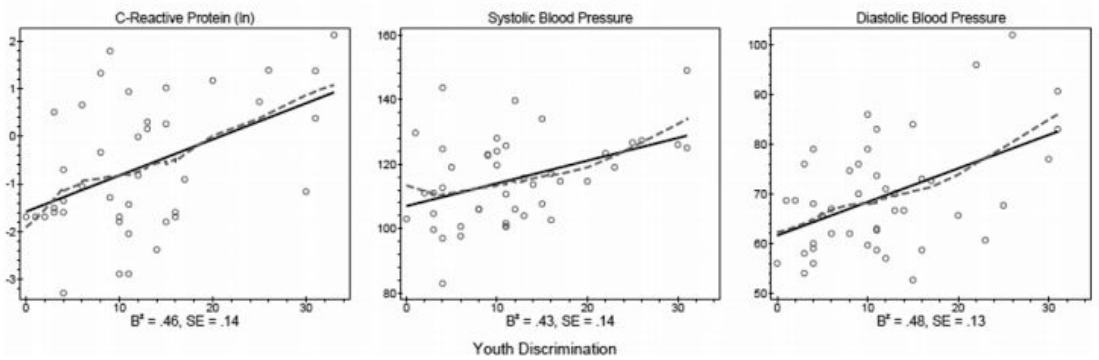


Figure 1.
Bivariate Distribution of CVD Risk Markers Regressed on Youth Discrimination
Note: Standardized coefficients reported.

Disparities in Health

- Ischemic Heart Disease
  - Inversely related to education, income, poverty status

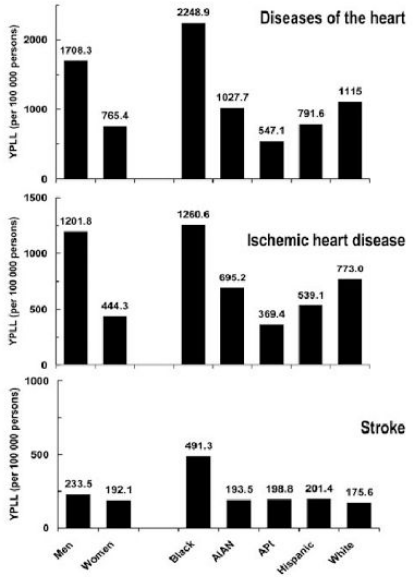


Figure 4. Years of potential life lost (YPLL) before 75 years of age resulting from diseases of the heart, ischemic heart disease, and stroke, United States, 2001. API indicates Asian or Pacific Islander; AIAN, American Indian or Alaska Native. Source: CDC, Health United States, 2003.

TABLE 4. Age-Adjusted Prevalence of Circulatory Diseases by Poverty Status* Among Persons ≥18 Years of Age: United States, 2002[12]

	Age-Adjusted Percentage, %			
Poverty Status*	Reported Heart Disease†	Reported Coronary Heart Disease‡	Reported Hypertension	Reported Stroke
Poor	14.0 ± 0.7	9.4±0.6	26.1±0.8	4.1±0.4
Near poor	12.4±0.5	7.5±0.4	23.1±0.7	3.6±0.3
Not poor	11.4±0.3	6.3±0.2	20.6±0.3	2.2±0.2

*Poverty status is based on family income and family size using the US Census Bureau's poverty thresholds for the previous calendar year. "Poor" persons are defined as having incomes below the poverty threshold. "Near poor" persons have incomes of 100% to <200% of the poverty threshold. "Not poor" persons have incomes that are ≥200% of the poverty threshold.

†Heart disease includes coronary heart disease, angina pectoris, heart attack, or any other heart condition or disease.

‡Coronary heart disease includes coronary heart disease, angina pectoris, or heart attack.

Policy Implications

- Epidemiology, basic science inform policy
  - Clean Air Act reviews guidelines every 5 years
- Reports from Institute for Health Metrics and Evaluation (IHME) and WHO meant specifically for policymakers.
- Trump Presidency leading to uncertainty about policies/regulations
  - Promises to bring back coal, deregulate energy/auto industry
- Your thoughts?

Policy Implications

Thank You

Thanks to:
Lorelei Walker (CHE)
Nancy Hepp (CHE)