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

Heart Disease Death Rates, 2011-2013
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics
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

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

Cooper et al. *Circulation*, 2000
Cardiovascular Disease Trends - US

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

Traditional Cardiovascular Disease Framework

- Emphasis on individual-level risk factors
  - Diet
  - Exercise
  - Smoking
- Tendency to focus on adults

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

<table>
<thead>
<tr>
<th>The population level</th>
<th>The individual, health-care level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protecting people from tobacco smoke and banning smoking in public places</td>
<td>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%</td>
</tr>
<tr>
<td>Warning about the dangers of tobacco use</td>
<td>Aspirin therapy for acute myocardial infarction</td>
</tr>
<tr>
<td>Enforcing bans on tobacco advertising, promotion and sponsorship</td>
<td></td>
</tr>
<tr>
<td>Raising taxes on tobacco</td>
<td></td>
</tr>
<tr>
<td>Restricting access to retailed alcohol</td>
<td></td>
</tr>
<tr>
<td>Enforcing bans on alcohol advertising</td>
<td></td>
</tr>
<tr>
<td>Raising taxes on alcohol</td>
<td></td>
</tr>
<tr>
<td>Reducing salt intake and salt content of food</td>
<td></td>
</tr>
<tr>
<td>Replacing trans-fat in food with polyunsaturated fat</td>
<td></td>
</tr>
<tr>
<td>Promoting public awareness about diet and physical activity, including through mass media</td>
<td></td>
</tr>
</tbody>
</table>
Our Cardiovascular Disease Framework

- Developmental Origins of Health and Disease
- Barker Hypothesis

Undernutrition in pregnancy → Fetal growth retardation, low birth weight → Adult Disease

Social Factors
Smoking
Stress
Genetics

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 miRNAs.
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

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

- Life Course Model

Our Cardiovascular Disease Framework

- Ecological Model
We have been led by the science to embrace a systems model of health — one that recognizes the interplay of multiple factors that can impact health across the lifespan and across the globe.
Environmental Factors in Cardiovascular Disease

- Smoking
- Pollution
- Metals
- Bisphenol a
Smoking

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

Homa et al. MMWR Morb Mortal Wkly Rep. 2015
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/dhisp2atlases)
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
• Major contributor to worldwide CVD burden
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 primary 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

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
  - Stroke
  - Peripheral Arterial Disease

- Children
  - Thickening of arteries, signs of myocardial infarction

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
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
Disparities in Health

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

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

<table>
<thead>
<tr>
<th>Poverty Status</th>
<th>Reported Heart Disease</th>
<th>Reported Coronary Heart Disease</th>
<th>Reported Hypertension</th>
<th>Reported Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>14.0 ± 0.7</td>
<td>9.4 ± 0.6</td>
<td>26.1 ± 0.8</td>
<td>4.1 ± 0.4</td>
</tr>
<tr>
<td>Near poor</td>
<td>12.4 ± 0.5</td>
<td>7.5 ± 0.4</td>
<td>23.1 ± 0.7</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>Not poor</td>
<td>11.4 ± 0.3</td>
<td>6.3 ± 0.2</td>
<td>20.6 ± 0.3</td>
<td>2.2 ± 0.2</td>
</tr>
</tbody>
</table>

*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

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