Overview of Atherosclerosis and Chemical Stressors

Wayne Cascio, MD, FACC

Acting Director, National Health and Environmental Effects Research Laboratory

Office of Research & Development, US EPA

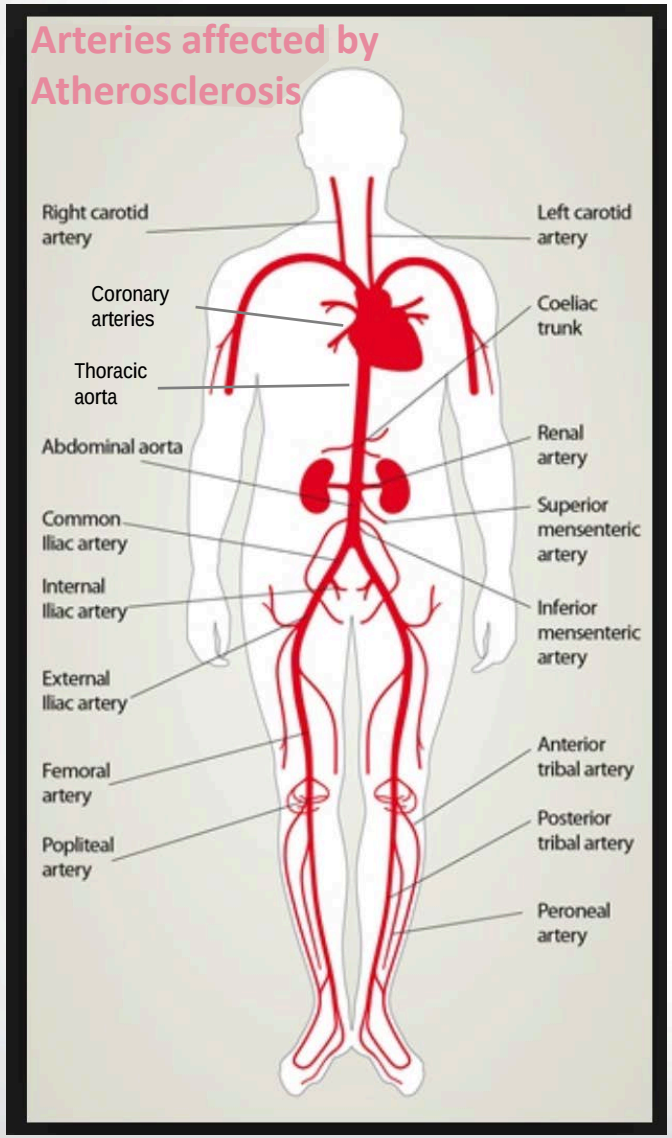
Research Triangle Park, NC

Wayne Cascio, MD

- *No conflicts of interest*
- *The presentation represents the opinions of the speaker and does not necessarily represent the policies of the US EPA*

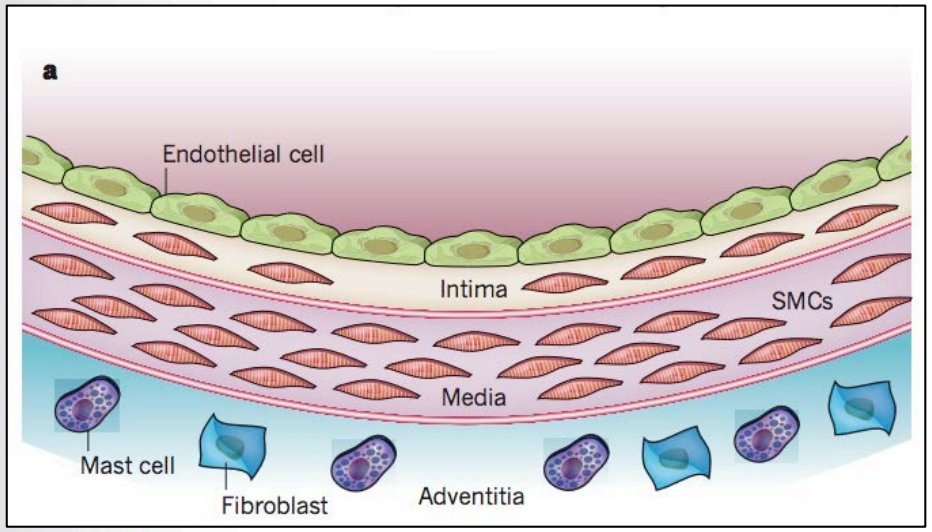
Clinical-Pathology of Atherosclerosis

Vascular Beds Affected and Clinical Presentations



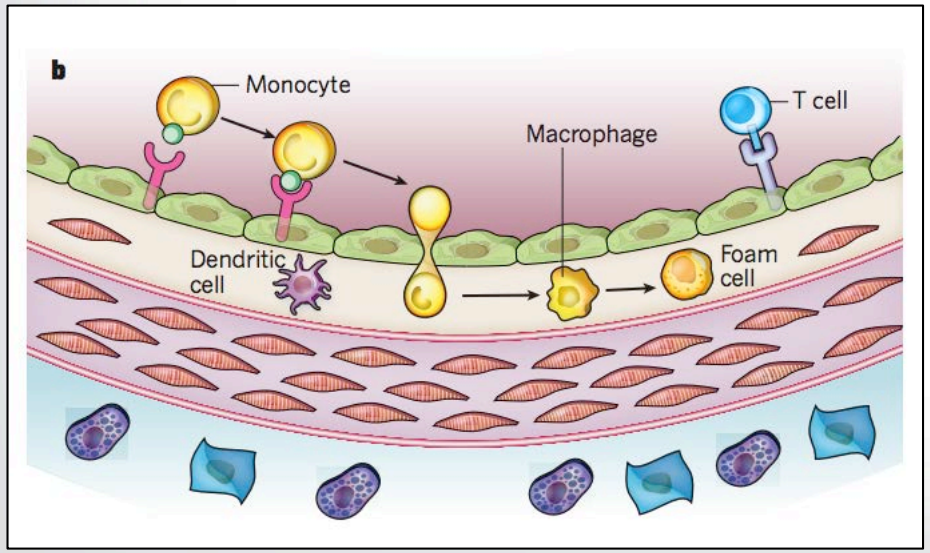
- *Coronary artery disease (CAD)*
  - Angina, Unstable angina, Myocardial infarction
  - Heart failure
- *Cerebrovascular atherosclerotic disease*
  - Ischemic stroke
  - Transient ischemic attacks
- *Aortic atherosclerotic disease*
  - Aneurysm, Dissection
- *Peripheral arterial vascular disease (PAD)*
  - Renal, Mesenteric and Peripheral limb ischemia, Claudication

Stages in the Development of Atherosclerosis
Changes at the Cellular Level



The normal artery contains three layers:

- **Inner layer, the tunica intima**
  - lined by endothelial cells
- **Middle layer, or tunica media**
  - SMCs embedded in a complex extracellular matrix
- **Adventitia, the outer layer of arteries**
  - contains mast cells, nerve endings & microvessels

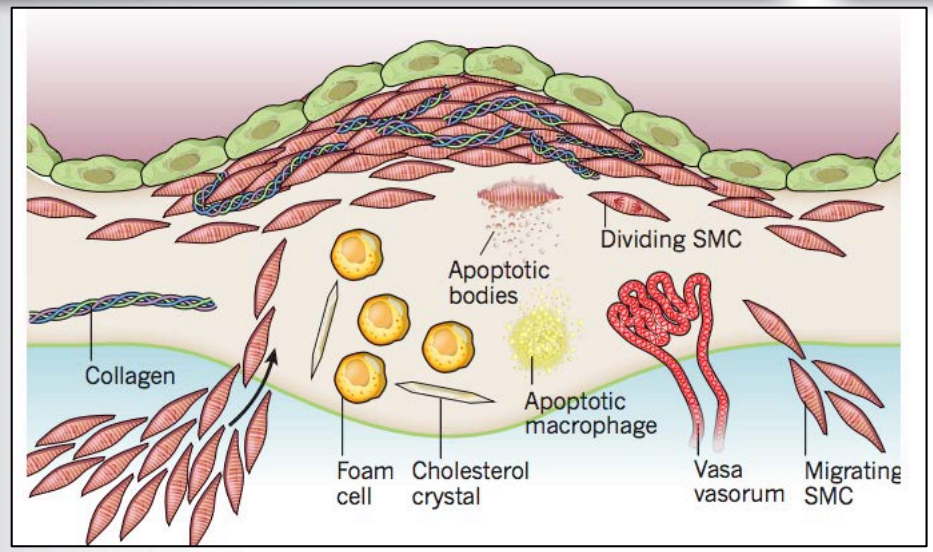


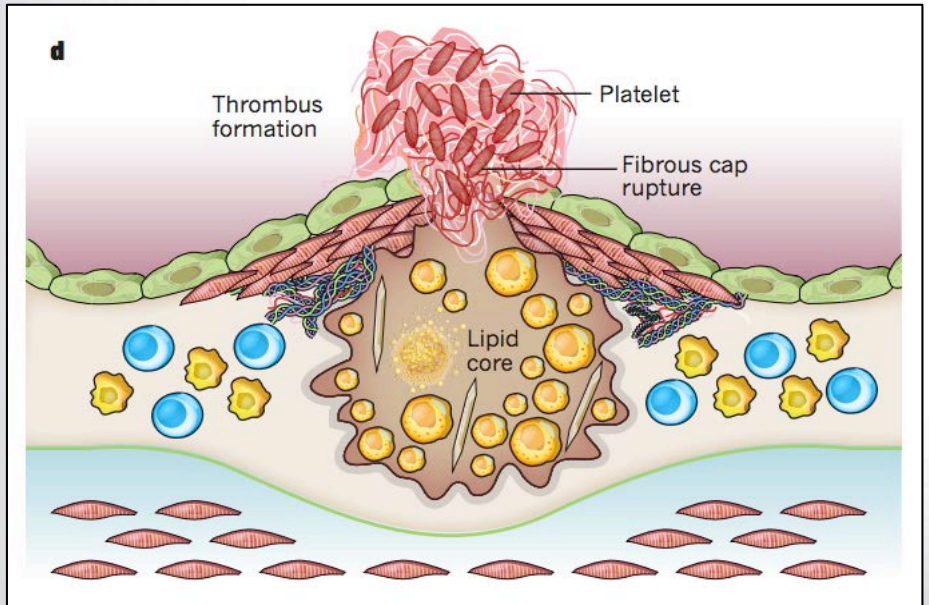
The initial steps of atherosclerosis include:

- **Adhesion of leukocytes to the activated endothelial monolayer**
- **Migration of the bound leukocytes into the intima**
- **Maturation of monocytes into macrophages**
- **Uptake of lipid - foam cells**

From Libby P, et al. *Nature* 2011

Stages in the Development of Atherosclerosis
Changes at the Cellular Level





Lesion progression:

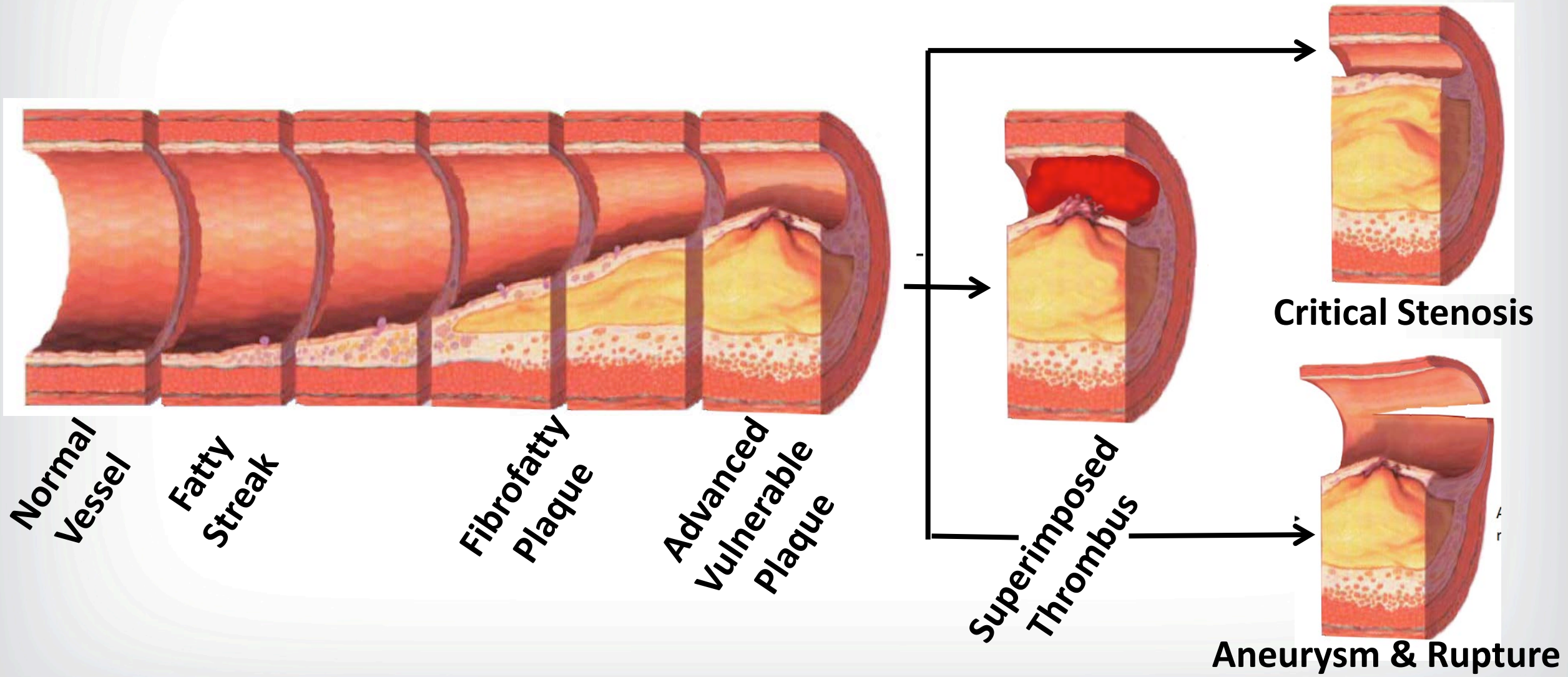
- **Migration of SMCs from the media to the intima**
- **Proliferation of SMCs and synthesis of extracellular matrix macromolecules (e.g. collagen, elastin)**
- **Plaque macrophages and SMCs can die**
- **Extracellular lipid derived from dead and dying cells can accumulate in the central region of a plaque**
  - the lipid or necrotic core
- **Plaques - cholesterol crystals and microvessels**

Thrombosis:

- **Fracture of the plaque's fibrous cap**
- **Blood coagulation components**
  - in contact with tissue factors in the plaque's interior
- **Triggers thrombus formation**

From Libby P, et al. *Nature* 2011

Initiation, Progression, and Complications of Atherosclerosis



https://upload.wikimedia.org/wikipedia/commons/5/5b/Late_complications_of_atherosclerosis.PNG

Global Burden of Cardiovascular Disease

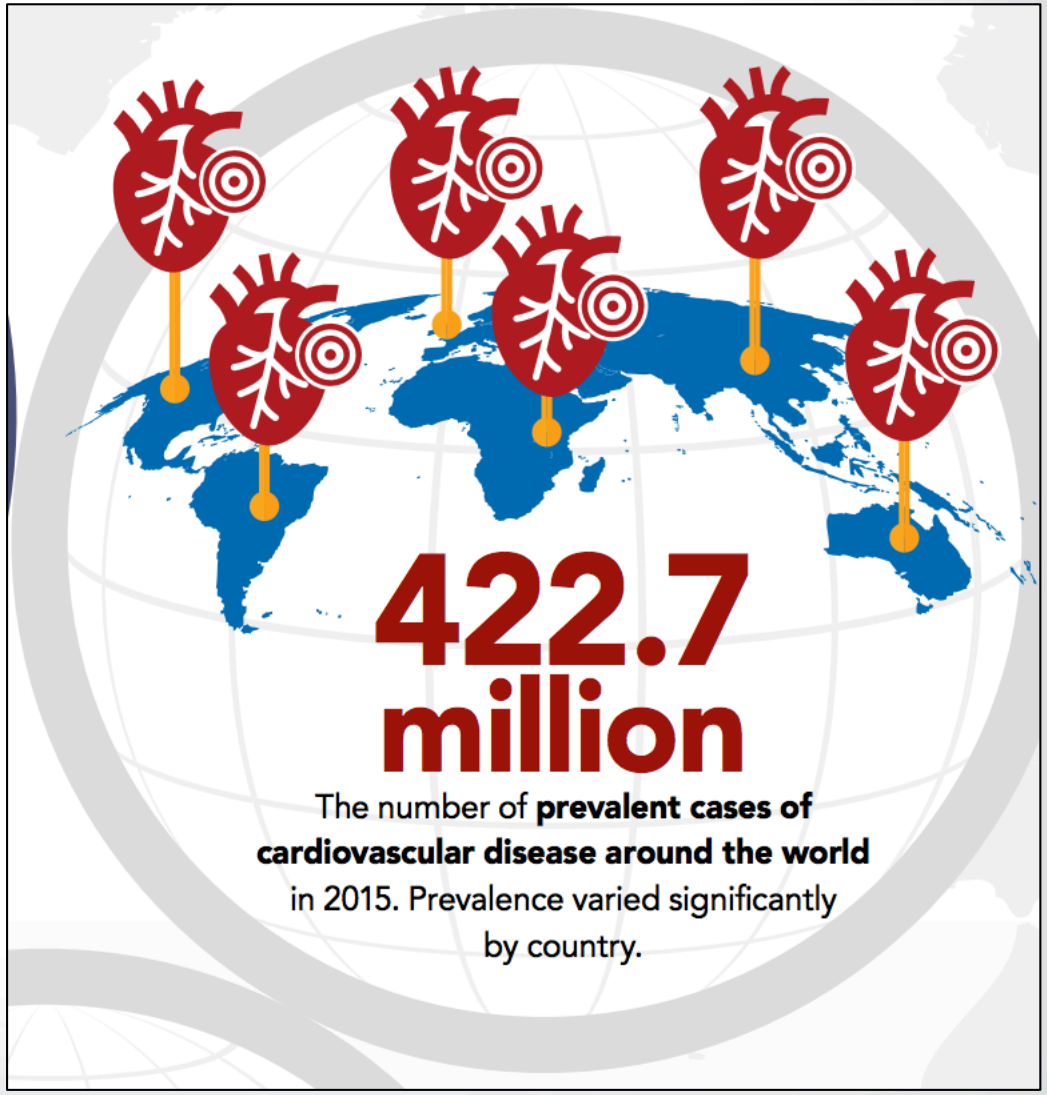
Largely driven by complications of atherosclerosis in 2015

In 2015 the number of deaths due to:

- Cardiovascular disease ~18 Million
- Ischemic heart disease ~9 Million
- Stroke ~6.3 Million

Between 1990 and 2015 the:

- Estimated increase in the number deaths from cardiovascular disease ~ 5.3 Million

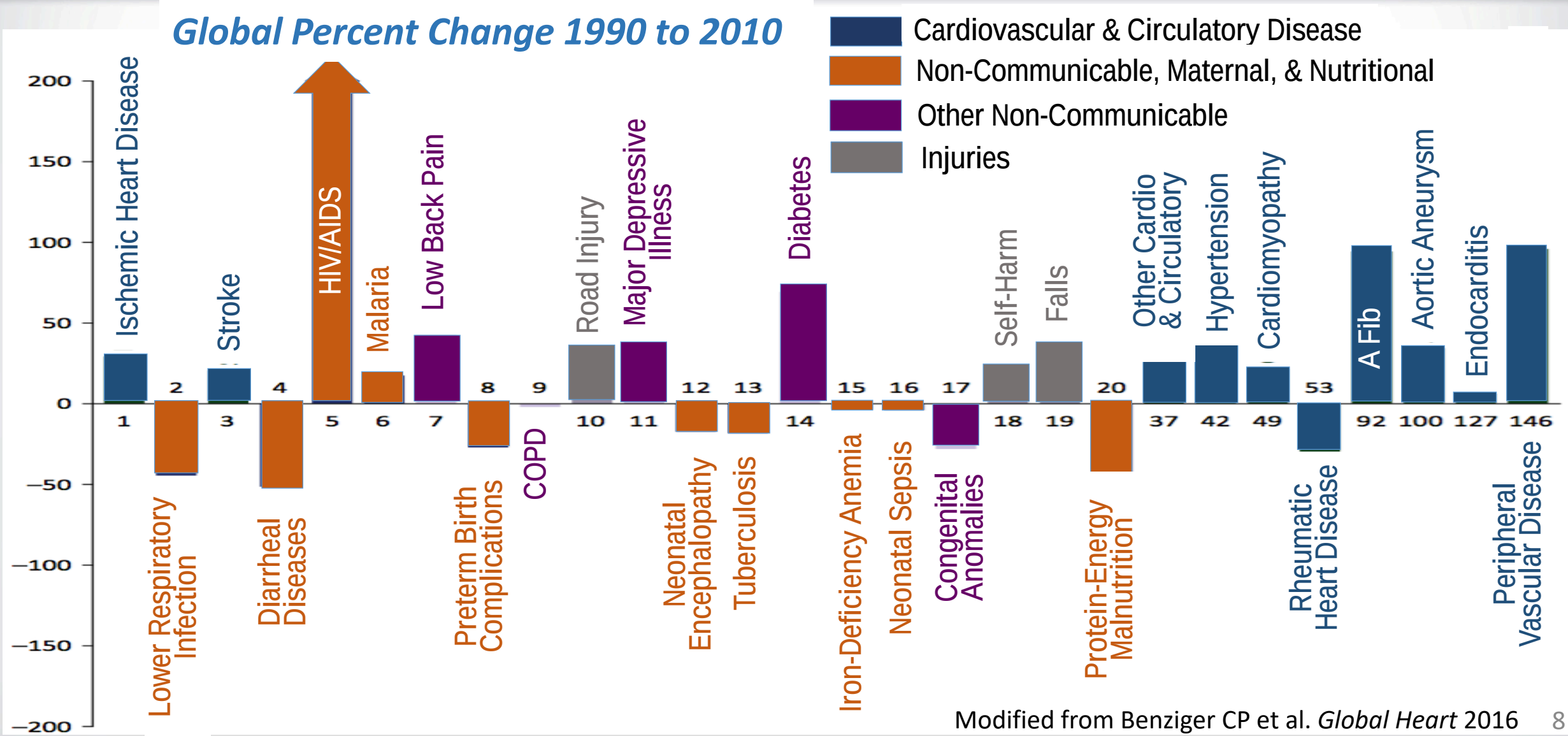


Roth G et al. *J Am Coll Cardiol* 2017

Cardiology June 2017

Temporal Trends for Cardiovascular Disease

Disability-Adjusted-Life-Years: Changes 1990 to 2010

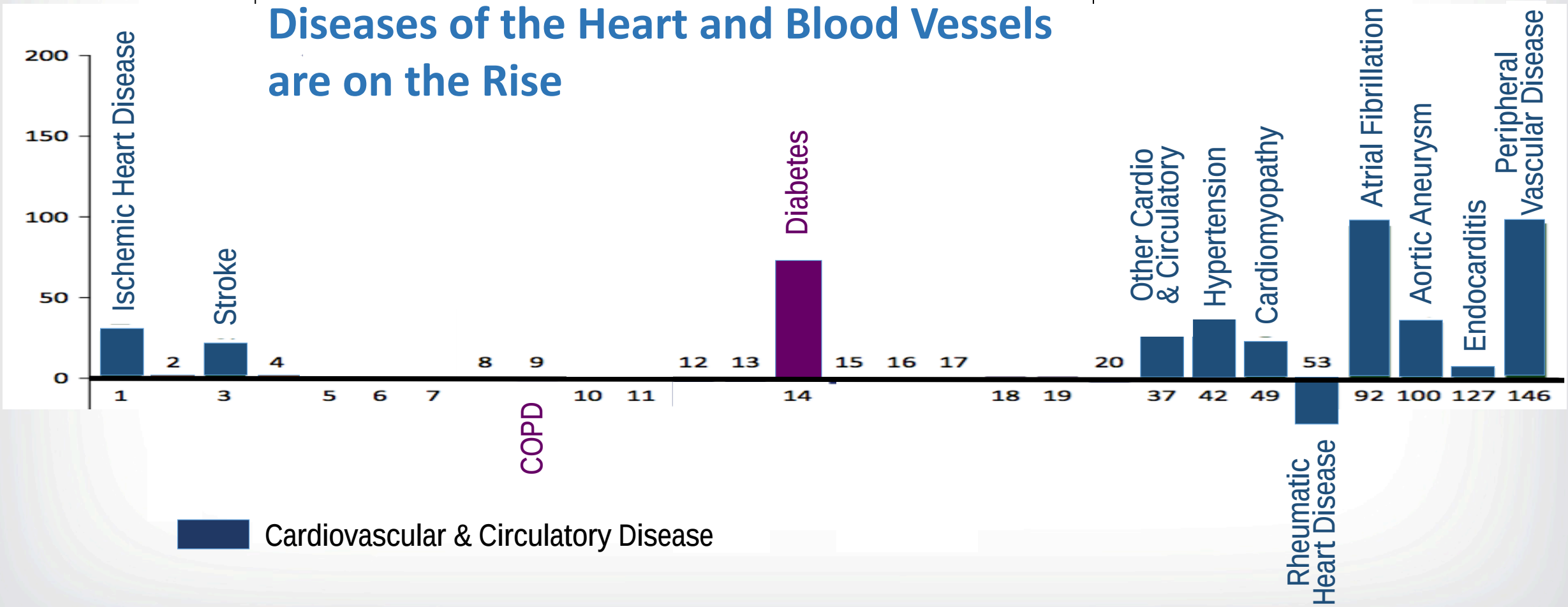


Modified from Benziger CP et al. *Global Heart* 2016

Temporal Trends for Cardiovascular Disease

Comparison with leading causes of DALYs

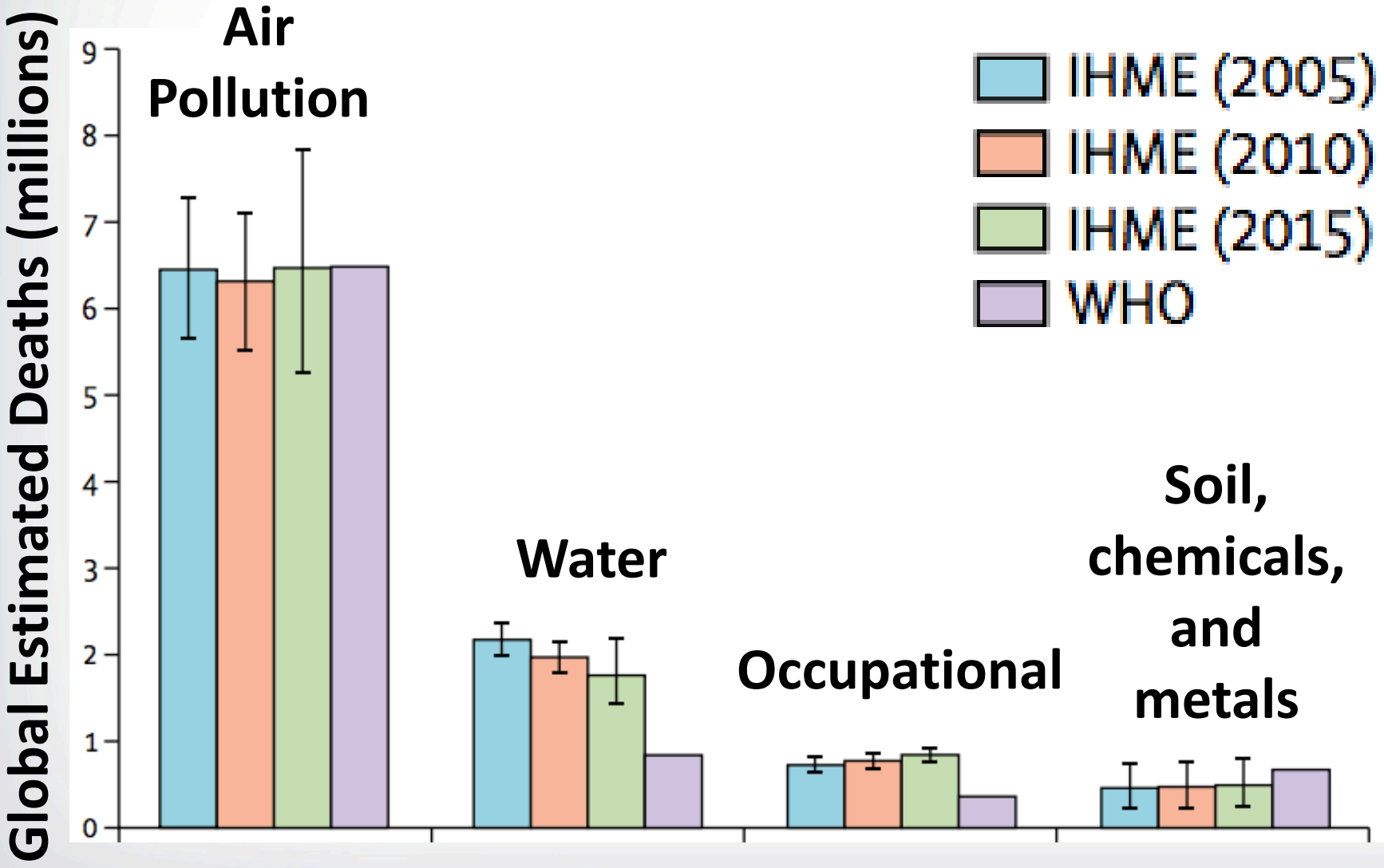
Global Percent Change 1990 to 2010



Modified from Benziger CP et al. *Global Heart* 2016

Global Estimated Deaths by Pollution, 2015

Putting Different Types of Pollution into Perspective



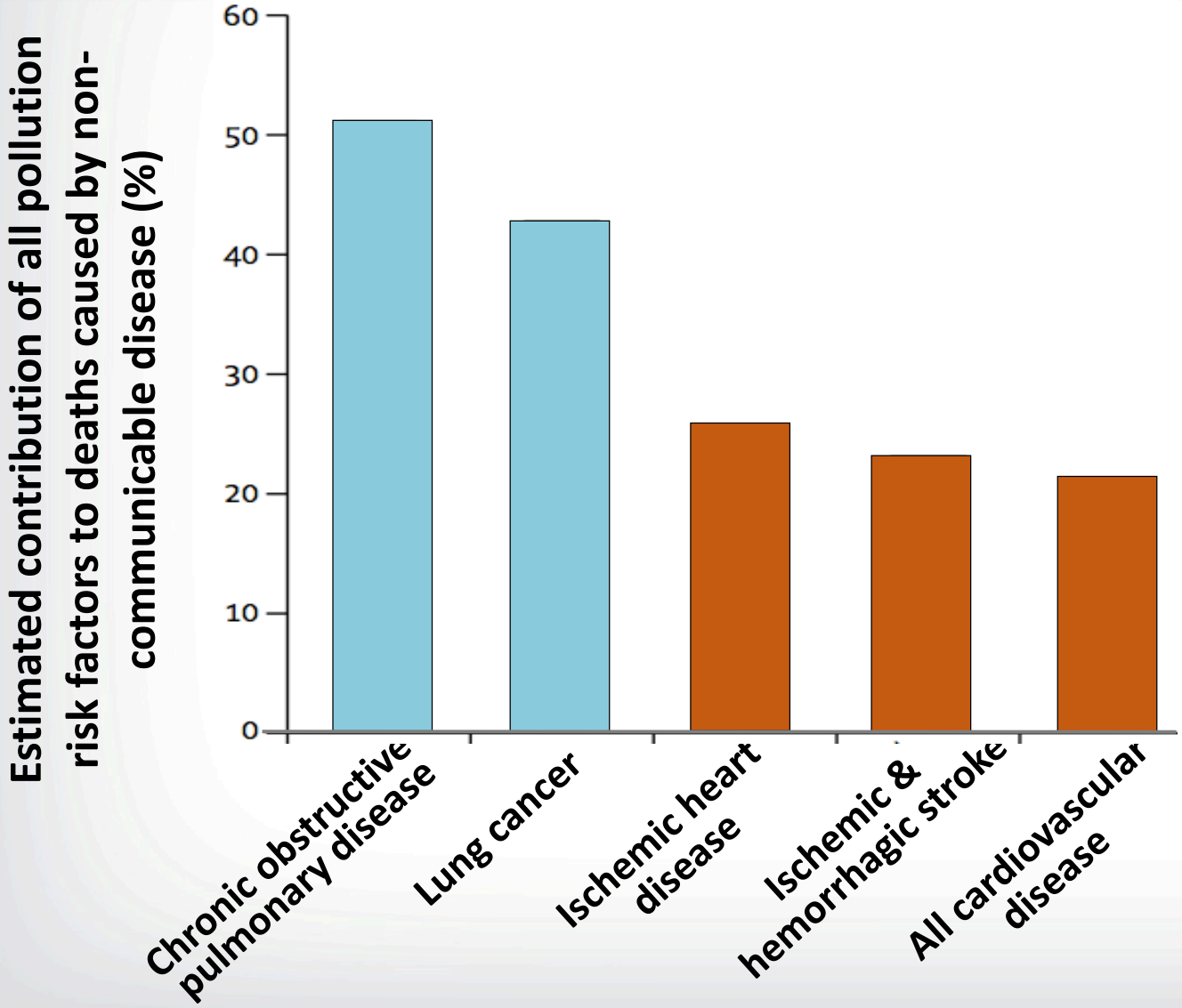
Among different types of pollutants - air pollution is the dominant driver of mortality on the global scale

Data from the GBD study and WHO

IHME = Institute for Health Metrics and Evaluation

From Landrigan PJ et al. *Lancet* 2018; 391: 462–512

Contribution of Pollution to Deaths Caused by Non-Communicable Diseases, 2015



Air pollution contributes to:

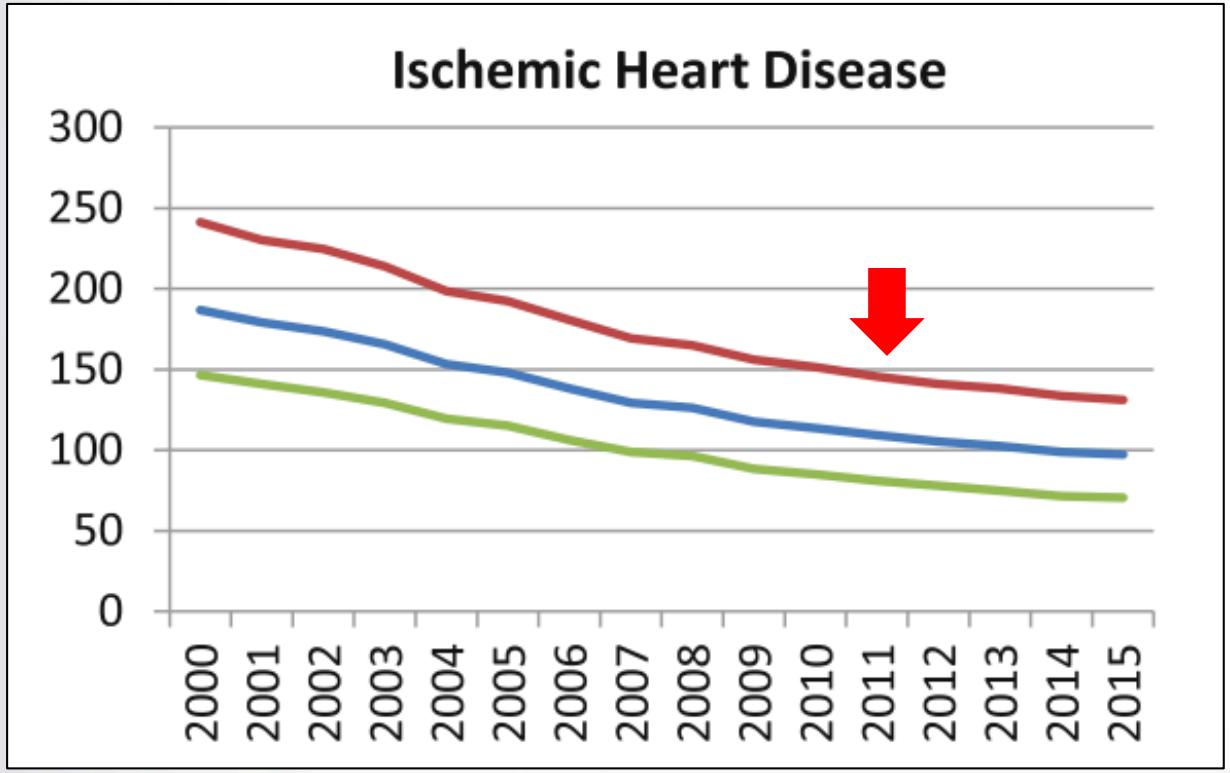
- **25% of ischemic heart disease**
- **over 20% of ischemic and hemorrhagic stroke**
- **20% of all cardiovascular disease**

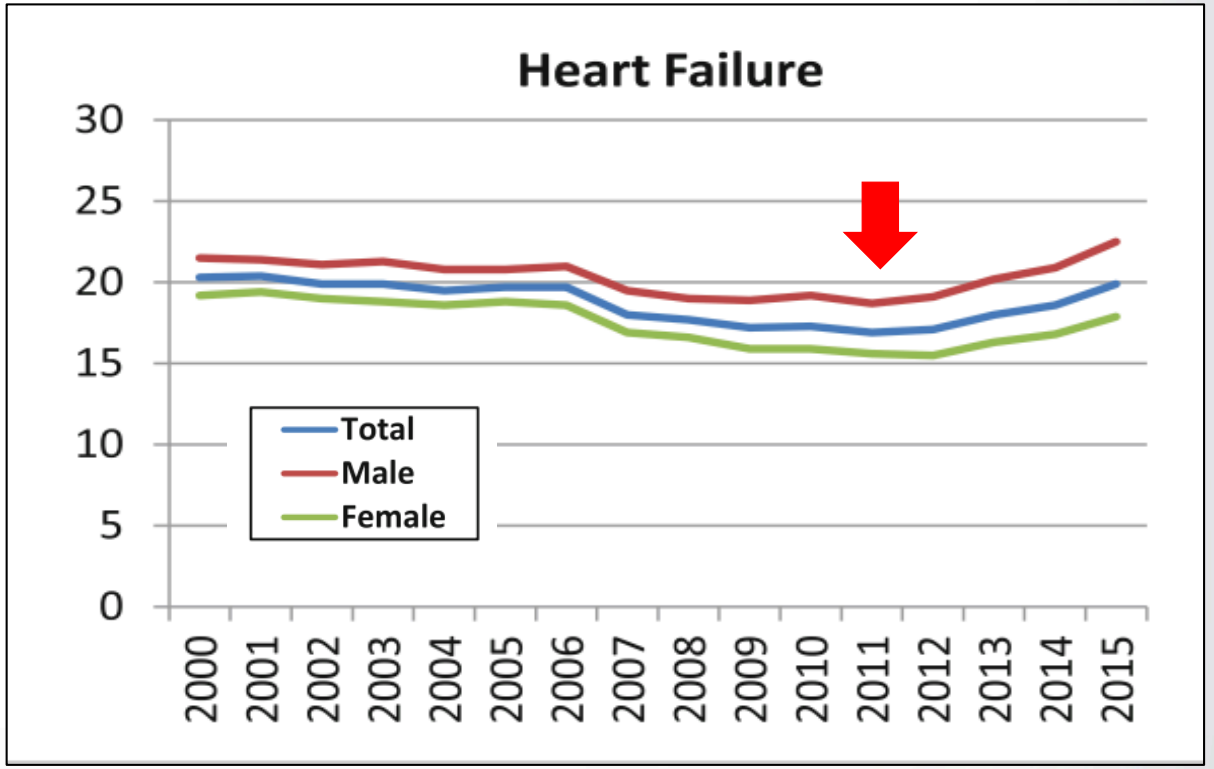
Landrigan PJ et al. *Lancet* 2018; 391: 462–512

Recent U.S. Mortality Trends Within Heart Disease

Age-Adjusted Mortality Rates

Rate of decline slowed from 4.96% for 2000-2011 to 2.66% for 2011-2015





Sidney S et al. *BMC Cardiovasc Disord* 2017

Cardiovascular Disease

A Costly Burden for the U.S. Projections through 2035

In 2015, 102.7 million (41.5%) of the U.S. population had at least one CVD condition:

- Coronary Heart Disease 16.8 million
- Stroke 7.5 million
- Congestive Heart Failure 5.8 million
- Atrial Fibrillation 5.2 million
- High Blood Pressure 96.1 million

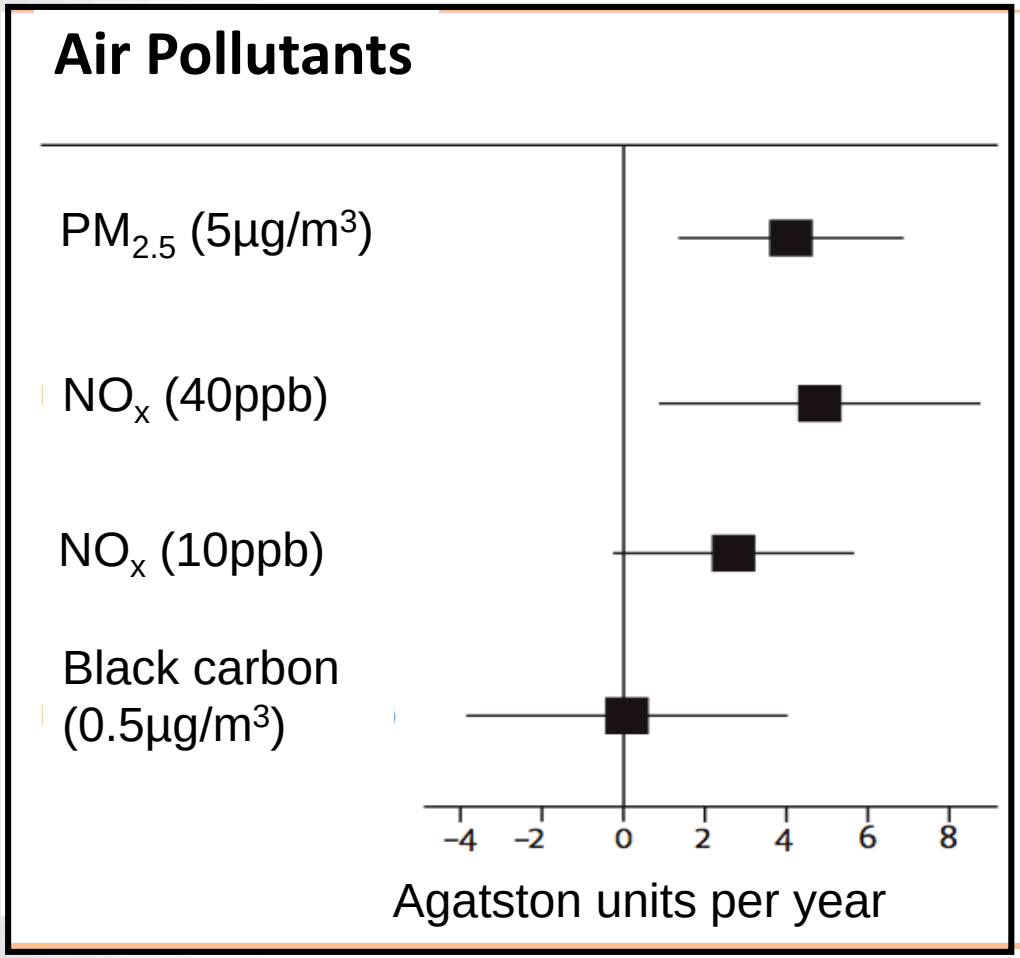
In 2035, the number of Americans with CVD is projected to rise to 131.2 million (45%) of the total U.S. population

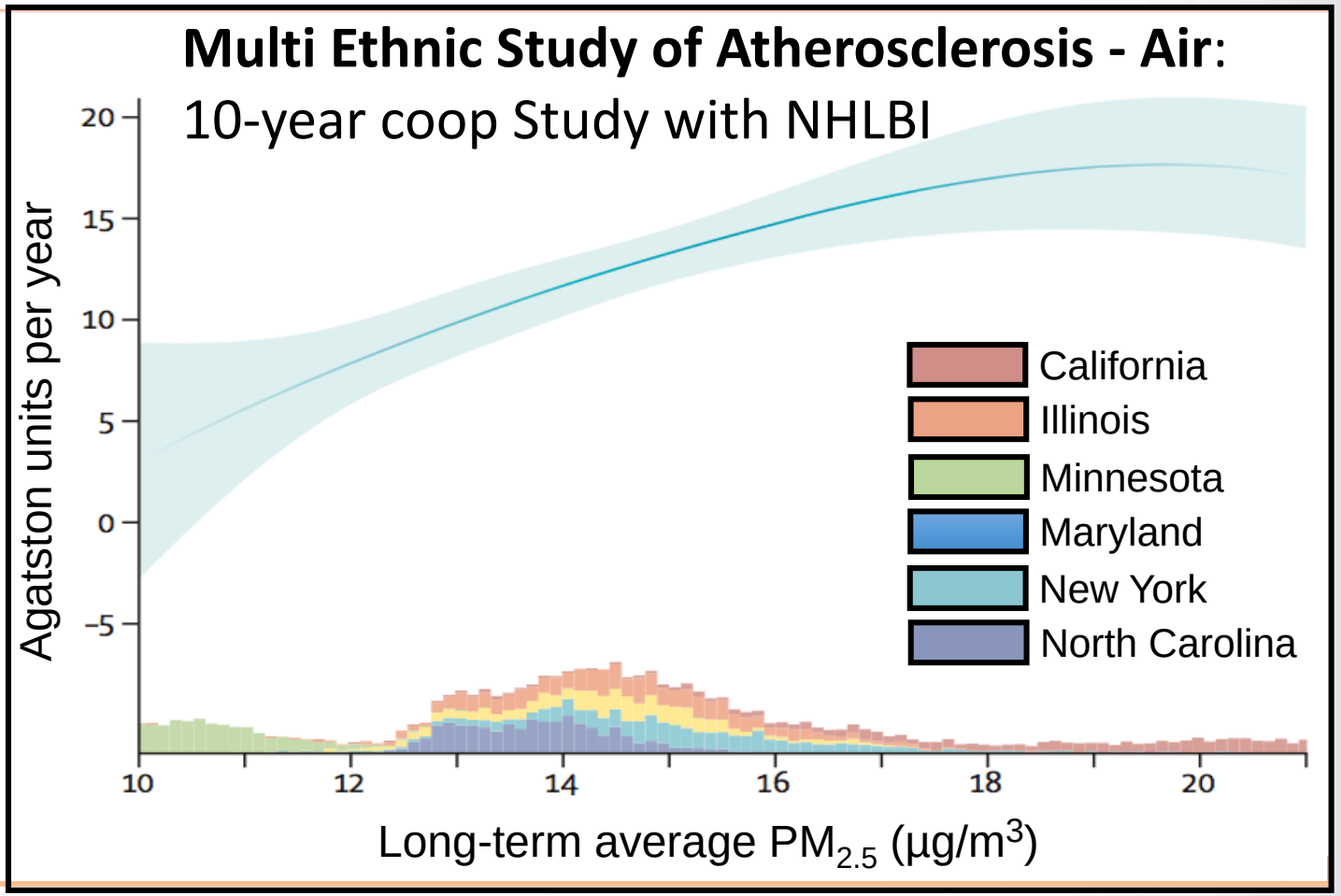
This means additional increases of:

- Coronary Heart Disease 7.2 million
- Stroke 3.7 million
- Congestive Heart Failure 3.0 million
- Atrial Fibrillation 2.0 million
- High Blood Pressure 27.1 million

Statistics from American Heart Association CVD Burden Report 2017

Long-Term $PM_{2.5}$ & NO_2 Exposure
Increases Coronary Artery Calcium



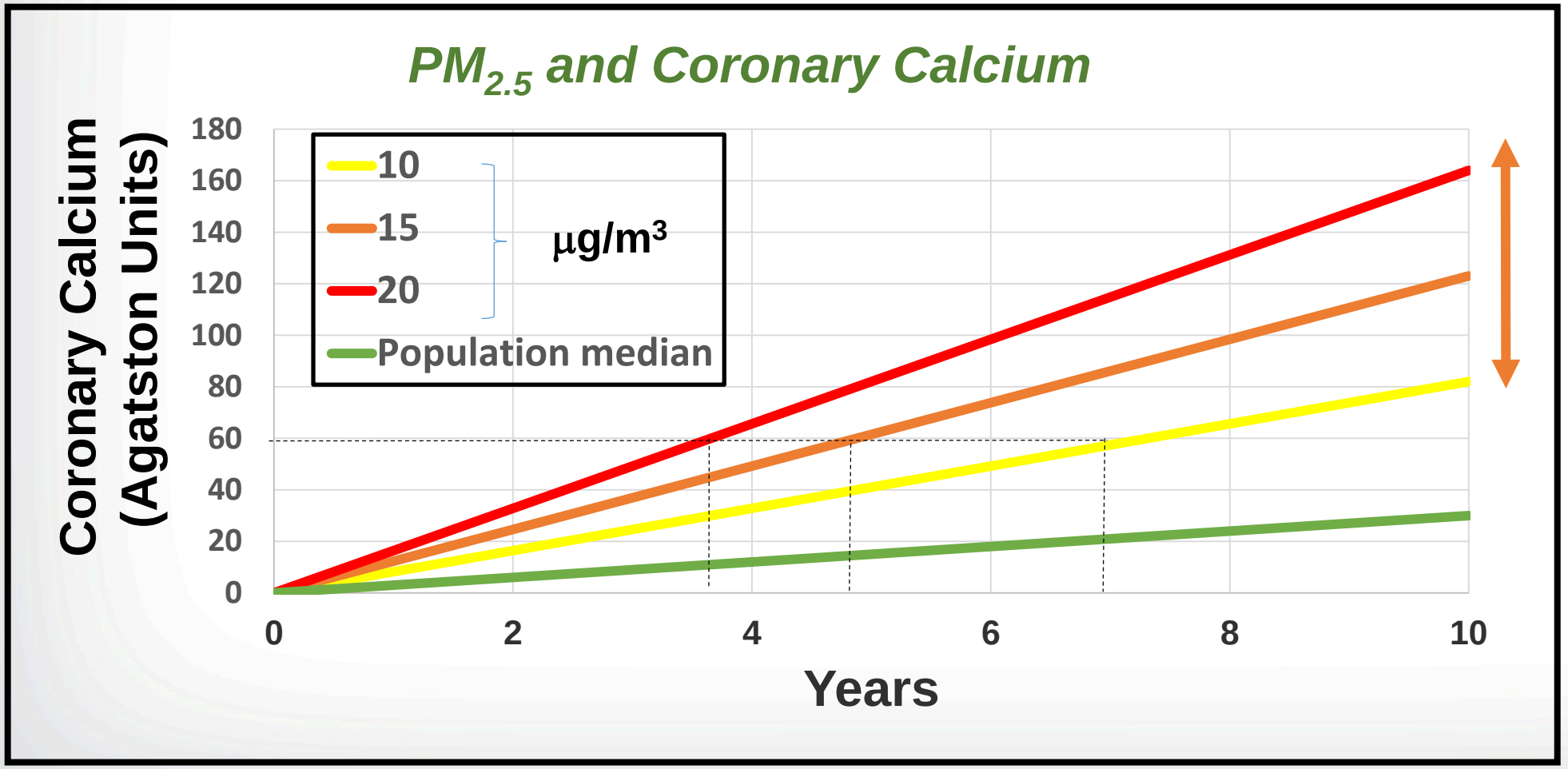


Long-term $PM_{2.5}$ and NO_2 increased coronary calcium, an indictor of atherosclerosis

From Kaufman JD et al. *Lancet* 2016

Long-Term $PM_{2.5}$ & Nox Exposure
Associated Atherosclerosis Progression

MESA Air Study – Led by University of Washington



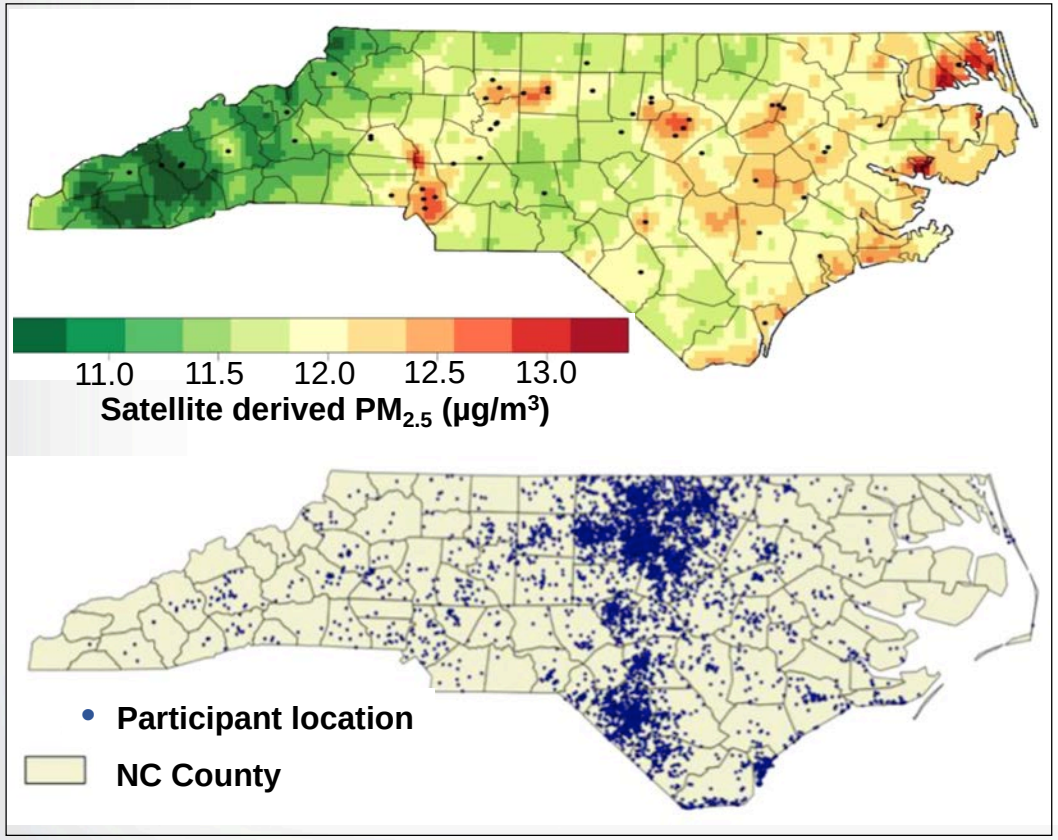
After 10 years 80 Agatston Unit difference between annual $PM_{2.5}$ of 10 and 20 µg/m³

From Kaufman JD, et al. *Lancet* 2016

Health & Long-Term Air Pollution Exposure

Association between PM and Coronary Artery Disease

5,679 patients who underwent coronary angiography at Duke University between 2002–2009 and resided in North Carolina*



1 µg/m³ increase in annual average $PM_{2.5}$ was associated with an:

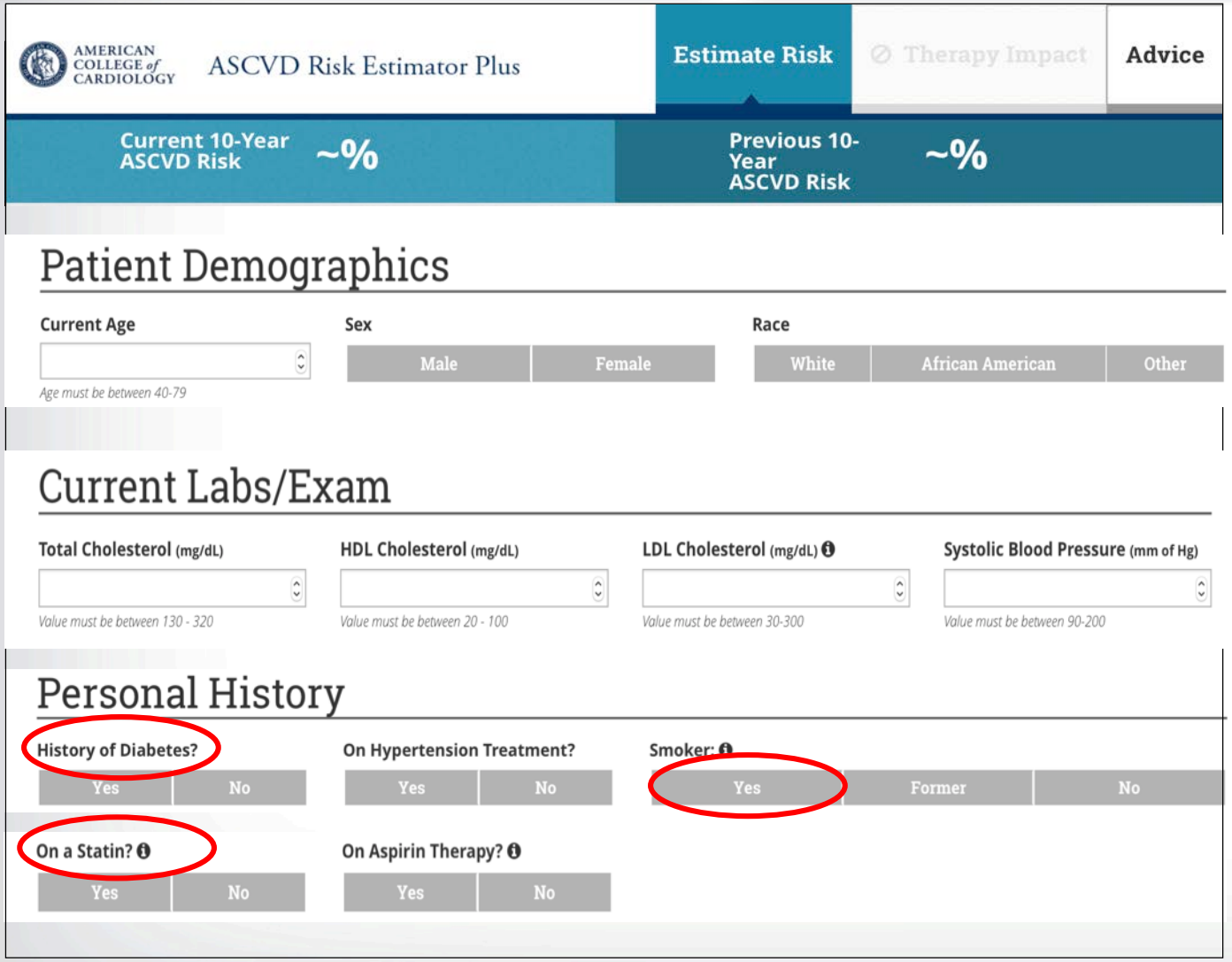
- **11.1% relative increase in odds of significant CAD**
- **14.2% increase in the odds of having had a heart attack during the previous year**

6,575 Ohio residents undergoing elective diagnostic coronary angiography found the same relationship*

*McGuinn LA, et al. *Environ Res* 2016 **Hartiala J, et al. J *Am Heart Assoc* 2016

Air Pollution Worsens Vascular Risk Factors

Risk Factors for Atherosclerosis and Air Quality



http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

Poor Air Quality:

Age – might accelerate aging

Total Cholesterol – increases cholesterol

HDL – decreases HDL particle number

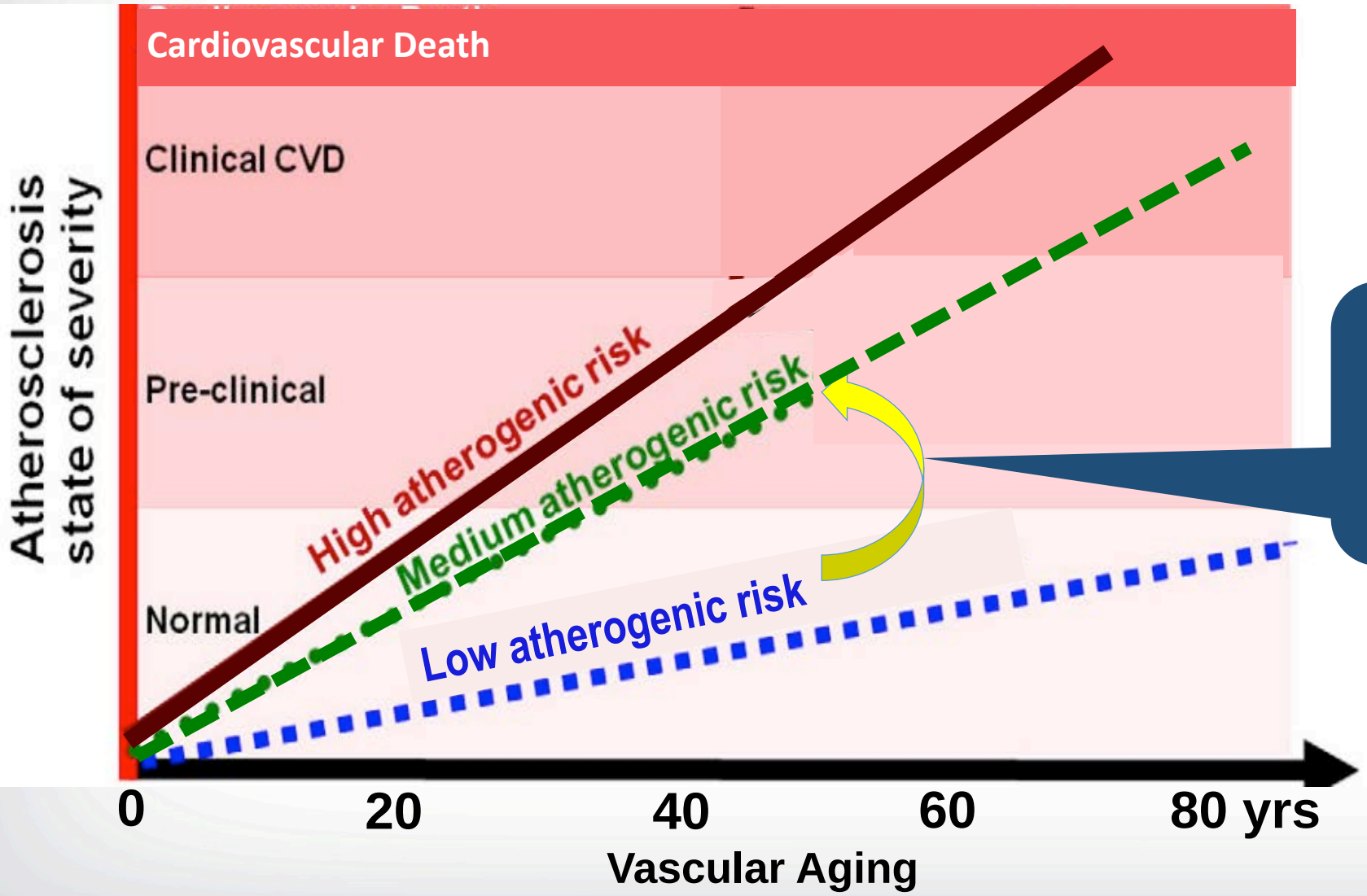
LDL – oxidizes LDL and ox-LDL receptor

Systolic BP – increases blood pressure

Diabetes – associated with type II diabetes

Statin Therapy – might protective

Environmental Toxicant Exposures Can Accelerate the Aging Process

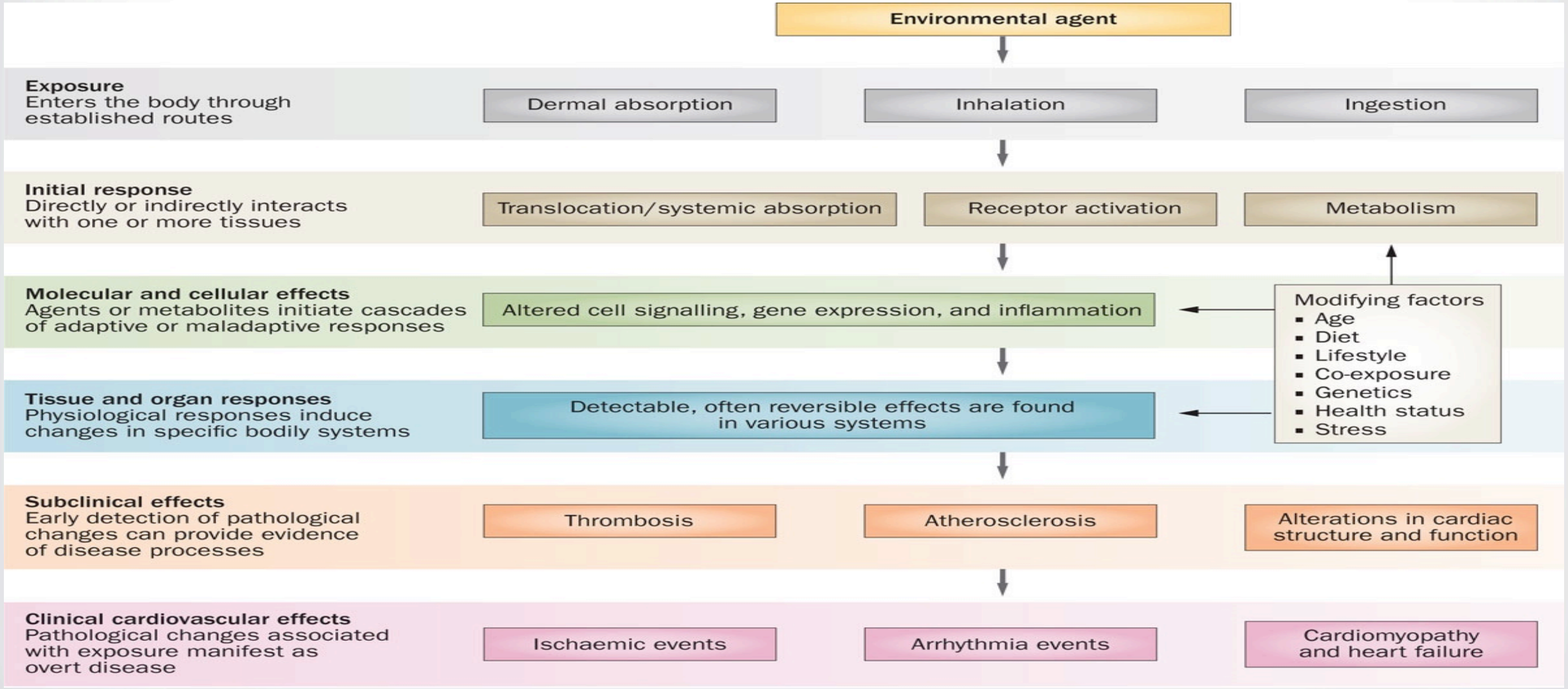


Long-term Health Effects
(Cumulative effects of toxicants)

- **Accelerate aging process**
- **Hasten organ dysfunction**

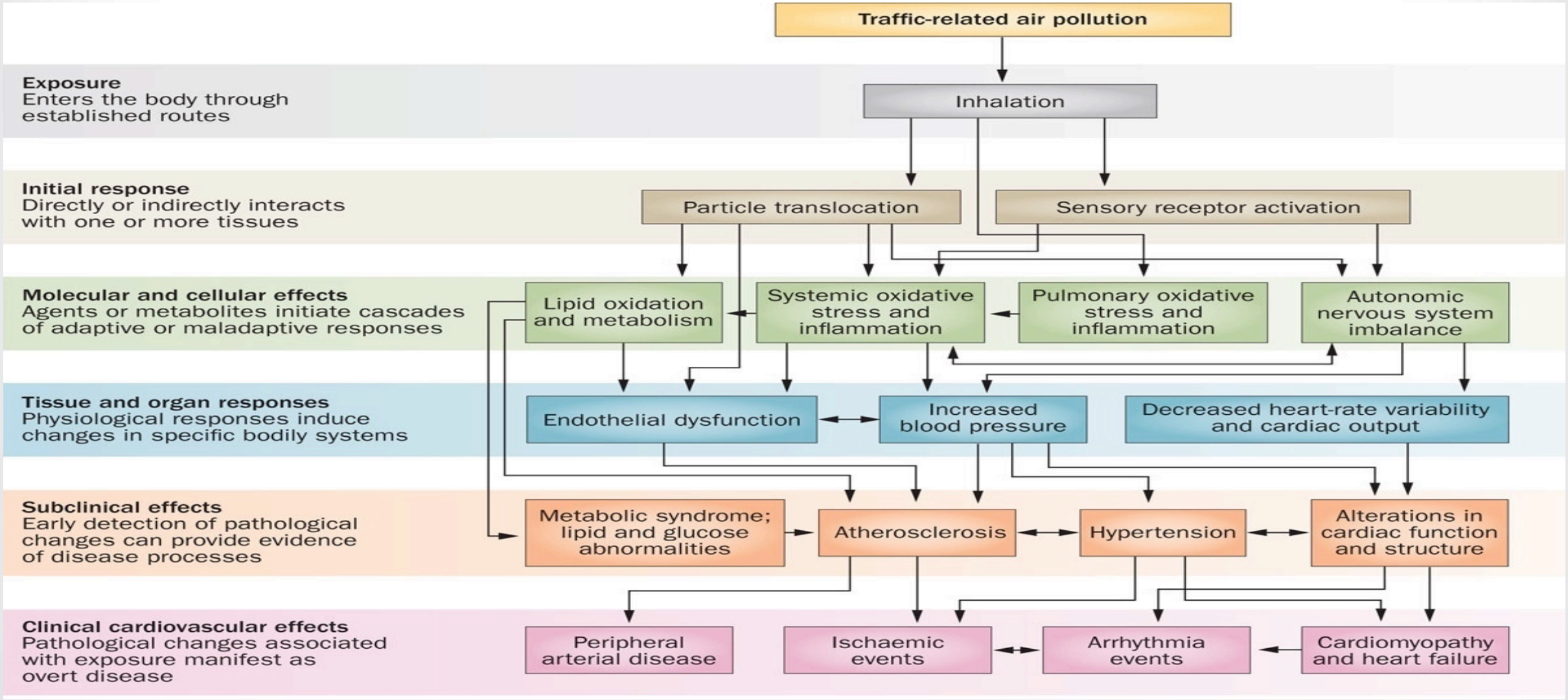
Modified from N. Künzli et al. *Progress in Cardiovascular Diseases* 2011

Framework Describing the Environmental Factors in Cardiovascular Disease



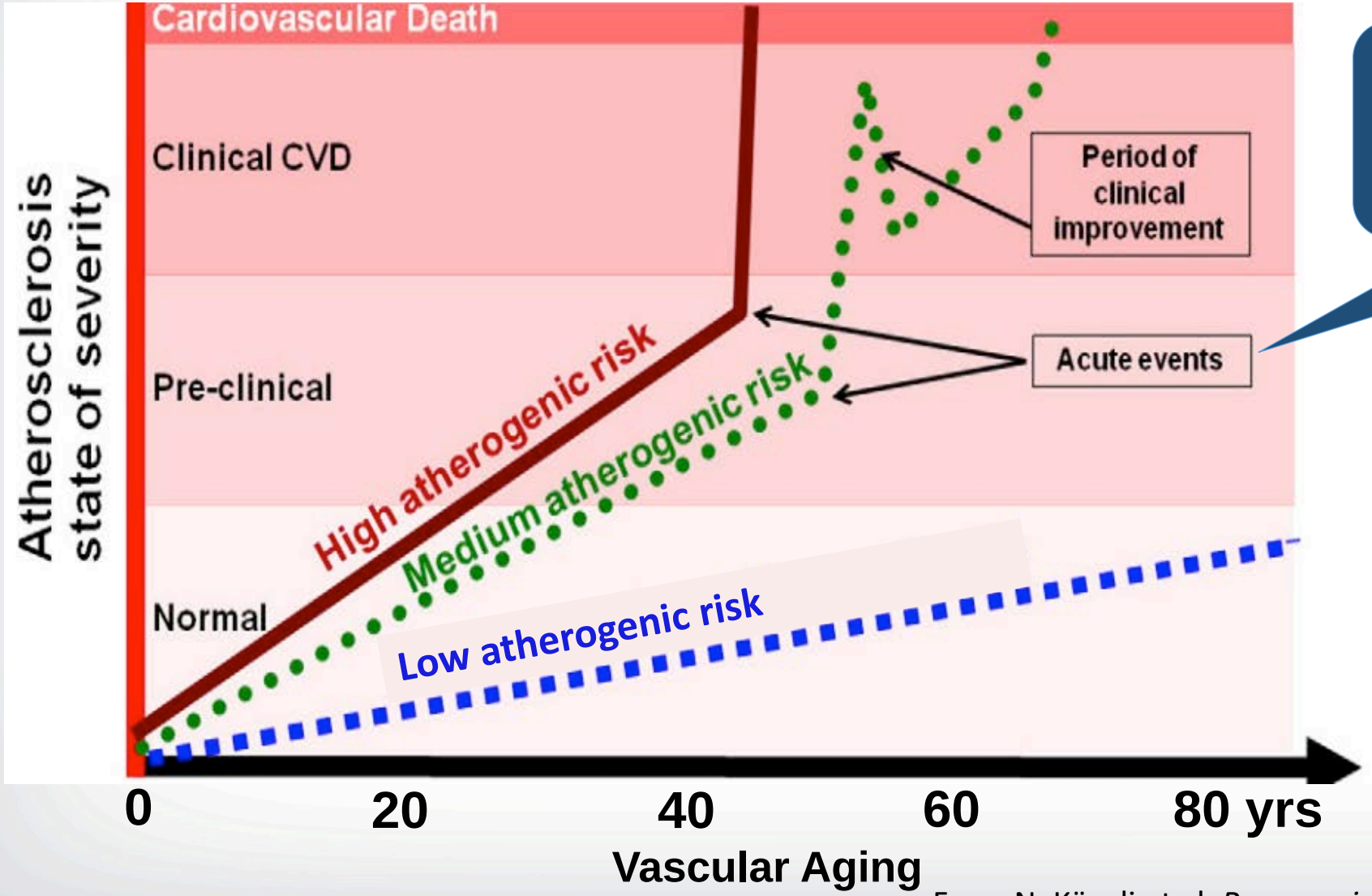
From Cosselman, K. E. *et al. Nat. Rev. Cardiol.* 2015

Cardiovascular Effects of Chronic Exposure to Traffic-Related Air Pollution



From Cosselman, K. E. *et al. Nat. Rev. Cardiol.* 2015

Environmental Toxicant Exposures Can Trigger Clinical Cardiovascular Events

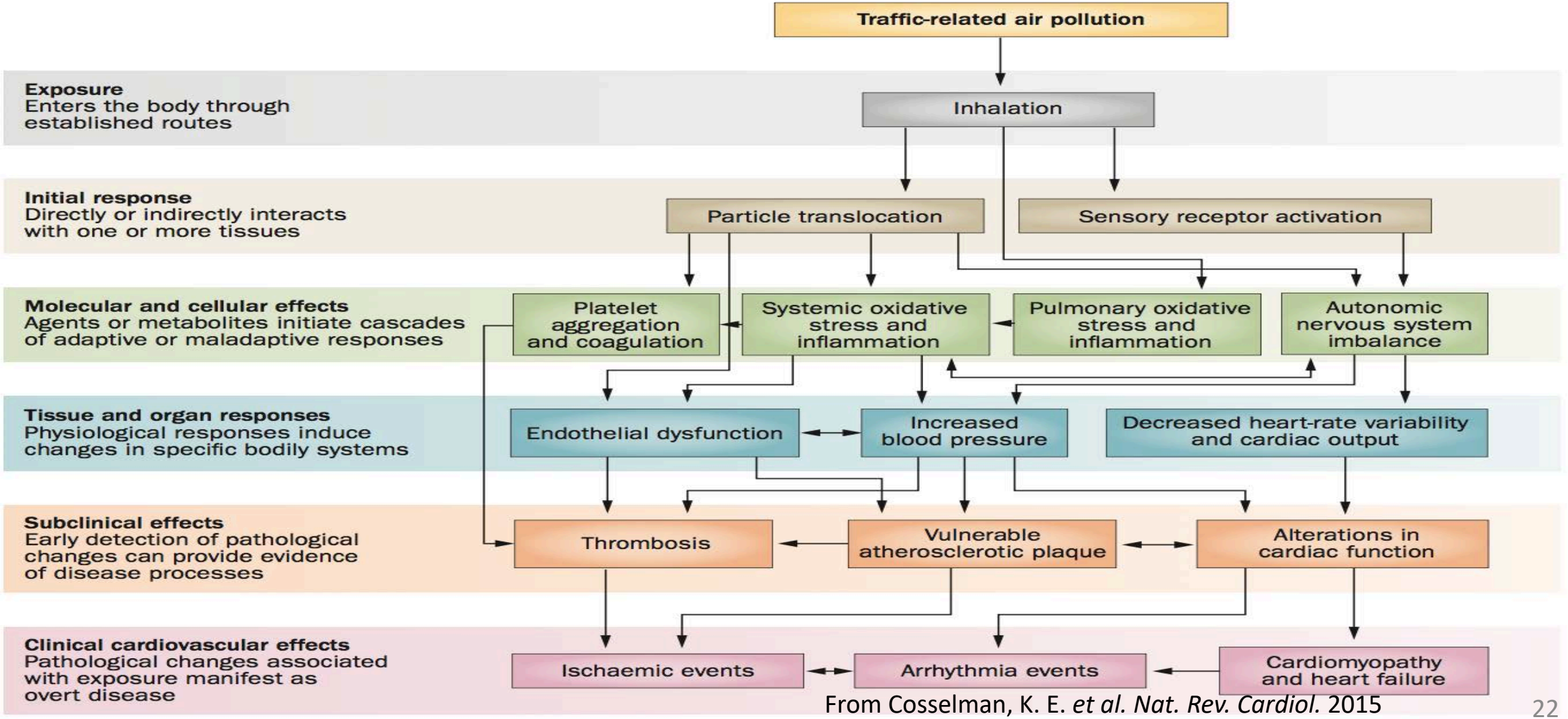


Short-term Health Effects

- Triggering of clinical events
- Precipitate organ dysfunction

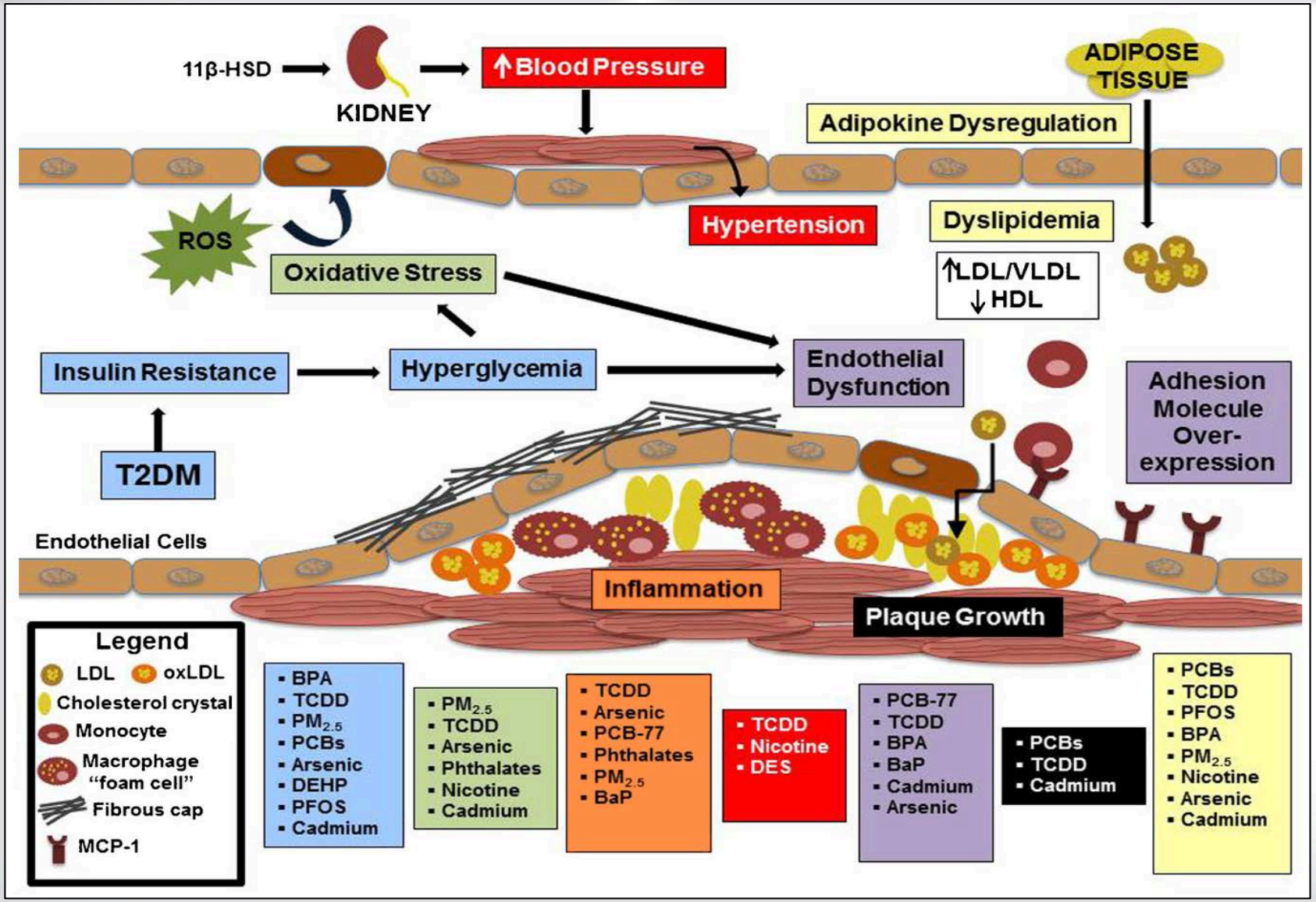
From N. Künzli et al. *Progress in Cardiovascular Diseases* 53: 334, 2011

Cardiovascular Effects of Acute Exposure to Traffic-Related Air Pollution



From Cosselman, K. E. *et al. Nat. Rev. Cardiol.* 2015

Contributions of Environmental Pollutants to Cardiovascular Disease Pathology



Compounds and mechanisms related to the development of vascular disease observed in either:

- ***in vivo*** **exposure studies**
- ***in vitro*** **cellular models**

Curr Diab Rep 14:494, 2014

Thank you

Wayne E. Cascio, MD, FACC
Acting Director, National Health and Environmental Effects Research Laboratory
Office of Research and Development
U.S. Environmental Protection Agency

Email: cascio.wayne@epa.gov

- No conflicts of interest
- The presentation represents the opinions of the speaker and does not necessarily represent the policies of the US EPA