Understanding Obesity Relative to Metabolic Syndrome, Inflammation and Climate Change

Objectives

• Demonstrate the impact of obesity to our future well-being as a global society
• Apply the underlying pathophysiology and epidemiology from both obesity and climate change into a patient centered strategy focusing on health
• Identify potential interactions through inflammation between obesity, metabolic syndrome and climate change

References


Questions

1. Which of the following best represents the interaction between obesity, climate change and cardiovascular risk?
   A. Over 95% of the population in the United States lives in an environment where particulate matter will not have an effect on their CVD risk
   B. Chronic but not short term exposure to fine particulate matter (PM$_{2.5}$) induces an increase cardiovascular risk especially in those with central obesity
   C. A reduction in particulate matter has been shown to reduce cardiovascular mortality only in those with baseline obesity as evidenced by BMI > 30 kg/m$^2$
   D. Ultrafine particles <1 um (PM$_1$) originate mostly from crushing and grinding and do not induce pulmonary oxidative stress, systemic inflammation or an increased CVD risk
   E. Ozone as a single pollutant does not increase CVD risk when corrected for fine particles (PM$_{2.5}$) but ozone does increase the risk for respiratory death
2. An obese patient asks you to explain the interactions between carbohydrates, fats and weight. Which most accurately describes the best response?
   A. Both glucose and fructose are metabolized by almost every tissue and therefore have an equal propensity to be stored as fat
   B. **Fructose but not glucose is metabolized like fat, such that 30% of its calories are converted to fat**
   C. When either glucose or fructose is consumed without soluble fiber it markedly diminishes its ability to be absorbed and thus reduces the risk for lipogenesis
   D. Fructose is acutely metabolized by the brain resulting in stimulation of the hypothalamus to increase appetite
   E. High fructose corn syrup is less sweet than glucose or sucrose and therefore can be taken in greater quantities

3. Which of the following statements has been substantiated a controlled randomized trial?
   A. Eating breakfast versus skipping breakfast is protective against obesity
   B. Breast feeding is protective against obesity in children
   C. Numerous recent trials have conclusively proven that preventing obesity is easier than treating obesity
   **D. Once fitness is accounted for, metabolically healthy but obese individuals have a relatively benign condition with a similar prognosis as metabolically normal weight individuals**
   E. The evidence based trials demonstrated that the vast majority of obesity is a result of lack of willpower
Yet Another Inconvenient Truth
OR
The New Deadly Quartet

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Global Warming
An Inconvenient Truth

• U.N. Intergovernmental Panel on Climate Change (IPCC)
  – 600 scientists from 40 countries

• Concluded for the first time that evidence of the earth’s rising temperature was “unequivocal” & this warming was greater than 90% due to human activity

• Even if all greenhouse-gas emissions ended today, the earth would continue to warm through the rest of the century

IPCC February 2007
10 of the hottest years ever recorded were noted in the past 14 years with 2005 as the hottest year ever and the winter 2013-14 warmest ever in CA

Summer of 2012 recorded as third hottest ever in USA (measured since 1895)

1968 when CO₂ broached 300-320 for the First time in over 50,000 years

Stott BMJ 2006;332:1385
Gillis Science NY Times Jan 21,2104
Another Inconvenient Truth

- Over the past 30-40 years despite advances in coronary artery bypass & percutaneous intervention strategies, advanced therapies for myocardial infarction, unstable angina and heart failure...

as well as age adjusted reductions in total cholesterol, systolic blood pressure, smoking and physical inactivity...

Cardiovascular disease still remains the number one killer of adults in the United States
In Mississippi, obesity in children ages 10-17 years is 44.4%.

No state under 20%.
From 2000-2004 the World Health Organization gathered information about obesity rates in 36 different countries. 29/36 had less obesity than the USA.

...self induced diseases amplify the genetics of atherosclerosis.
Metabolically Healthy Obesity

• Several definitions with most describing a person with high BMI but normal insulin sensitivity and absence of diabetes, dyslipidemia or hypertension (vs absence of metabolic syndrome)

• Estimated prevalence of varies from 20-30% among obese people
ATP III: Components of Metabolic Syndrome

- Abdominal Obesity
- Atherogenic Dyslipidemia (↑TG, ↓ HDL)
- Elevated Blood Pressure
- Insulin Resistance ± glucose intolerance

Need 3 out of 5 criteria

Iacobellis J Clin Lipid 2007;1:599
Twin Epidemics: Parallels in Prevalence Overweight/Obesity and Metabolic Syndrome

Ford JAMA 2002;287:356
Metabolic Syndrome Increases CV Risk

Estimated relative risk

Heterogeneity $P < 0.001$

Combined

McNeill 2005 – W
McNeill 2005 – M

Rutter 2004
Hunt 2004
McNeill 2005 – W
McNeill 2005 – M

Ford 2004
Katzmarzyk 2004
Ridker–high CRP 2003
Satlar 2003
Girman 2004
Ford 2004
Katzmarzyk 2004
Ridker–low CRP 2003
Resnick 2003
Lakka 2002
Onat 2002

W = Women; M = Men

Original ATP III definition
Modified ATP III definition
Differences in Risk with Obesity
(Aerobics Center Longitudinal Study ACLS)

• 42,265 subjects followed from 1979-2003
  – 12,829 (29%) were obese using BF% > 25% (m) and > 30% (w)
  – 46% of these obese metabolically healthy (0-1 risk factors for metabolic syndrome)
• Compared to normal weight, metabolically normal

Ortega Eur Heart J 2013;34:389
Hazard Ratio for CVD and Cancer Using Body Fat %

Ortega Eur Heart J 2013;34:389
Once adjusted for fitness the metabolically healthy obese (BF%) no longer had a higher risk compared to normal BF peers.
Differences in Risk with Obesity

(Aerobics Center Longitudinal Study ACLS)

• A better cardio-respiratory fitness level should be considered a characteristic of the subset of metabolically healthy obese phenotype
  – Once fitness is accounted for, metabolically healthy but obese individuals have a relatively benign condition with a similar prognosis as metabolically normal weight individuals

Ortega Eur Heart J 2013;34:389
Graded Exercise

• 4 groups of sedentary post-menopausal women were enrolled

• Comparison of NIH Consensus Conference levels of exercise:
  – 50% (4kcal/kg) = 72.2 min/wk of exercise
  – 100% (8kcal/kg) = 135.8 min/wk of exercise
  – 150% (12 kcal/kg) = 191.7 min/wk of exercise

• Exercise tolerance improved – not weight

Church et al JAMA 2007;297:2081
Graded Exercise Improves Oxygen Uptake but Not Body Weight

Church et al JAMA 2007;297:2081-2091
Prevalence of Moderate or High Fitness and BMI in Women

Cannot look at someone and determine fitness

Percent at Moderate Fitness

Transition Metabolically Healthy (MHO) to Unhealthy Status (MUO)

- 3052 overweight/obese subjects followed for 10 years
  - 20.8% metabolically healthy (MHO) at baseline
- Half MHO transitioned to MUO over 10 yrs
  - Factors predicting MUO increased waist and/or waist/hip (central obesity) & sedentary
  - Factors predicting continued MHO were healthy diet & exercise

Schroder Eur J Nut 2013
Soriguer J Clin Endo Meta 2013;98:2318
Differences in Risk with Obesity
(Aerobics Center Longitudinal Study ACLS)

Characteristics of metabolically healthy obese phenotype include:

- Lower visceral fat
- Lower inflammatory markers (ie CRP)
- Smaller adipose cell size
- Improved cardio-respiratory fitness

Primeau Int J Obes 2911;35:971
Ortega Eur Heart J 2013;34:389
Walk the Walk

- More than half of patients who were prescribed physical activity were more active a year later
- Maintaining a healthy lifestyle throughout young adulthood is associated with lower CV risk profile in middle age (CARDIA study)

http://www.exrx.net/
http://exerciseismedicine.org/
http://healthyprogress.net/

Dobson BMJ 2008;337:Oct 15
Grandes Arch Int Med 2009;169(7):694
Liu Circ 2012;125:996
Why does CVD remain our number one killer?

Climate Change is the greatest threat to human health in the 21st century

Editorial BMJ
March 2014
Twin Epidemics of Obesity and Global Warming

Two Inconvenient Truths

BMI 25-30
BMI >30

CO₂ Content in Atmosphere

National Center for Chronic Disease Prevention National Center for Health Statistics
Particulate Matter (PM)

- Coarse PM with aerodynamic diameter 2.5-10um ($\text{PM}_{10-2.5}$) from crushing and grinding, depositing in upper tracheo-bronchia
- Fine particles $<$2.5 um ($\text{P}_{2.5}$) originate mostly from combustion can be inhaled deeply into lung alveoli entering pulmonary and possibly systemic circulation
- Ultrafine particles $<$0.1 um ($\text{PM}_{0.1}$) primarily from vehicle emissions translocate from alveoli to systemic circulatory system

*Li Rev Environ Health 2012;27:133*
Air Pollution and Atherosclerosis

• Although both gaseous (eg, ozone) and particulate pollutants are linked, evidence is strongest for particulate matter (PM) as the greater risk for CV disease.
  – Most data to date (hundreds of studies) associate CV risk with PM <2.5 µm (PM$_{2.5}$)
  – Approximate range in US in 2010 = 5-35 µg/m$^3$ with annual mean Environmental Protection Agency standard of 15 µg/m$^3$

_Clearfield Curr Ather Rep 2008;10:273
Brook Curr Athero Reports 2010;12:291_
Fine Particulate Matter vs Ozone and CVD Mortality

- 448,850 subjects followed from 96 metropolitan areas for 18 yrs
  - Long term exposure to fine particulate matter (<2.5 µm) was risk factor for CVD & CV mortality

- Ozone as a single pollutant did not increase CVD when corrected for PM$_{2.5}$ but ozone did increase the risk for respiratory death

Jerrett NEJM 2009;360:1085
Mechanistic Pathways where Particulate Matter (PM) can promote atherosclerosis

Particulate Matter induces pulmonary
Oxidative stress & inflammation

Acute activation
of lung autonomic nervous system (ANS)

Can trigger ACS via Vasoconstriction & plaque instability

Subacute & chronic response with systemic spill-over into circulation

Systemic oxidative stress & inflammation

Activated or inflamed fat ↑ Adipokines (PAI-1, resistin)

Activated liver Acute phase response ↑ clotting factors, Fibrinogen, CRP

Cell inflammation Activated WBC, Platelets, MPO

Increase cytokine Expression IL-6, TNFα

Oxidized lipids & Dysfunctional HDL

Brook Curr Athero Reports 2010;12:291
Acute vs Chronic Exposure

• Short term exposure over a few hours to days increases risk of MI, stroke, HF exacerbation, arrhythmias, SCD
  – Risk approximate 1% increase in acute CV mortality per 10 μg/m³ of PM$_{2.5}$

• Chronic exposure (years) lead to 6-13% increase in total mortality and 10-28% increase in CV mortality per 10 ug/m³ increase in PM$_{2.5}$
  – Suggests cumulative exposure promotes CV risk over years by enhancing progression and vulnerability of atherosclerotic plaque

Beelen Lancet 2014;383:785
Hoek Environ Health 2013;12:43
Brook Circ 2010;121:2331
Sun JAMA 2005;204:3003
Exposure to Air Pollution is Associated with Adverse CV Events

Harvard Six Cities Study (1977-1988)

Characteristics of the Study Population and Mean Air-Pollution Levels in Six Cities

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PORTAGE, Wis.</th>
<th>TOPEKA, KANS.</th>
<th>WATERTOWN, MASS.</th>
<th>HARRIMAN, TENN.</th>
<th>ST. LOUIS</th>
<th>STEUBENVILLE, OHIO</th>
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</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>1,631</td>
<td>1,239</td>
<td>1,336</td>
<td>1,258</td>
<td>1,296</td>
<td>1,351</td>
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<tr>
<td>Person-years of follow-up</td>
<td>21,618</td>
<td>16,111</td>
<td>19,882</td>
<td>17,836</td>
<td>17,715</td>
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<td>No. of deaths</td>
<td>232</td>
<td>156</td>
<td>248</td>
<td>222</td>
<td>281</td>
<td>291</td>
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<td>Deaths/1000 person-years</td>
<td>10.73</td>
<td>9.68</td>
<td>12.47</td>
<td>12.45</td>
<td>15.86</td>
<td>16.24</td>
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<tr>
<td>Female sex (%)</td>
<td>52</td>
<td>56</td>
<td>56</td>
<td>54</td>
<td>55</td>
<td>56</td>
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<tr>
<td>Smokers (%)</td>
<td>36</td>
<td>33</td>
<td>40</td>
<td>37</td>
<td>35</td>
<td>35</td>
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<tr>
<td>Former smokers (%)</td>
<td>24</td>
<td>25</td>
<td>25</td>
<td>21</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Average pack-years of smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current smokers</td>
<td>24.0</td>
<td>25.6</td>
<td>25.2</td>
<td>24.5</td>
<td>30.9</td>
<td>28.0</td>
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<tr>
<td>Former smokers</td>
<td>18.0</td>
<td>19.7</td>
<td>21.8</td>
<td>21.1</td>
<td>22.0</td>
<td>25.0</td>
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<tr>
<td>Less than high-school education (%)</td>
<td>25</td>
<td>12</td>
<td>22</td>
<td>35</td>
<td>45</td>
<td>30</td>
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<tr>
<td>Average age (yr)</td>
<td>48.4</td>
<td>48.3</td>
<td>48.5</td>
<td>49.4</td>
<td>51.8</td>
<td>51.6</td>
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<tr>
<td>Average body-mass index</td>
<td>26.3</td>
<td>25.3</td>
<td>25.5</td>
<td>25.1</td>
<td>26.0</td>
<td>26.4</td>
</tr>
<tr>
<td>Job exposure to dust or fumes (%)</td>
<td>53</td>
<td>28</td>
<td>38</td>
<td>50</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td>Total particles (μg/m³)</td>
<td>34.1</td>
<td>56.6</td>
<td>49.2</td>
<td>49.4</td>
<td>72.5</td>
<td>89.9</td>
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<tr>
<td>Inhalable particles (μg/m³)</td>
<td>18.2</td>
<td>26.4</td>
<td>24.2</td>
<td>32.5</td>
<td>31.4</td>
<td>46.5</td>
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<tr>
<td>Fine particles (μg/m³)</td>
<td>11.0</td>
<td>12.5</td>
<td>14.9</td>
<td>20.8</td>
<td>19.0</td>
<td>29.6</td>
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<tr>
<td>Sulfate particles (μg/m³)</td>
<td>5.3</td>
<td>4.8</td>
<td>6.5</td>
<td>8.1</td>
<td>8.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Aerosol acidity (nmol/m³)</td>
<td>10.5</td>
<td>11.6</td>
<td>20.3</td>
<td>36.1</td>
<td>10.3</td>
<td>25.2</td>
</tr>
<tr>
<td>Sulfur dioxide (ppb)</td>
<td>4.2</td>
<td>1.6</td>
<td>9.3</td>
<td>4.8</td>
<td>14.1</td>
<td>24.0</td>
</tr>
<tr>
<td>Nitrogen dioxide (ppb)</td>
<td>6.1</td>
<td>10.6</td>
<td>18.1</td>
<td>14.1</td>
<td>19.7</td>
<td>21.9</td>
</tr>
<tr>
<td>Ozone (ppb)</td>
<td>28.0</td>
<td>27.6</td>
<td>19.7</td>
<td>20.7</td>
<td>20.9</td>
<td>22.3</td>
</tr>
</tbody>
</table>

*Air-pollution values were measured in the following years: total particles, sulfur dioxide, nitrogen dioxide, and ozone, 1977 through 1985; inhalable and fine particles, 1979 through 1985; sulfate particles, 1979 through 1984; and aerosol acidity, 1985 through 1988.

Exposure to Air Pollution is Associated with Adverse CV Events

*Harvard Six Cities Study*


Characteristics of the Study Population and Mean Air-Pollution Levels in Six Cities

1/3 of US population live in areas with unhealthy levels of air quality

Or >100 million US citizens live in areas with unhealthful levels of particulate pollution.

And >200 million are currently overweight or obese


Sun JAMA 2005;294:3003
Sun Inhal Toxicol 2008;20:127
30-40 Year Trends

• In 1982 AHA, AMA and USDA recommended to decrease fat intake from 40% to 30% of calories.

• We succeeded in doing this but the result was our weight going up by 25 pounds.

http://www.usda.gov/trpp#ENR%20V11N3fenrv11nJp44.PDF
Lustig Nature 2012;482:27
The Plan to Sell Product

55 mg sodium per can Coke + caffeine (mild stimulant & diuretic) increases free water clearance thus the increased sodium and the decrease in water causes increased thirst.

The increased salt is masked by sugar to allow us to take in more

http://www.usda.gov/trpp#ENR%20V11N3fenrv11nJp44.PDF
Lustig Nature 2012;482:27
Glucose Metabolism

• Example of how glucose metabolized ie 120 calories (2 slices of white bread)
  – 80% glucose used by every cell for energy
    • 20% or 24 calories to liver
  – Most of glucose to the liver stored as glycogen
    • Glycogen will not injure the liver since it is non-toxic form of glucose storage
    • Only about 1 calorie from the original 120 calories used for VLDL production

Lustig Nature 2012;482:27
Sucrose Metabolism

120 calories (glass of OJ) from sucrose (half glucose & half fructose)

- The 60 calories from glucose
  - 12 to liver and 48 to body
- All 60 calories from fructose to liver
  - only liver can metabolize fructose
  - fructose is not metabolized by the brain so has no acute symptoms
- The liver must metabolize 72 calories
  - 5x calories from glucose alone

Choi BMJ 2008;334:300
Feig JAMA 2006;300:924
Nguyen J Peds 2009
Fructose is not Glucose

• Fructose increases the calorie load to liver resulting in denovo lipogenesis (↑TG)
  – Fructose blocks leptin signaling to the brain (brain doesn’t recognize you ate something)
  – Fructose also does not suppress gherlin (hunger hormone)
• All of which tricks the brain in wanting to eat more (to increase energy substrate) and exercise less (to preserve energy)

Low Fat Diet Myth

• The typical low fat diet isn’t really low fat if it is substituting fructose for fat
• Fructose although a carbohydrate is metabolized like fat, such that 30% calories converted to fat
• That is why many low fat diets do not work

Parks J Nutr 2004;134: 1333
Schwarz Diabetes 2005;54:1907
High Fructose Corn Syrup

- HFCS is main component of soft drinks because it’s 20% sweeter than regular table sugar (*sucrose*)
  - HFCS is also cheaper
  - Current US consumption of HFCS = 63 lbs per person/yr
- HFCS is 42-55% fructose + glucose
- HFCS is essentially equivalent to sucrose which is 50% fructose connected to glucose by an ether linkage

*Collino World J Diab 2011;2(6):77*
Fructose Increasing in American Diet

▲Consumption fruits & vegetables decreased from 24 g in 1978 to 15 g/d today
And fiber reduced from 100g to 15g

Why is this trend related to obesity?

Bray Am J Clin Nut 2007
J Clin Investigation 2010
When a calorie is not a calorie

When you sit down to a meal, your brain is looking for nutrients, not calories and will prod you to eat until satisfied. That’s why it is harder to push away fries or ice cream than vegetables or fruits.

<table>
<thead>
<tr>
<th>Additional lb/drink/d</th>
<th>Additional lb/day</th>
<th>Smoker-related lb</th>
<th>Former smoker-related lb</th>
<th>Sleep (&lt;6 or &gt;8 hrs)</th>
<th>Sleep-related lb</th>
<th>Watch TV-related lb</th>
<th>Physical activity-related lb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alchohol</td>
<td>0.41</td>
<td>5.17</td>
<td>0.14</td>
<td>0.31</td>
<td>-0.31</td>
<td>0.31</td>
<td>-1.76</td>
</tr>
</tbody>
</table>

Mozaffarian NEJM 2011;364:2392
Changes in Diet and Lifestyle

Nuts versus French Fries

**NUTS**
- Take longer to chew
- Contain fat and fiber that take longer to digest
- Your stomach stays fuller, and you feel satisfied longer
- **SO YOU EAT LESS AT YOUR NEXT MEAL**

Net loss of 0.57 pounds

**FRENCH FRIES**
- Cooked starch is quickly broken down
- Causes spike in glucose and insulin secretion leading to hunger
- **SO YOU EAT MORE AT YOUR NEXT MEAL**

Net gain of 3.35 pounds

Mozaffarian NEJM 2011;364:2392
However, the start of a vicious cycle

**Ingredients in Similac Isomil Formula for infants**

- 43.2% Corn syrup solids
- 14.6% soy product isolate
- 11.5% high oleic acid safflower oil
- 10.3% sucrose (sugar)
- 8.4% soy oil
- 8.1% coconut oil

Kim Obesity 2006;15:1107
The start of a vicious cycle

The earlier you expose a child to sweets the more they crave it later.

The more sugar a pregnant women eats the more gets across the placenta causing developmental programming which can change a newborns adiposity before birth.

1. Kim Obesity 2006;15:1107
Obesity Myths or Unproven Propositions Assumed as Fact

- Obesity is just a function of lack of willpower
- Preventing obesity is easier than treating obesity
- Regular eating vs skipping breakfast is protective against obesity
- Snacking contributes to weight gain and obesity
- Breast feeding is protective against obesity

Casazza NEJM 2013;368:446
Obesity, Diet, Climate Change and Cardiovascular Disease

Tying These Concepts Together
Obesity and Global Warming

Energy as Common Denominator

- **Obesity** = excess energy intake over expenditure
  - Overnutrition, inactivity → “metaflammation”

**Metaflammation** = immune system reacts at a lower level to pro-inflammatory environmental inducers (inflammation caused by spillover fat, inactivity and environmental factors) than to acute injury or microbes for which it had no time to adapt

**Metaflammation is to chronic disease what inflammation is to acute disease (injury or infection)**
Obesity and Global Warming

Energy as Common Denominator

- Environment = excess carbon from energy sources over the capacity of environmental sinks (oceans, soil, plants) to absorb carbon
  - Industrial waste, pollution → “ecoflammation”

Ecoflammation is a result of the post-industrial environment driven by exponential economic growth particularly increase fossil fuels since 70s worldwide

Egger MJA 2010;193:635
Epidemiologic Transition

- Epidemiologic transition is when the incidence of chronic disease surpasses that of infectious diseases as the major cause of human mortality.

*Frenk Health Policy Plan 1989;4:29*
We have arrived

- In September 2011 the U.N. declared that for the first time in human history, chronic non-communicable diseases such as heart disease, cancer and diabetes pose a greater health burden worldwide than do infectious diseases, contributing to 35 million deaths annually.
- Today, worldwide, there are 30% more people who are *obese* than are undernourished.

*Lustig Nature 2012;482:27*
State of the Air 2014

• In USA air quality improved from a decade ago but 132 million (42%) Americans still live in communities where air pollution levels too high
  – 25 million live in counties with all three air pollutants (ozone, short and long term PM$_{2.5}$) too high

• Since 1970 population increased 52%
  – Vehicle miles traveled increased 167%

American Lung Association 2014
Ozone pollution is smog, which is a highly irritating, but invisible gas.

Year-round particle pollution is the average level of microscopic bits of solids and aerosols in the air.

Short-term particle pollution are days with spikes in those bits of pollution.

Sources of pollution:
- Paint
- Factory
- Trucks
- Cars
- Fire
# Most Air Polluted Cities USA

## State of the Air 2014

<table>
<thead>
<tr>
<th>Ozone</th>
<th>Year Round PM $\text{PM}_{2.5}$</th>
<th>Short Term PM $\text{PM}_{2.5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Los Angeles CA</td>
<td>Fresno CA</td>
<td>Fresno CA</td>
</tr>
<tr>
<td>2. Visalia-Porterville CA</td>
<td>Visalia CA</td>
<td>Visalia CA</td>
</tr>
<tr>
<td>3. Bakersfield CA</td>
<td>Bakersfield CA</td>
<td>Bakersville CA</td>
</tr>
<tr>
<td>4. Fresno CA</td>
<td>Los Angeles CA</td>
<td>Los Angeles CA</td>
</tr>
<tr>
<td>5. Sacramento CA</td>
<td>Modesto CA</td>
<td>Modesto CA</td>
</tr>
<tr>
<td>6. Houston TX</td>
<td>Pittsburgh PA</td>
<td>Pittsburgh PA</td>
</tr>
<tr>
<td>7. Modesto CA</td>
<td>El Centro CA</td>
<td>Fairbanks AK</td>
</tr>
<tr>
<td>8. Washington/Baltimore</td>
<td>El Paso TX</td>
<td>Salt Lake City UT</td>
</tr>
<tr>
<td>9. Dallas / Fort Worth TX</td>
<td>St Louis MO</td>
<td>El Paso TX</td>
</tr>
<tr>
<td>10. Las Vegas NV</td>
<td>Phoenix AZ</td>
<td>San Jose CA</td>
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<tr>
<td>11. Phoenix AZ</td>
<td>Cincinnati OH</td>
<td>Logan UT</td>
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<tr>
<td>12. New York NY</td>
<td>Philadelphia PA</td>
<td>Missoula MT</td>
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<td>13. St Louis MO</td>
<td>New York NY</td>
<td>Davenport IA</td>
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<td>14. Tulsa OK</td>
<td>Louisville KY</td>
<td>Chicago ILL</td>
</tr>
<tr>
<td>15. Cincinnati OH</td>
<td>Macon GA</td>
<td>Phoenix AZ</td>
</tr>
</tbody>
</table>
Obesity Trends* Among U.S. Adults & 2014 Most Polluted Cities With Life Expectancy from Birth

**Triple Whammy**

- Obesity > 30% Plus
- Most air polluted cities plus
- Decreased life expectancy

80-81.3 yrs
78.4-80 yrs
77.2-78.4 yrs
75-77.2 yrs
Summary

• All calories are not the same
• All obesity is not the same
• All air pollutants are not the same
• And yet CVD remains #1 killer

So what can we do?
Relative Increase in Hepatic Fat with High-Fructose Diet

Bremer Peds 2012;129:1-14
CONCLUSIONS: Fructose and Energy Balance Study

Regardless of the Order of Feeding, a Week of Complex CHO vs. of a Week High Fructose Diet:

Hepatic DNL is Consistently Higher

Postprandial Triglycerides are Higher

Liver Fat Content is Higher and Suppression of Glucose Production is Blunted

The Features of Long Term Fructose Feeding are Detectable and Reversible after a Week of Feeding

Bremer Peds 2012;129:1-14
AOA Resolution 435-A

- At the 2011 AOA House of Delegates, House Resolution 435-A was approved to have all DOs address the obesity epidemic in their practices.
Bringing this Full Circle
What we potentially can DO

- The CIRT and CANTOS trials are investigating the concept of reducing CV events by decreasing inflammation independent of lipid lowering.

Ridker Circ 2012;126:2739
Everett Am Heart J 2013;166:199
How to lower Inflammation

**Best Results**
- Exercise & weight loss
- Statins
- **Anti-inflammatory meds**
- Mixed results
  - Alcohol in low amounts
  - Multivitamins
  - Omega 3 fatty acids
  - Fibrates
  - Niacin
  - PPAR gamma (TZD)
  - Clopidogrel, abciximab,
  - CCB and nitrates
  - ARB

**No CRP Effect** (*neutral effect*)
- Aspirin ±
- COX-1 and 2
- Ezetimibe (monotherapy)
- Stanol ester ± (monotherapy)
- *Both ezetimibe and stanols may ↓ CRP when added to statin*

*Anti-inflammatory Meds*
- Methotrexate
- TNFα inhibitor
- IL-6 inhibitor
- IL-18 inhibitor
# Anti-Inflammatory Meds & CRP

<table>
<thead>
<tr>
<th></th>
<th>Statin</th>
<th>MTX</th>
<th>Infliximab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Tocilizumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Canakinumab&lt;sup&gt;3&lt;/sup&gt;</th>
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<tr>
<td>TC</td>
<td>↓↓</td>
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<td>LDL</td>
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<td>HDL</td>
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<td>CRP</td>
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1. TNFα inhibitor  
2. IL-6 inhibitor  
3. IL-16 inhibitor
Methotrexate Effects in Obesity

• Methotrexate lowered adipose tissue inflammatory markers (↓ TNF, IL-6, leptin)
  • Also reduced macrophage infiltration and inflammation

• Methotrexate increased anti-inflammatory adipokines (adiponectin, IL-10)

Thomaz Pharm Res 2009;60:341
Deoliveira Mol Cell Endo 2012;
## LDM and CVD: Observational Evidence

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR* (95 % CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
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<tbody>
<tr>
<td>Wichita</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
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<tr>
<td></td>
<td></td>
<td>0.3 (0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.3 – 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
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<tr>
<td>Netherlands</td>
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<td>van Helm 2006</td>
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<td>Miami VA</td>
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<td>Pradanovich 2005</td>
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<td>CORRONA</td>
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<td>QUEST-RA</td>
<td>RA</td>
<td>0.85 (0.8 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
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<td>Narango 2008</td>
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<td>0.82 (0.7 – 0.9)</td>
<td>MI</td>
<td>LDM</td>
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<td>0.89 (0.8 - 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
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</tbody>
</table>

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Meta-analysis showed low dose MTX Associated with 21% lower risk for total CVD and 18% lower risk for MI

Micha AJC 2011;108:1362
Cardiovascular Inflammation Reduction Trial

CIRT

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
DM or Metabolic Syndrome

Open Label Active Run-In
LDM 5-15 mg/wk

Randomized
LDM 15-20 mg/wk +
1 mg folate

Randomized
Placebo mg/wk +
1 mg folate

N = 3,500

25% RRR,
3.0 year median f/u

Nonfatal MI, Nonfatal Stroke, Cardiovascular Death
What can we DO
Cardiac Autonomic Activity and Obesity with Metabolic Syndrome

• Visceral obesity more than total fat mass correlates with muscle sympathetic nerve activity
• Increased Low Frequency (LF) to High Frequency (HF) ratio which is an index of sympatho-vagal balance noted in obese compared to lean pts
• Low heart rate variability, sympathetic overactivity and/or reduced parasympathetic activity, related to metabolic syndrome represents a state of low grade inflammation (ARIC)

Alvarez Circ 2002;106:2533
Muscelli J Clin Endo Metab 1998;83:2084
Liao Diab Care 1998;21:2116
What can we DO: Part 2
Manipulative Techniques and Sympathetic Activity

• Chiropractic thoracic spine thrust at T3-4 did **not** result in a decrease of sympathetic activity in 100 patients with chronic neck pain

• However, an osteopathic intervention with rib raising decreased salivary alpha-amylase (a marker of hypothalmus-pituitary-adrenal activity)
  – The reduction in amylase suggested a decrease in sympathetic activity

*Sillevis J  Man Manip Ther  2010;18:181
Van Stegeren Phychoneuroendo 2006;31:137
Henderson JAOA 2010;110:324
OSTEOPATHIC Trial

- The OSTEOPATHIC trial evaluated osteopathic manual treatment and ultrasound therapy in 455 patients with low back pain.
  - A subgroup from the OSTEOPATHIC trial demonstrated the inflammatory marker, TNF-α, was significantly reduced when measured one month after last OMT treatment.
  - Other cytokines (IL-1β, IL-6, IL-8, IL-10) did not show any significant improvement from the manipulative therapy.

OMT and Cytokines

- 2 studies of healthy subjects (20 & 33 subjects) half treated with OMT (7 minute protocol) or sham
  - 40 different cytokines evaluated immediately after OMT (30 & 60 minutes)
  - Baseline CRP 2.5-3.0 mg/L not changed after OMT
  - TNFα also not significantly changed

- CRP usually elevates within 4 hours of stimuli such that lack of earlier response not unexpected

Walkowski PLOSone 2014;9:e90132
The premise of the Reducing Inflammation with Osteopathic Treatment (RIOT) trial will determine whether OMT will blunt changes in serum inflammatory cytokines and adipokines, as well as heart rate variability in asymptomatic subjects with a CRP > 2 mg/L who are also obese or have the metabolic syndrome.
Environmental and Lifestyle Inducers of Metaflammation

Egger Obesity Rev 2009'9:459