The New Deadly Quartet for CVD: Obesity, Metabolic Syndrome, Climate Change and Inflammation or Another Inconvenient Truth

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Objectives

• Explore the possible reasons why cardiovascular diseases remain the number one cause of mortality in this nation and globally

• Appreciate the significance of obesity and its ramifications to our future well-being

• Understand potential interaction between obesity, metabolic syndrome, climate change/air pollution with subclinical inflammation as a possible Syndemic

• Grasp how we, as health care professionals, can make a difference
How about expanding to CVD?

From 1980 to 2014, CVD mortality decreased from 507/100,000 in 1980 to 253/100,000 in 2014 (50.2% decrease).

Had rate of CVD Death not fallen since 1968 estimated that 1.7m CVD deaths would have occurred in 2014 if the trend had continued.

Instead the actual CVD death rate in 2014 was 846,000 therefore an equal number CVD deaths were averted in 2014.

Roth JAMA 2017;317:1976
A 54 year old white female presents with fatigue

- The patient has been fatigued for several months and also has noted some dyspnea when she climbs one flight of stairs
  - Denies chest pain
  - Occasional nausea noted with or without epigastric discomfort treated with prn OTC meds (H2 blocker or proton pump inhibitor)
  - These symptoms have been progressive over the past month
CVD Risk Factors
54 year old white female

• No history of HBP, DM, hyperlipidemia, or CHD
• **Smokes** ½ to 1 pack cigarettes since age 20
• Menopause 2-3 yrs ago, not on HRT
• **Family history**: Father MI age 50, diabetic
  Mother type 2 DM
• Vital signs: Height 5’2”, weight 170 lbs,
  BMI 31 kg/m², waist 38”, BP 136/82, pulse 86
• TC 192 mg/dl, LDL 110, HDL 38, TG 220
• FBG 115 mg/dl, ABI 146/136 (1.07)
54 year old white female, smoker, BP 136/82, with LDL 110 & HDL 38 mg/dl

10 year risk = 9.9% AA vs 7.0% WH

<table>
<thead>
<tr>
<th>Your 10 year ASCVD Risk (female)</th>
<th>9.9% (AA)</th>
<th>7.0% (WH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 y risk for someone your age with optimal risk factors</td>
<td>1.6% (AA)</td>
<td>1.2% (WH)</td>
</tr>
<tr>
<td>Your Lifetime ASCVD Risk</td>
<td>39% (AA)</td>
<td>39% (WH)</td>
</tr>
<tr>
<td>Lifetime risk for someone age 54 with optimal risk factors</td>
<td>8% (AA)</td>
<td>8% (WH)</td>
</tr>
</tbody>
</table>

[Graph showing percentages: 45.00%, 40.00%, 35.00%, 30.00%, 25.00%, 20.00%, 15.00%, 10.00%, 5.00%, 0.00%]

http://my.americanheart.org/cvriskcalculator
The patient is started on TLC diet and a stress test is performed

- The patient is able to reach 85% maximal heart rate for her age after 6 minutes on a modified Bruce protocol, the test is stopped due to SOB & fatigue but no chest pain
- At maximum exertion the patient exhibits 0.4 mm ST segment elevation in the inferior leads. Myocardial perfusion imaging also reveals equivocal inferior wall ischemia
A heart catheterization is performed

- The heart catheterization reveals a normal ejection fraction with no focal wall abnormalities
- Coronary arteriography reveals no significant obstruction with symmetrically smallish arteries
- The test is interpreted as negative for significant coronary disease
- The patient is returned to your care

What do you recommend?
10 Year CV Risk < 7.5% (9.9% AA vs 7.0% WH)

Subjects 21-75 years with LDL 70-189 but w/o ASCVD or DM
- Estimated 10 year risk in those 40-75 yrs < 7.5%

Probable Lower Risk
Assess 30 year or lifetime risk in those 21-59 years

Lifetime Risk
39%

10 year risk 5%-7.5%
OR
Lifetime risk ≥ 40% for anyone aged 21-59 years

- In selected individuals consider additional risk factors for decision to treat

Goff J Am Coll Cardiol 2014 July 1;63:2935-59
http://myamericanheart.org/cvriskcalculator
Additional Risk Factors

10 Year < 7.5%
Lower risk

Lifetime risk for those
21-59 years ≥ 40% (39%)
Or if 21-75 yrs plus other
Risk Factor
• LDL 160-189 110
• + Family hx
• CRP ≥ 2 mg/L 5.0
• ABI < .9 1.07
• CAC ≥ 300 Agatstan

Negative Catheterization
Consider moderate
dose statin

Goff J Am Coll Cardiol 2014 July 1;63:2935-59
http://myamericanheart.org/cvriskcalculator
30 Year Lipid Trends from NHANES (1976-2006)

**LDL < 100**
- NHANES II 1976-1980: 17%
- NHANES III 1988-1994: 23%
- NHANES IV 1999-2006: 31%

**HDL > 40**
- NHANES II 1976-1980: 82%
- NHANES III 1988-1994: 79%
- NHANES IV 1999-2006: 77%

**TG < 200**
- NHANES II 1976-1980: 86%
- NHANES III 1988-1994: 86%
- NHANES IV 1999-2006: 82%

**BMI**
- NHANES II 1976-1980: 25.5
- NHANES IV 1999-2006: 28.7

Cohen AJC 2010;106:969

NHANES II 1976-1980
NHANES IV (1999-2006)
All Obesity is NOT the same

A pound is not a pound
and a BMI is not a BMI

Metabolically Healthy Obesity (MHO)

• Several definitions with most describing a person with high BMI but normal insulin sensitivity
  – Many definitions allow some metabolic risk
• Estimated prevalence varies from 20-30% among obese people

Boonchaya Curr Athero Rep 2014;16:441
Hinnouho Diab Care 2013;36:2294
Characteristics of MHO

- High total fat mass (BMI)
- Low visceral fat
- Low or normal TG
- High or normal HDL
- Low inflammatory markers (ie CRP)
- And no evidence of the metabolic syndrome
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 waist/hip
  - Factors predicting continued MHO were healthy diet & exercise

Soriguer J Clin Endo Meta 2013;98:2318
DXA images are of two adults with the same BMI.
The Flip Side: Normal Weight Central Obesity

- 15,184 NHANES III subjects followed 14.3 yrs
- Persons with normal weight (BMI < 25) but central obesity had worst long term survival
- A man with BMI 22 and central obesity (W/H >1.0) had risk 1.87x compared to same BMI but no central obesity (W/H < .9)

Sahakyan Ann Int Med 2015;163:827
Central obesity (waist circumference) +

Plus two of the following factors:

- TG > 1.7 mmol/L (150 mg/dl)
- HDL-C < 1.03 mmol/L (40 mg/dl) men
- HDL-C < 1.3 mmol/L (50 mg/dl) women
- BP > 130/85 or treatment for hypertension
- FPG > 5.6 mmol/L (100 mg/dl)
## Updated Waist Circumference Criteria for Different Ethnic Groups

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATP III, AHA/ACC</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 102 cm, 40 inches</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 88 cm, 35 inches</td>
</tr>
<tr>
<td><strong>IDF: European, USA, Canada Middle East, Sub-Saharan Africa</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 94 cm, 37 inches</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80 cm, 31 inches</td>
</tr>
<tr>
<td><strong>South Asian, Japanese, Chinese, Ethnic Central &amp; South American</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>≥ 90 cm, 35 inches</td>
</tr>
<tr>
<td>Women</td>
<td>≥ 80 cm, 31 inches</td>
</tr>
</tbody>
</table>

*Genest Can J Cardiol 2009;25:567*  
*Alberti Lancet 2005;366:1059*
Metabolic Syndrome Increases CV Risk


Original ATP III definition
Modified ATP III definition
W = Women; M = Men

Estimated relative risk

Heterogeneity P < 0.001

Combined

1.74
Prevalence Metabolic Syndrome in Adults in USA

• NHANES 2003-2012 demonstrated the prevalence of metabolic syndrome is 35% in all adults and 50% in those aged > 60 yrs

• Those with 4 or 5 risk factors for metabolic syndrome had higher risk than those with only 3 risk factors

Such as our patient

Aguilar JAMA 2015;313:1973
Number of Metabolic Risk Factors and Mortality

• 30,365 men followed for 13.6 years at the Cooper Clinic
• All five components of metabolic syndrome were significantly associated with both all cause and CV mortality
• A continuum of risk was noted as the number of risk factors increased

Ho AJC 2008;102:689
Increase Mortality Risk with Increasing Metabolic Risk Factors

So our patient’s risk 7.0% (WH) or 9.9% (AA) can increase 1.7-5 fold with 5 metabolic risk factors

Ho AJC 2008;102:690
Differences in Metabolic 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 these groups to normal weight and metabolically normal

Ortega Eur Heart J 2013;34:389
Metabolically unhealthy obese subjects had 38% higher risk for CV mortality than metabolically healthy obese subjects.
Why does CVD remain our number one killer?

Does Climate Change Play a Role?

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

Editorial BMJ
March 2014
Global Warming
An Inconvenient Truth

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

• Concluded 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 because of the amount of carbon already in the atmosphere

IPCC February 2007
Reaffirmed October 2014
2016 ACP Calls For Urgent Action on Climate Change

• A global effort is required to reduce anthropogenic greenhouse emissions (i.e., those caused by humans) and address the health impact of climate change

• Physicians are encouraged to become educated about climate change, its effect on human health, and how to respond to future challenges.

• Medical schools and continuing medical education providers should incorporate climate change-related coursework into curricula.

Crowley Annals Int Med 2016; 164:608
14 of the hottest years ever recorded were noted in the past 15 years. 2016 recorded as the hottest year ever with July hottest month ever (measured since 1880) with CO₂ level the highest in 800,000 years. 1968 when CO₂ broached 300-320 ppm for the first time in over 50,000 years.

Stott BMJ 2006;332:1385
National Oceanic and Atmospheric Admin 2017
Today’s Ton of CO$_2$ is Worse Than a Ton Emitted Decades Ago

1 metric ton of CO$_2$ emissions

1960

400 Kg of CO$_2$ remain in atmosphere

2006

450 Kg of CO$_2$ remain in atmosphere

Source: UCS; Data from Canadell et al. 2007, PNAS
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
Flegal JAMA 2002;288:1723 National Oceanic and Atmospheric Admin 2017
Air Pollution and Atherosclerosis

- Air pollution is a heterogenous mixture of gases and vapors interacting with solid and liquid particulate matter in atmosphere
- 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$_{2.5}$) {size $\sim$1/50 the width of a human hair or half size of RBC}
  - Approximate range in US for PM$_{2.5}$ = 5-35 µg/m$^3$ with annual mean Environmental Protection Agency standard of 12 µg/m$^3$
Particulate Matter (PM)

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

*Li Rev Environ Health 2012;27:133*
Micrometers of Atmospheric PM

2.5 µm
Air Pollution as a Global Burden of Disease

• Ambient PM$_{2.5}$ was the fifth-ranking global mortality risk factor in 2015.

• Behind:
  – High systolic BP
  – Smoking
  – High fasting glucose
  – High cholesterol
  – High BMI 7$^{th}$
  • Did not measure waist circumference

Cohen Lancet 2017;389:1917
Air Pollution: A Global Burden of Disease

- Exposure to PM$_{2.5}$ estimated to have caused 4.2 million deaths and 103.1 million disability-adjusted life-years (DALYs) in 2015
  - Representing 7.6% of total global deaths and 4.2% of global DALYs
  - 3%-3.5% deaths in USA
    - 59% of these in east and south Asia.
    - Mostly reflecting attributable risk from CVD

Cohen Lancet 2017;389:1907
2015 deaths attributable to ambient PM$_{2.5}$
Deaths attributable to ambient particulate matter pollution by year and cause

Largest impact on CVD

Cohen Lancet 2017;389:1907
PM and obesity can symbiotically augment and enhance 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

Cell inflammation
Activated WBC, Platelets,

Increase cytokine Expression
IL-6, TNFα

Oxidized lipids
Dysfunctional HDL
? Increase TG, LDL

Further activate inflamed fat
↑ Adipokines (PAI-1, resistin)

Activates liver acute phase response
↑ clotting factors, Fibrinogen, CRP

Brook Curr Athero Reports 2010;12:291
Shanley Epidemiol 2016:27:291
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 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 development of chronic underlying disease state that exponentially augments future CV risk over years by enhancing progression and vulnerability of atherosclerotic plaque

Multi-Ethnic Study of Atherosclerosis and Air Pollution

• In this prospective 10-year cohort study, measured coronary artery calcium by CT in 6795 participants aged 45–84 years enrolled in the (MESA Air) in six metropolitan areas in the USA.

• From 2000-2010 the participant specific pollutant concentrations averaged over a range from $9.2–22.6$ μg PM$_{2.5}$/m$^3$

*Kaufman Lancet 2016;388:696*
Multi-Ethnic Study of Atherosclerosis and Air Pollution

- For each 5 μg PM$_{2.5}$/m$^3$ increase, coronary calcium progressed by 4·1 Agatston units/yr

Increased PM$_{2.5}$ and traffic related air pollution within metropolitan areas in ranges commonly encountered worldwide, are associated with progression of CAC consistent with acceleration of atherosclerosis.

Kaufman Lancet 2016;388:696
Air Pollution and Mortality in US Medicare Population

- 60,295,443 Medicare beneficiaries followed from 2000-2012
  - Increase 10 ug/m$^3$ PM$_{2.5}$ increased all-cause mortality 7.3%
  - When analysis limited to those with baseline PM$_{2.5} < 12$ ug/m$^3$ (ie below NAAQ Standard) an increase 10 ug/m$^3$ PM$_{2.5}$ ↑ mortality 13.6%
  - For men, African American, Hispanic, Asian and people on Medicaid the risk was statistically higher than overall population

Di NEJM 2017;376:2513
Exposure to Air Pollution is Associated with Adverse CV Events


### 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>
</tr>
</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>
</tr>
<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>
<td>17,914</td>
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<tr>
<td>No. of deaths</td>
<td>232</td>
<td>156</td>
<td>248</td>
<td>222</td>
<td>281</td>
<td>291</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Smokers (%)</td>
<td>36</td>
<td>33</td>
<td>40</td>
<td>37</td>
<td>35</td>
<td>35</td>
</tr>
<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>
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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>
</tr>
<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>
</tr>
<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>47.4</td>
<td>56.6</td>
<td>49.2</td>
<td>49.4</td>
<td>72.5</td>
<td>87.8</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Sulfate particles (µg/m³)</td>
<td>5.5</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.*

Since 2001 the average PM$_{2.5}$ for all 6 cities < 18 ug/m$^3$
- Predicted decrease in CV mortality ~30-40%
- and total mortality ~15-20%
- Response relationship was linear down to PM$_{2.5}$ of <5 ug/m$^3$
ATP III: Components of Metabolic Syndrome

- Abdominal Obesity
- Atherogenic Dyslipidemia
- Elevated Blood Pressure
- Insulin Resistance \(\pm\) glucose intolerance
- Pro-inflammation
  - Obese subjects with metabolic syndrome had significantly greater amounts of small dense LDL particles and higher CRP than obese subjects without metabolic syndrome

Iacobellis J Clin Lipid 2007;1:599
# Does it make sense?

## Emerging Risk Factors

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Prospective Studies</th>
<th>Commercial Assay</th>
<th>Additive to Lipids</th>
<th>Additive to FRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>++</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>SAA</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Interleukin-18</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Myeloperoxidase</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>sCD40 ligand</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LpPLA2</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

Ridker Circ 2004;109(25 suppl):IV6-19
Risk Factors for Future Cardiovascular Events: WHS

Lipoprotein(a)
Homocysteine
IL-6
TC
LDLC
sICAM-1
SAA
Apo B
TC: HDLC
hs-CRP
hs-CRP + TC: HDLC

Relative Risk of Future Cardiovascular Events

Attributable Risk CRP > 3mg/L from CV Risk Factors

Weighted multiple logistic regression analysis

Miller Arch Int Med 2005;165:2063
Link Between Inflammation, Immunity and Obesity

Like a continuous bacterial infection

- The immune system designed to combat bacterial infection (Th1) is constantly activated in obesity (visceral) by inflammatory cytokines released by hypertrophic adipocytes and/or apoptotic adipocytes in visceral adipose.

- This creates a state of persistent inflammation contributing to development of vascular and other chronic disease.

Chawla Nat Rev Immunol 2011;11:85
Winer Immuno and Cell Biol 2012;90:755
Pathogenesis of Obesity Related Insulin Resistance and Visceral Fat Inflammation

Inflammatory cytokines

Adipocyte Expansion

Excess Energy

Dysfunction

Hypoxemia, Oxidative Stress and ER Stress

Apoptotic

Innate

M1 macrophage Recruitment

M1 Polarization

Pro-inflammatory Milieu:
TNF, IL-1B, IL-6, IL-8, CRP

Insulin Resistance Atherosclerosis

Schipper Trends in Endo & Metab 2012;23:407
Obesity and Metaflammation

Energy as Common Denominator

• Obesity = excess energy intake over expenditure
  – Overnutrition, inactivity $\rightarrow$ “metaflammation”

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

Metaflammation is to chronic disease what inflammation is to acute disease (injury or infection)

Egger MJA 2010;193:635
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
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 as a population weigh 25 pounds more than we did 40 years ago.

• In part because we increased soft drinks 41% and increased fruit drinks 35%.

http://www.usda.gov/trpp#ENR%20V11N3fenrv11nJp44.PDF
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
  – Glucokinase converts glucose to glucose-6-phosphate then to glycogen
    • Most of glucose is stored in liver as glycogen
    • No amount of glycogen will hurt the liver since glycogen is non-toxic form of glucose storage
Sucrose Metabolism

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

- All 60 calories from fructose to liver metabolized by fructokinase to form fructose-1 phosphate which stimulates
  - gluconeogenesis sustaining insulin secretion and
  - de novo lipogenesis
- The 60 calories from glucose (12 to liver and 48 to body)

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% of its calories is converted to fat

A high fructose diet is a high fat diet

Parks J Nutr 2004;134:1333
Schwarz Diabetes 2005;54:1907
Fructose is not Glucose

- Fructose is not metabolized by the brain so has no acute symptoms and does not directly stimulate insulin
- Fructose increases caloric load to liver
- Acute fructose ingestion does not stimulate insulin because no fructose receptor on Beta cell, if insulin doesn’t go up then leptin won’t go up (brain doesn’t recognize you ate something)
  – Fructose does not suppress gherlin (hunger hormone)

High Fructose Corn Syrup

• HFCS is main component of soft drinks because it’s 20% sweeter than regular table sugar *(sucrose)*
  – And glucose is 26% less sweet than sucrose

• HFCS is also cheaper & accounts for 40% of all added caloric sweeteners
  – Current US consumption of HFCS = 63 lbs person/year

*Collino World J Diab 2011;2(6):77*
Perfect Storm from 3 Political Winds Resulting in Increasing Fructose Intake

1. Richard Nixon & USDA Secretary Earl Butz (1968-72)
   - Nixon’s war on poverty: The cost of food was increasing and the need to make food cheap, so food would not be an issue in a presidential election

2. Development of high fructose corn syrup
   - Invented mass production in 1967 in Japan (Dr Yoshiyuki Takasaki) and introduced to American market in 1975

3. Premise: Dietary fat increased LDL and LDL correlated with CAD based on Seven Countries Study (by Keys)
   - Percent calories from saturated fat correlated to prevalence CAD (1967 McGandy NEJM article)
   - 1982 USDA, AMA, and AHA call for dietary fat restriction to stop heart disease

McGandy NEJM 1967;277:186
Kearns JAMA Int Med Sept 2016
Correlation Fat, Sugar & Death Rate

Sugar Consumption lb/year

Death Rate per 100,000

Percent Sat Fat Calories in Diet

United States
Australia
Canada
England
Denmark
Italy
Japan

McGandy NEJM 1967;277:186
Kearns JAMA Int Med Sept 2016
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
Why are HFCS drinks bad?

Typical soft drink contains 55 mg sodium + caffeine (mild stimulant and diuretic) which increases free water clearance thus the increased sodium and the decrease in water causes increased thirst.

The increased salt is masked by sugar (especially HFCS) to allow us to take in more

http://www.usda.gov/trpp#ENR%20V11N3fenrv11nJp44.PDF
HFCS for Infants?

Ingredients in 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
SUGAR FOR INFANTS!

Why is there an epidemic of obese six-month-olds?

No one chooses to be obese; this is a problem of a system gone out of control.

Leptin (fat cell hormone) which tells us we have had enough is not working correctly.

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

Half is sugar (corn syrup & sucrose)
A baby milk shake

Typical soft drink is 10.5% sucrose
What’s the difference?

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

- No one chooses to be obese, this is a problem of a system gone out of control.

- Leptin (fat cell hormone) which tells us we have had enough is not working correctly.

1. Kim Obesity 2006;15:1107

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
Fructose at the Center of Obesity Epidemic

- Fructose consumption has increased in past 40-50 years coinciding with obesity epidemic
- A calorie is not a calorie (fructose is not glucose)
- Hepatic fructose metabolism leads to metabolic syndrome:
  - Hypertension
  - De novo lipogenesis, dyslipidemia, steatosis
  - Inflammation
  - Insulin resistance
  - Obesity
  - CNS leptin resistance promoting continuous consumption
- Fructose is a chronic hepatotoxin (*alcohol without the buzz*)

Is Fructose at the Center of Obesity? Epidemic?

- Fructose (sucrose or HFCS) consumption has increased coinciding with obesity epidemic
- A calorie is not a calorie (fructose is not glucose)


Reducing fructose for 9 days in children who ingest high levels of fructose while keeping the diet otherwise the same.

Can result in significant reductions in:
- Conversion of sugar to fat
- Liver fat deposition
- Triglycerides

In just 9 days !!!

Lustig Obesity 2016;24;453

Reducing fructose for 9 days in children who ingest high levels of fructose while keeping the diet otherwise the same.

Also can result in significant reductions in:

- Small dense LDL
- Apo B
- Apo CIII

All associated with an atherogenic profile

Gugliucci Atheroscler 2016 253:171
CHOPPS Program

• Soda 41% increase in soft drinks and 35% increase in fruit drinks

• Average can of soda 150 calories x 365 days then divide by 3500 (number of calories per pound) = 15.6 pounds per year

→ Removal of carbonated (fructose) drinks from schools in England (CHOPPS Program) for a year found the prevalence of obesity remained the same (-0.2%)

Compared to keeping soda in the schools where rate of obesity continued to rise (+7.5%)

James BMJ 2004;328:1237

(CHOPPS Program = Christchurch obesity prevention project in schools)
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.

High fiber foods expand in the stomach, slowing digestion and augmenting satiety. So taking in right calories can help prevent the need for more calorie intake later.

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
Easy to Use Recommendations For Lifestyle Intervention

- Get rid of all sugar liquids-only water and milk
- Eat your carbohydrate with fiber (fruit, vegetables)
- Wait 20 minutes for second portion
- Buy your screen time minute for minute with physical activity
Once adjusted for fitness the metabolically healthy obese no longer had a higher risk compared to metabolically healthy, normal weight peers.

HR Adjusted for Fitness

<table>
<thead>
<tr>
<th></th>
<th>Met abnormal obese</th>
<th>Met normal obese</th>
<th>Met normal normal wt</th>
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<tbody>
<tr>
<td>CV Mort</td>
<td>1.8</td>
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<tr>
<td>CVE</td>
<td>1.6</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Cancer Mort</td>
<td>1.6</td>
<td>1.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Ortega Eur Heart J 2013;34:389
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 and better prognosis than their obese peers with abnormal metabolic profiles

Ortega Eur Heart J 2013;34:389
HOW MUCH?

Let your patients know the important role of physical fitness as a health marker.

135.8 min/week of moderate exercise (minimum goal)

Moderate exertion = 60-65% target HR or conversational dyspnea

Ortega Eur Heart J 2013;34:389
Added Benefit
How to lower CRP

Best Results
• Exercise & weight loss
• Statins

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
Life Expectancy and Obesity

• CDC age adjusted mortality data for 2015 compared to 2014 found death rates increased in 2015 (possibly first time in 100 years).

• This CDC data for 2015 suggests we may have reached a tipping point where technology advances can no longer compensate.

Ludwig JAMA 2016;315:2269
Ma JAMA 2015;314:1731
A Physician’s Guide to Climate Change, Health and Equity

- The Guide explores the complex and multifaceted connections between climate change and health, disproportionate burdens and the impacts on health equity, and opportunities for solutions.
- It is meant to be a resource that you can use to prepare for conversations with your patients, media interviews, visits with legislators or policymakers, news media articles, or presentations such as Grand Rounds, conferences, community talks and more.

Syndemics and the Biosocial Conception of Health

Population level clustering of social and health problems

- The syndemic model of health focuses on the biosocial complex, which consists of interacting co-present or sequential diseases and the social and environmental factors that promote and enhance the negative effects of disease interaction.

_Singer Lancet 2017;389:941_
Is the Deadly Quartet the Syndemic of our Time?

- Syndemic involving the adverse interactions between the obesity epidemic and climate change have resulted in the increase of non-communicable diseases (CVD, DM, NAFLD), behavioral conditions, toxic exposures and over nutrition.
Global Burden of Disease 2015

- 79 metabolic, environmental and occupational, and behavioral risk factors or clusters of risks from 1990 to 2015 in 195 countries and territories
  - In 2015, all risks combined contributed to 57·8% of deaths and 41·2% of DALYs worldwide
  - Risk exposure increased for various leading risks, particularly metabolic risk factors
    - Among the top five risk factors, high BMI increased the most from 1990 to 2015 while summary exposure value also increased.

Lancet 2016;388:1659
Syndemic Model for Deadly Quartet

Dysmetabolic Obesity

Adverse Interaction

Climate Change and Air Pollution

Enhanced disease transmission, progression & negative health outcomes

Singer Lancet 2017;389:941
Syndemic Dilemma

- Many physicians believe that public health and societal issues “are not our job” and therefore ignore the increasing complexity of patient care.
- Most physician’s clinical training explicitly focus on diagnosis and treatment without considering how social problems impact medical problems.

*Mendehall Lancet 2017;389:951*
Inconvenient Truths

- Climate change is real and so is the marked increase in obesity and metabolic syndrome
- Increased air pollution, has been shown to induce ischemia, prothrombosis & inflammation all prevalent in obese metabolic syndrome patients
- We have the unique opportunity to positively impact both of these inconvenient truths