The Metabolic Syndrome: A Defeated Emperor
What were (are) the problems?
Well…

1. There was no agreed upon pathogenic reason to identify people with the metabolic syndrome

2. It was a relatively poor way to identify people at risk for diabetes or CVD

3. There was no evidence whatsoever that diagnosing metabolic syndrome improves patient outcomes

4. We should, instead, be thinking and acting upon cardiometabolic risk and not the metabolic syndrome
Definitions of the Metabolic Syndrome

- There are many definitions, including a “harmonized” one.
- No definition has been accompanied by data on its sensitivity, specificity and positive predictive value—especially related to another definition or to any other way to predict an adverse outcome.
Do we have the best “rules”
i.e. cutpoints?
### NCEP Metabolic Syndrome definition (any three of the five criteria)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>$\geq 130$ or $\geq 85$ mmHg</td>
</tr>
<tr>
<td>FPG</td>
<td>$\geq 100$ mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>$\geq 150$ mg/dl</td>
</tr>
<tr>
<td>HDL Women</td>
<td>$&lt; 50$ mg/dl</td>
</tr>
<tr>
<td>HDL Men</td>
<td>$&lt; 40$ mg/dl</td>
</tr>
<tr>
<td>Waist Women</td>
<td>$&gt; 35$ inches</td>
</tr>
<tr>
<td>Waist Men</td>
<td>$&gt; 40$ inches</td>
</tr>
</tbody>
</table>
Nuances in the definitions can have huge effects

SBP>130 \textbf{AND} DBP>85

\textbf{or}

SBP>130 \textbf{OR} DBP>85

The latter scoops up about 60\% \textbf{more} people than the former

\textbf{Does it matter?} We don’t know.
Here’s another example:

- WHO defines “obesity” as “BMI > 30 or waist/hip ratio > 0.9 (males); > 0.85 (females)”

- This could be interpreted as
  - “Chose either BMI or waist/hip to measure, and see if your patient meets that criterion”

- Or it could be interpreted as
  - “Measure both BMI and waist/hip and say your patient meets the criterion if he/she has either one”

- The former interpretation scoops up about half as many people as the latter
New “Harmonized” Definition (any three of the five criteria)

BP  $>$130 or $>$85 mmHg
FPG $>$100 mg/dl
Triglycerides $>$150 mg/dl
HDL Women $<$50 mg/dl
Men $<$40 mg/dl
Elevated waist circumference Popul. and country specific

Alberti, KGMM et al. Circulation.120:1640-1645, 2009
Waist Circumference Thresholds*

1. Europids (IDF) – male ≥ 94cm ; female ≥ 80cm
2. European (ECS) – male ≥ 102cm ; female ≥ 88cm
3. South Asians – male ≥ 90cm ; female ≥ 80cm
4. Canada – use #2
5. Japanese – male ≥ 85cm ; female ≥ 90cm
6. Eastern Mediterranean & Middle East – use #1
7. South American – use #3
8. Sub-Saharan African – use #1

* Mixed ethnicity---” make a pragmatic decision “
  Hispanics---??
  Ethnic group vs country of residence----the latter is “ logical ”
The measurement of waist circumference*

“The subject stands and the examiner, positioned at the right of the subject, palpates the upper bone to locate the iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at normal minimal inspiration”

* NHANES Protocol
What are the criteria for adding a sign/symptom?

Associated with CVD?

Then how about LDL, smoking, age, family history, etc.?
What are the criteria for adding a sign/symptom?

Associated with insulin resistance?
# Insulin resistance in those with MS

<table>
<thead>
<tr>
<th>Author</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheal et al. Diabetes</td>
<td>46%</td>
<td>93%</td>
<td>76%</td>
<td>N=443, no diabetes, 40% overweight</td>
</tr>
<tr>
<td>Liao et al. Diabetes Care</td>
<td>20 - 50%</td>
<td>92%</td>
<td>56%</td>
<td>N=74, no diabetes</td>
</tr>
<tr>
<td>McLaughlin et al. Ann</td>
<td>52%</td>
<td>85%</td>
<td>78%</td>
<td>N=258, no diabetes, 100% overweight or obese</td>
</tr>
<tr>
<td>Sierra-Johnson et al.</td>
<td>42%</td>
<td>94%</td>
<td>72%</td>
<td>N=256, no HBP, no diabetes</td>
</tr>
</tbody>
</table>
So is insulin resistance the “cause”?

- There is a strong relationship between insulin resistance and the components of the metabolic syndrome
- If it’s a cause, it certainly isn’t the only one
- All the definitions of metabolic syndrome are relatively insensitive measures of insulin resistance
How well does the definition of the Metabolic Syndrome predict diabetes?
## Metabolic Syndrome and the risk of diabetes (Insulin Resistance Atherosclerosis Study*)

<table>
<thead>
<tr>
<th>Definition</th>
<th>OR** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATPIII</td>
<td>4.14 (2.79 – 6.16)</td>
</tr>
<tr>
<td>AHA / NHLBI</td>
<td>3.84 (2.59 – 5.69)</td>
</tr>
<tr>
<td>IDF</td>
<td>3.40 (2.28 – 5.06)</td>
</tr>
<tr>
<td>IGT alone</td>
<td>5.42 (3.60 – 8.17)</td>
</tr>
</tbody>
</table>

* Incident of diabetes in 822 subjects followed for a mean of 5.2 years

** Adjusted for age, sex and ethnicity

Hanley et al., *Circulation* 112:3713-3721, 2005
Metabolic Syndrome and the risk of diabetes
(Framingham – 8 year follow-up)

Wilson et al. Circulation 112:3066-3072, 2005
How well does the Metabolic Syndrome predict CVD?
Relationship between Metabolic Syndrome and events

Most studies show a relationship between MS and events…

but is the “whole greater than the parts”?

There is no evidence that the “syndrome” carries any risk above its component parts
## Does the Metabolic Syndrome Predict CVD?
(Data from MRFIT*)

<table>
<thead>
<tr>
<th>Variable (CVD Mortality)</th>
<th>Odds Ratio**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP III definition</td>
<td>1.49 (1.35 - 1.64)</td>
</tr>
<tr>
<td>one condition</td>
<td>1.09 (0.86 - 1.39)</td>
</tr>
<tr>
<td>two conditions</td>
<td>1.29 (1.02 - 1.63)</td>
</tr>
<tr>
<td>three conditions</td>
<td>1.51 (1.19 - 1.92)</td>
</tr>
<tr>
<td>four conditions</td>
<td>1.98 (1.55 - 2.53)</td>
</tr>
<tr>
<td>five conditions</td>
<td>2.98 (2.24 - 3.95)</td>
</tr>
</tbody>
</table>

* Incident CVD in 4,588 men, 35-57 y.o followed for 18 years
** Adjusted for age, race, education, family history, smoking

Metabolic Syndrome and the risk of CVD
(Framingham – 8 year f/u)

Wilson et al. Circulation 112:3066-3072, 2005
How well does the Metabolic Syndrome guide treatment?
## Treating the Metabolic Syndrome

### What factor(s) will you treat? What is the goal of therapy?

<table>
<thead>
<tr>
<th>BMI</th>
<th>TRI</th>
<th>BP</th>
<th>HDL</th>
<th>FPG</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>145</td>
<td>160/95</td>
<td>41</td>
<td>95</td>
<td>180</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>TRI</th>
<th>BP</th>
<th>HDL</th>
<th>FPG</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>115</td>
<td>140/90</td>
<td>70</td>
<td>115</td>
<td>70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>TRI</th>
<th>BP</th>
<th>HDL</th>
<th>FPG</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>120</td>
<td>125/80</td>
<td>60</td>
<td>130</td>
<td>80</td>
</tr>
</tbody>
</table>

*Previous MI*

### Does therapeutic intervention change because the patient has the “metabolic syndrome”?

- No changes needed since all values are within normal range.
### Importance of Metabolic Syndrome and the risk of an MI

<table>
<thead>
<tr>
<th>Mrs. Smith</th>
<th>Mr. Jones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Age - 45</td>
<td>Age - 55</td>
</tr>
<tr>
<td>FPG - 115</td>
<td>FPG - 99</td>
</tr>
<tr>
<td>SBP - 133/86</td>
<td>SBP - 160/95</td>
</tr>
<tr>
<td>Tri - 160</td>
<td>Tri - 148</td>
</tr>
<tr>
<td>BMI - 25</td>
<td>BMI - 30</td>
</tr>
<tr>
<td>HDL - 65</td>
<td>HDL - 42</td>
</tr>
<tr>
<td>LDL - 125</td>
<td>LDL - 160</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>Smoker</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic syndrome?</th>
<th>Yes</th>
<th>Metabolic syndrome?</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-year risk of MI?</td>
<td>17%</td>
<td>30-year risk of MI?</td>
<td>77%</td>
</tr>
</tbody>
</table>
How did that happen?

- Different risk factors have different effects
- Each risk factor is a continuous variable; discrete thresholds are artificial.
- There are many other important risk factors
  - Age
  - Sex
  - Race/ethnicity
  - Family history
  - Behaviors (e.g. smoking, exercise)
  - Medical history (e.g. angina)
Summary

• No biological rationale for the algorithm; no obvious inclusion/exclusion rules

• Insulin resistance as the unifying etiology is unlikely

• No “syndrome” risk above the component risk

• The diabetes or CVD predictive value is fair, at best

• Treatment of syndrome is no different than treatment of components; value of diagnosis is unclear.

• There are better, easier, and cheaper ways to predict diabetes or CVD
Clinical Issues

- Conveys to patients they have a distinct disease – when they don’t
- The presence or absence of the “syndrome” can be very misleading
- Detracts from the need to prioritize treatment based on benefits, risks, and cost
- Underemphasizes other very important CVD risk factors (e.g. LDL, smoking, history)
The Metabolic Syndrome: Time for a Critical Appraisal

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

Richard Kahn, PhD¹
John Buse, MD, PhD²
Ele Ferrannini, MD³
Michael Stern, MD⁴

DOI 10.1007/s00125-009-1620-4

FOR DEBATE

The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation

R. K. Simmons • K. G. M. M. Alberti • E. A. M. Gale • S. Colagiuri • J. Tuomilehto • Q. Qiao • A. Ramachandran • N. Tajima • I. Brajkovich Mirchov • A. Ben-Nakhi • G. Reaven • B. Hama Sambo • S. Mendis • G. Roglic
There is no definitive definition

Cannot quantify the risk of CVD or diabetes

There are better risk prediction algorithms

Omits important risk factors; not all the same

Should not be applied as a clinical diagnosis

Has limited practical utility

Or... (as said by K.Borch-Johansen and N.Warham)

“May the metabolic syndrome rest in peace”
But…

- Risk factor clustering does occur, and should be appreciated

- We need a better understanding of why that happens, what it means and what we should do about it
What are we really trying to do?

Reduce cardiometabolic risk
Abnormal Lipid Metabolism

LDL ↑
ApoB ↑
HDL ↓
Trigly. ↑

Cardiometabolic Risk
Global Diabetes / CVD Risk

Overweight / Obesity

Age, Race, Gender, Family History

Insulin Resistance Syndrome
↑ Lipids
↑ BP
↑ Glucose

Age, Genetics

Smoking
↓ Physical Activity

↑ Blood Pressure

Hypercoagulation

Inflammation

LDL ↑
ApoB ↑
HDL ↓
Trigly. ↑
What should we do?

- To identify people at high risk for diabetes:
  - Do an A1c or FPG test
- To identify people at high risk of CVD:
  - Count risk factors and treat each risk factor individually
- Take weight loss and exercise seriously
- Treat problems aggressively
Thank You