The Metabolic Syndrome: Does it Matter?

Richard Kahn, PhD
What’s all the fuss about?
It’s because…

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

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

3. There is no evidence whatsoever that diagnosing metabolic syndrome improves patient outcomes
Definitions of the Metabolic Syndrome

- We get a new definition about every 2 years
- We now have 7 definitions
- No definition has been accompanied by data on its sensitivity, specificity and positive predictive value
For Example:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>&gt;130 / &gt;85 mmHg</td>
<td>&gt;130 or &gt;85 mmHg or on Rx.</td>
</tr>
<tr>
<td>FPG</td>
<td>≥100 mg/dl</td>
<td>≥100 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>HDL - Women</td>
<td>&lt;50 mg/dl</td>
<td>&lt;50 mg/dl</td>
</tr>
<tr>
<td>- Men</td>
<td>&lt;40 mg/dl</td>
<td>&lt;40 mg/dl</td>
</tr>
<tr>
<td>Waist - Women</td>
<td>&gt;35 inches</td>
<td>&gt;35 inches</td>
</tr>
<tr>
<td>- Men</td>
<td>&gt;40 inches</td>
<td>&gt;40 inches</td>
</tr>
</tbody>
</table>

Why the change?
Nuances in the definitions can have huge effects

\[
\text{SBP} > 130 \ \text{AND} \ \text{DBP} > 85 \\
\text{or} \\
\text{SBP} > 130 \ \text{OR} \ \text{DBP} > 85
\]

The latter scoops up about 60% more people than the former

Does it matter? We don’t know.
New IDF Definition

- High waist circumference plus (any two):
  - Trig. - > 150 mg/dl or Rx
  - HDL - women < 50mg/dl; men < 40 mg/dl or Rx
  - BP - > 130 mmHg or ≥ 85 mmHg or Rx
  - FPG - ≥ 100 mg/dl or diabetes

Those with ↑ BP, ↑ FPG, ↑ Trig., ↓ HDL, but modest waist… are they fine? (But they have MS by ATPIII)

Those who are obese and have FPG of 100-125mg/dl and no other MS factor, are they really not at risk for diabetes or CVD?
Relationship between BMI and waist circumference

Helke MF et al., Am J Clin Nutr 83:47, 2006
By the way, if the purpose of central obesity is to identify people with IR, BMI does as well as waist circumference and both of those do considerably better than waist/hip ratio.
How about the people with borderline values?

BMI - >25 but <30 kg/m²
BP - >130 but <140 mmHg
TRI - >150 but <200 mg/dl
FPG - >100 but <126 mg/dl
HDL - >40 but <60 mg/dl

Do these people have increased risk?
Proportion of CHD events according to the number of borderline & elevated risk factors

(Risk Factors – BP, LDL, HDL, BG, Smoking)


![Graph showing the proportion of CHD events according to the number of risk factors for men and women. The risk factors include SBP 120-139, DBP 80-89, LDL 100-159, HDL 40-59, IFG 110-125 or IGT 140-199, and Former smoker. The graph indicates that the proportion of CHD events increases with the number of risk factors.]

Events %

0 20 40 60 80 100

Men (35-74 years)

Women (35-74 years)

3-5 Risk Factors
2 Risk Factors
1 Risk Factor
Borderline Only

SBP 120-139
DBP 80-89
LDL 100-159
HDL 40-59
IFG 110-125 or IGT 140-199
Former smoker
Do we have the best “rules”
i.e. cutpoints?
What are the criteria for adding a sign/symptom?

Associated with CVD?

Then how about LDL, smoking, age, family history, etc.?
Associated with insulin resistance?

Then how about adding…

Adiponectin
C-reactive protein
Age
Others?
## 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 Intern Med</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. Diabetes Care</td>
<td>42%</td>
<td>94%</td>
<td>72%</td>
<td>N=256, no HBP, no diabetes</td>
</tr>
</tbody>
</table>
## Likelihood of IR in overweight / obese people

<table>
<thead>
<tr>
<th>Marker</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight / Obese alone</td>
<td>50%</td>
</tr>
<tr>
<td>Triglyceride $\geq 130$ mg/dl</td>
<td>70%</td>
</tr>
<tr>
<td>Triglyceride / HDL ratio $\geq 3.0$</td>
<td>67%</td>
</tr>
<tr>
<td>ATP III Criteria</td>
<td>78%</td>
</tr>
</tbody>
</table>

*Insulin resistance = highest tertile*

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
*(San Antonio Heart Study)*

<table>
<thead>
<tr>
<th></th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP III</td>
<td>53</td>
<td>85</td>
<td>31</td>
</tr>
<tr>
<td>WHO</td>
<td>43</td>
<td>87</td>
<td>30</td>
</tr>
<tr>
<td>FPG ≥ 97 mg/dl</td>
<td>43</td>
<td>92</td>
<td>39</td>
</tr>
</tbody>
</table>

Metabolic Syndrome and the Risk of Diabetes
(Framingham – 8 Year Follow-Up)

Wilson et al. Circulation 112:3066-3072, 2005
How Well Does the Definition of the Metabolic Syndrome Predict Cardiovascular Events?
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  

Eberly LE et al, Diabetes Care 29:123-130, 2006
Does the Metabolic Syndrome Predict CVD?  
(Data from British Women’s Heart & Health Study*)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio**(CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDF definition</td>
<td>1.32 (1.03 – 1.70)</td>
</tr>
<tr>
<td>ATP III definition</td>
<td>1.38 (1.00 – 1.93)</td>
</tr>
<tr>
<td>WHO definition</td>
<td>1.45 (1.00 – 2.10)</td>
</tr>
<tr>
<td>BP &gt; 130/85 or on Rx</td>
<td>2.09 (1.14 – 3.74)</td>
</tr>
<tr>
<td>BMI &gt; 30 or WHR (&gt;0.85)</td>
<td>1.31 (1.07 – 1.61)</td>
</tr>
</tbody>
</table>

* Incident CHD in 3589 women, 60-79 y.o followed for a median of 4 years  
** Age adjusted  

Does the Metabolic Syndrome Predict CVD?  
(Data from San Antonio Heart Study*)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio**(CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP III definition</td>
<td>1.56</td>
<td>.028</td>
</tr>
<tr>
<td>Adjusted for diabetes</td>
<td>1.11</td>
<td>.658</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.63</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* CVD mortality in 5,158 people followed for 7-8 years  
** Adjusted for age and gender

Stern MP et al. Atheroscler Suppl 6:3-6, 2005
Wilson et al. Circulation 112:3066-3072, 2005
How Should We Treat Patients With The Metabolic Syndrome?
# 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>
<tr>
<td>30</td>
<td>115</td>
<td>140/90</td>
<td>70</td>
<td>115</td>
<td>70</td>
</tr>
<tr>
<td>32</td>
<td>120</td>
<td>125/80</td>
<td>60</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Previous MI</td>
</tr>
</tbody>
</table>

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

Previous MI
# 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>

**Metabolic syndrome?**  Yes  No  
**30-year risk of MI?**  17%  77%
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 algorithms, nor are there obvious inclusion/exclusion rules
- Insulin resistance as the unifying etiology is unlikely
- There is no “syndrome” risk above the component risk
- The diabetes or CVD predictive value is fair, at best
- It doesn’t guide treatment decisions
- There are better, easier, and cheaper ways to predict diabetes or CVD

So what good is it?
Advantages

- “Physicians need simple constructs to detect problems, not risk scores or fancy algorithms.”
- “People so labeled are more likely to lose weight and exercise.”
- “It’s a good reminder to look for risk factors.”
- “It draws attention to the obesity problem.”
Problems

● 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 very important CVD risk factors (e.g. LDL, smoking, history)
And More Problems…

- Each component, regardless of its value, has equal “impact”

- The “rules” (3 of 5; one mandatory and 2 of 4) have no scientific basis
In Other Words…

There is no scientific rationale, or underpinning, for any of the metabolic syndrome definitions.

It’s an algorithm looking for a purpose.
Possible “Purposes”

1. If we want to predict diabetes
   - Do an FPG or 2hr OGTT

2. If we want to predict CVD
   - Do an FPG or OGTT
   - Simple way: count risk factors (and treat each one appropriately)
   - Better way: use a risk calculator (e.g. the “PhD” at diabetes.org)

3. Identify and treat the overweight / obese patient
   - Measure BMI or waist circumference
   - Get serious about patients who are overweight or obese
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
- Smoking
- ↓ Physical Activity
- ↑ Blood Pressure
- Inflammation
- Hypercoagulation

Insulin Resistance Syndrome

- ↑ Lipids
- ↑ BP
- ↑ Glucose

Insulin Resistance

- Genetics

Age

Overweight / Obesity

Abnormal Lipid Metabolism

Age, Race, Gender, Family History

Inflammation

Hypercoagulation

Blood Pressure

↑ Lipids

↑ BP

Glucose

Insulin Resistance Syndrome

↑ Lipids

↑ BP

↑ Glucose

Age Genetics

Insulin Resistance

Smoking

↓ Physical Activity
Thank You !