Week 4, Lecture 6

Metabolic syndrome
• Names
• Definitions
• Prevalence
• Trends
• Morbidity and mortality associated with metabolic syndrome
• Remaining questions/uncertainties for future studies
- Kylin 1923: Hypertonic-hyperglycemia-hyperuricemia-syndrome
- Reaven 1988: Syndrome X
  - Resistance to insulin-stimulated glucose uptake
  - Glucose intolerance
  - Hyperinsulinemia
  - Increased VLDL triglycerides
  - Low HDL cholesterol
  - Hypertension
- Alberti et al. 1998: WHO proposal
What is the metabolic syndrome?

• A constellation of anthropometric, physiologic, and biochemical abnormalities that occur together more frequently than expected by chance and are linked by "insulin resistance" and that increase the risk for developing CVD or DM.
  – Anthropometry
  – Lipids
  – Blood pressure
  – Glucose
  – Insulin resistance
  – Inflammation
  – Thrombosis
  – Fibrinolysis
• Reaven (1988):
  – “Series of related variables that tends to occur in the same individual and may be of enormous importance in the genesis of CAD. … The common feature of the proposed syndrome is insulin resistance, …”

• WHO: A clustering of abnormal glucose tolerance with one or more other CVD risk components

• NCEP/ATP III:
  – “Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the metabolic syndrome”
  – “Multiplex risk factor for cardiovascular disease”
Many names

- Metabolic syndrome (WHO, NCEP)
- Metabolic syndrome X (MESH heading)
- Dysmetabolic syndrome (ICD-9-CM code 277.7)
- Insulin resistance syndrome
- Syndrome X
- Dysmetabolic syndrome X
- Dysmetabolic cardiovascular syndrome
- Cardiovascular metabolic syndrome
- Cardiometabolic syndrome
- Metabolic cardiovascular syndrome
- Plurimetabolic syndrome
- Polimetabolic syndrome
• Multiple metabolic syndrome
• Multimetabolic syndrome
• Deadly quartet
• Reaven’s syndrome
• Athero-thrombogenic syndrome (ATS)
• Visceral adiposity syndrome
• Beer-belly syndrome
WHO 1998 definition:

- Glucose intolerance, IGT or DM (1999: IFG, IGT, DM) and/or insulin resistance* plus 2 or more of:

- Hypertension: $\geq 160/90$ mm Hg (1999: $\geq 140/90$ mm Hg)
- Dyslipidemia
  - Triglycerides $\geq 1.7$ mmol/L (150 mg/dL)
  - HDL
    - Men: $<0.9$ mmol/L (<35 mg/dL)
    - Women: $<1.0$ mmol/L (<39 mg/dL)
- Central obesity: BMI $\geq 30$ kg/m$^2$ and/or WHR $>0.9$ in men, $>0.85$ in women
- Microalbuminuria: UAER $\geq 20$ µg/min or UACR $\geq 20$ mg/g (1999: $\geq 30$ mg/g)

*"Under hyperinsulinaemic, euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation.”
NCEP/ATP III definition:

Three or more of:

- Abdominal obesity
  - Men
  - Women
- Triglycerides
- HDL cholesterol
  - Men
  - Women
- Blood pressure
- Fasting glucose*

- Waist circumference
  - >102 cm (>40 inches)
  - >88 cm (>35 inches)
- ≥150 mg/dL
  - <40 mg/dL
  - <50 mg/dL
- ≥130/85 mmHg
- ≥110 mg/dL
- Was further updated to >100 mg/dl
Both the WHO and NCEP/ATP III definitions include people with DM

Comment on WHO criteria

- Difficulty defining insulin resistance:
  - Gold standard for insulin resistance is difficult to perform in settings other than research ones
  - Definition of top quartile of surrogate measure
    - Which surrogate measure
    - How do we define the range of this measure
      » Total sample
      » Population reference
      » Nondiabetic participants
      » Other
NCEP/ATP III criteria:

• Are clinicians measuring waist circumference?
• Are clinicians diagnosing the metabolic syndrome in the United States?
EGIR (European Group for the Study of Insulin Resistance)

• Hyperinsulinemia
  – Upper quartile of nonDM participants

• Plus 2 or more of the following:
  – Hyperglycemia
    • FPG >=110 mg/dl (6.1 mmol/L)
  – Hypertension:
    • >=140 mm Hg or >=90 mm Hg and/or treatment
  – Dyslipidemia:
    • TG>180 mg/dl (2 mmol/L) and/or
    • HDLC <40 mg/dl (1 mmol/L) and/or
    • treatment
  – Central obesity
    • Men: >=94 cm ; women: >=80 cm
American College of Endocrinology

• Limited to people without diabetes
• Predisposing factors:
  – Diagnosis of CVD, hypertension, PCOS, NAFLD, AN
  – Family history of type 2 DM, hypertension, CVD
  – History of gestational diabetes or glucose intolerance
  – Non-Caucasian ethnicity
  – Sedentary lifestyle
  – BMI >25 kg/m² or waist circumference >40 inches in men, >35 in women
  – Age >40 years
• Considered the following four criteria:
  – Triglycerides ≥ 150 mg/dl
  – HDLC
    • Men: <40 mg/dl; Women: <50 mg/dl
  – Blood pressure:
    • ≥ 130 mm Hg or ≥ 85 mm Hg or treatment
  – Glucose:
    • Fasting glucose: 110-125 mg/dl or
    • 2-hour glucose: ≥ 140 mg/dl
Insulin Resistance - Definition

• A state (of a cell, tissue, system or body) in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response (Berson and Yalow, 1970)

• Notable historical events
  – Pancreatectomy in dogs in 1889 (Mering and Minkowski)
  – Discovery of insulin in 1922 (Best and Banting)
  – Insulin sensitivity /Oral glucose load in 1930s (Himsworth)
  – Direct measurement of plasma insulin using RIA in 1960s (Yalow and Berson)
  – Measurements of receptors and whole body insulin sensitivity (euglycemia clamp, isotope dilution etc. in 1970s, 80s)
How has insulin resistance criteria of WHO definition been implemented?

- Isomaa 2001: highest quartile of the HOMA-IR index
- Lakka 2002: hyperinsulinemia based on fasting insulin levels in the upper fourth
- Hu 2004: EGIR criteria: fasting plasma insulin values >highest sex- and cohort specific quartile of nondiabetic background population
Prevalence of the Metabolic Syndrome

Slides courtesy of Dr. Earl S. Ford
Behavioral Surveillance Branch
Division of Adult and Community Health
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention
US studies: NCEP/ATP III criteria

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>US men 20+ y</td>
<td>24.0</td>
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<tr>
<td>US women 20+ y</td>
<td>23.4</td>
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<tr>
<td>Filipina women 50-69 y</td>
<td>34.3</td>
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<tr>
<td>RB women 50-69 y</td>
<td>12.9</td>
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<tr>
<td>SHS 45-74 y</td>
<td>35.0</td>
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<tr>
<td>Pima 20+ y</td>
<td>31</td>
</tr>
<tr>
<td>SAHS MA men 30-79 y</td>
<td>29</td>
</tr>
<tr>
<td>SAHS MA women 30-79 y</td>
<td>32.8</td>
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<tr>
<td>SAHS white men 30-79 y</td>
<td>24.7</td>
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<tr>
<td>SAHS white women 30-79 y</td>
<td>21.3</td>
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<tr>
<td>FOS men 30-79 y</td>
<td>26.9</td>
</tr>
<tr>
<td>FOS women 30-79 y</td>
<td>21.4</td>
</tr>
<tr>
<td>IRAS</td>
<td>34.1</td>
</tr>
<tr>
<td>Arab-Am men 20-75 y</td>
<td>23</td>
</tr>
<tr>
<td>Arab-Am women 20-75 y</td>
<td>28</td>
</tr>
</tbody>
</table>

A comparison of prevalences of the metabolic syndrome derived using both NCEP/ATP III and WHO definitions.

Age-adjusted prevalence of the metabolic syndrome among United States adults aged ≥20 years using ATP III criteria, NHANES III 1988-1994
Prevalence of the metabolic syndrome among United States adults age ≥20 years using ATP III criteria, by age, NHANES III 1988-1994
Age-adjusted prevalence of the metabolic syndrome among United States adults age ≥20 years, by sex and race or ethnicity, NHANES III 1988-1994
Distribution of combinations of ≥3 NCEP/ATP III criteria, NHANES III 1988-94
What can we conclude from the prevalence studies?

• Very common across the world
  – Perhaps least common in skinnier northern European populations
• Men/women pattern differs by race or ethnicity:
  – Whites: Men > women
  – Nonwhites: Women > men
• Strongly related age
Changes in the age-adjusted prevalence of components of the metabolic syndrome among US adults aged ≥20 years

**All participants**

- Large waist
- High TG
- Low HDLC
- High BP or meds
- FPG 110+ or meds
- FPG 100+ or meds

**Men**

- Large waist
- High TG
- Low HDLC
- High BP or meds
- FPG 110+ or meds
- FPG 100+ or meds

**Women**

- Large waist
- High TG
- Low HDLC
- High BP or meds
- FPG 110+ or meds
- FPG 100+ or meds

Changes in the age-adjusted prevalence of the metabolic syndrome (original definition) among US adults aged ≥20 years


*Total*: 24.1% 27%

*Men*: 24.6% 25.2%

*Women*: 23.5% 29%

*p<0.05;  **0.05≤p<0.10*
Changes in the age-specific prevalence of the metabolic syndrome (original definition) among US men and women aged ≥20 years

* *p<0.05; ** 0.05≤p<0.10
Changes in the age-adjusted prevalence of the metabolic syndrome (modified) among US adults aged ≥20 years

![Bar chart showing changes in prevalence]

* NHANES 1999-2000

*\(p<0.05\); ** \(0.05 \leq p < 0.10\)
Changes in the age-specific prevalence of the metabolic syndrome (modified) among US men and women aged ≥20 years

* p<0.05; ** 0.05≤ p<0.10
• The age-adjusted prevalence of the metabolic syndrome among US adults has increased by a relative 12.1%:
  – More among women (+23.5%) than men (+2.2%)
  – Due to increases in abdominal obesity, blood pressure, and to a lesser degree triglyceride concentrations

• Using the original NCEP/ATP III definition, about 41 million US adults had the metabolic syndrome in 1990 and 54 million in 2000

• Based on the modified NCEP/ATP III definition, about 50 million US adults had the metabolic syndrome in 1990 and 64 million in 2000

• The increase in numbers is due to both an increase in the prevalence of the syndrome and growth in the US population.

• The modification of the NCEP/ATP III definition (FPG ≥100 mg/dL instead of 110 mg/dL) increased the prevalence of the syndrome by about absolute 5%:
  – Unadjusted: from 23.1% to 28%
  – Age-adjusted: from 24.1% to 29.2%
Risks associated with the Metabolic Syndrome
Risks associated with metabolic syndrome

- Increased all-cause mortality
- Increased cardiovascular disease
- Increased diabetes mellitus
- Alzheimer’s disease (Kalmijn 2000)
- Preeclampsia (Barden 1999)
- Breast cancer (Sinagra 2002)
Estimated relative risk

Estimated relative risk

Associations between metabolic syndrome (NCEP/ATP III definition) and all-cause mortality

Lakka 2002
Katzmarzyk 2004
Hunt 2004
Combined

Heterogeneity: p = 0.033

Estimated relative risk
Estimated relative risk

1.21

Heterogeneity: p = 0.077

Associations between metabolic syndrome (original and modified NCEP definition) and all-cause mortality
The metabolic syndrome and cardiovascular disease – NCEP definition
Associations between the metabolic syndrome (NCEP/ATP III definition) and cardiovascular disease

Estimated relative risk

Combined

Heterogeneity: \( p = 0.004 \)
Associations between the metabolic syndrome using BMI instead of waist circumference and cardiovascular disease

Heterogeneity: p < 0.001

Estimate of relative risk
Associations between the metabolic syndrome (original or modified NCEP/ATP III definition) and cardiovascular disease
The metabolic syndrome and cardiovascular disease – WHO definition
Associations between the metabolic syndrome (WHO definition) and cardiovascular disease

Estimated relative risk

Heterogeneity: \( p = 0.376 \)
Associations between the metabolic syndrome (WHO definition) and coronary heart disease

Estimate of relative risk

Heterogeneity: p = 0.749
The metabolic syndrome and diabetes – NCEP definition
Associations between metabolic syndrome and diabetes

Measures of relative risk and 95% CI
Associations between the metabolic syndrome (NCEP/ATP III definition) and diabetes incidence

Heterogeneity: $p < 0.001$
Associations between the metabolic syndrome (NCEP/ATP III or modified NCEP definition) and diabetes incidence

Heterogeneity: p < 0.001
Combined relative risks (random effects) and 95% CI calculated from meta-analyses between metabolic syndrome and CVD and DM

PAF = 6%
PAF = 13%
PAF = 15%
PAF = 34-39%

All-cause mortality  CVD-waist  CVD-BMI  DM
Figure 1. Estimated total number of people with (A) metabolic syndrome and (B) overweight by sex in adults aged 35–74 years in China, 2000–01

Gu et al. Lancet 2005
Figure 2. Age-specific prevalence of (A) metabolic syndrome and (B) overweight by sex in the study population

Gu et al. Lancet 2005
Is the metabolic syndrome of public health interest?

• Highly prevalent
• Associated with increased morbidity and mortality
  – All-cause mortality, CVD, DM, PCOS, NASH
• Likely to be very costly
• Preventable
Many questions remain:

- Can we select a single name?
- How do we best define the syndrome and can we have one definition?
- What exactly is the metabolic syndrome and is the metabolic syndrome a useful concept?
- How many metabolic syndromes are there?
- What are the underlying mechanisms for this syndrome?
- Do we know enough about risk factors for the metabolic syndrome?
- What is the best approach for surveillance?
• Is there a risk gradient for CVD, DM, and other adverse events among people with the metabolic syndrome?
• Do we know enough to treat people with the metabolic syndrome?
  – Are clinical trials needed?
• Have clinicians accepted the metabolic syndrome?
  – Diagnosis
  – Treatment
• Are our current guidelines for the prevention, detection, and treatment of the metabolic syndrome adequate?
• Do we know enough about the prevention of the metabolic syndrome?
  – Can findings from trials of DM prevention in high-risk populations be extended to people with MetS?
• Are there cost-effective interventions for primary prevention and secondary prevention?
• What is the cost of the metabolic syndrome in the US?
• Need to learn more about the metabolic syndrome in children and adolescents
Ten-Year Cumulative Incidence of Insulin Resistance Syndrome Components by Categories of Total Dairy Intake With Stratification by Baseline Overweight Status

Rates are adjusted for age, study center, caloric intake, race, sex, and baseline body mass index

Similar observations in WHS and in NHANES – Ford et al. Diabetes Care 2005

Table 2. Relative Risk (RR) of Type 2 Diabetes Among Men According to Total Dairy Intake

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quintile 1 (&lt;0.9)</th>
<th>Quintile 2 (0.9-1.3)</th>
<th>Quintile 3 (1.4-1.9)</th>
<th>Quintile 4 (1.9-2.9)</th>
<th>Quintile 5 (≥2.9)</th>
<th>P for Trend</th>
<th>RR per 1-Serving/d Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>262</td>
<td>272</td>
<td>246</td>
<td>220</td>
<td>243</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Person-years</td>
<td>89,160</td>
<td>92,646</td>
<td>90,145</td>
<td>89,820</td>
<td>90,943</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age- and BMI-adjusted RR (95% CI)†</td>
<td>1.0</td>
<td>0.97 (0.81-1.16)</td>
<td>0.92 (0.76-1.10)</td>
<td>0.77 (0.64-0.93)</td>
<td>0.82 (0.67-1.00)</td>
<td>.02</td>
<td>0.93 (0.88-0.99)</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unadjusted for dietary factors‡</td>
<td>1.0</td>
<td>0.99 (0.83-1.18)</td>
<td>0.95 (0.80-1.15)</td>
<td>0.79 (0.65-0.96)</td>
<td>0.82 (0.67-1.00)</td>
<td>.01</td>
<td>0.93 (0.87-0.98)</td>
</tr>
<tr>
<td>Adjusted for dietary factors§</td>
<td>1.0</td>
<td>0.98 (0.82-1.17)</td>
<td>0.92 (0.77-1.11)</td>
<td>0.75 (0.62-0.92)</td>
<td>0.77 (0.62-0.95)</td>
<td>.003</td>
<td>0.91 (0.85-0.97)</td>
</tr>
<tr>
<td>Adjusted for dietary factors (baseline)§</td>
<td></td>
<td>1.0</td>
<td>0.96 (0.80-1.14)</td>
<td>0.88 (0.73-1.06)</td>
<td>0.76 (0.63-0.93)</td>
<td>0.75 (0.61-0.93)</td>
<td>.003</td>
</tr>
</tbody>
</table>

*Includes all dairy foods except butter.
†Adjusted for total energy intake.
‡Adjusted for age (in 5-year categories), total energy intake, biennial follow-up time (6 periods), family history of diabetes (yes/no), smoking status (never smoked; former smoker; current smoker, 1-14 cigarettes/d; current smoker, 15-24 cigarettes/d; or current smoker, ≥25 cigarettes/d), BMI, kg/m² (<23.0, 3.0-23.9, 24.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-34.9, or ≥35.0), hypercholesterolemia (yes/no), hypertension (yes/no), physical activity (quintiles of metabolic equivalent tasks), and alcohol intake (0, 0.1-5.0, 5.1-14.0, 15-29, or ≥30.0 g/d).
§Additionally adjusted for cereal fiber intake, trans-fat intake, ratio of polyunsaturated to saturated fat, and glycemic load (all in quintiles).
||Using baseline (1986) dairy intake and covariates.

Choi et al. Arch Int Med 2005

Similar data observed in the WHS (in preparation)
Prospective cohort studies examining dietary magnesium intake in relation to incidence of metabolic-related chronic diseases (Song 2005)

**Type 2 Diabetes**
- The ARIC Study (Black) (1999): 0.98 (0.56, 1.71)
- The ARIC Study (White) (1999): 1.08 (0.77, 1.49)
- Iowa Women's Health Study (2000): 0.67 (0.55, 0.82)
- Nurses' Health Study (2004): 0.73 (0.65, 0.82)
- Health Professional Follow-up Study (2004): 0.72 (0.58, 0.89)
- Women's Health Study (2004): 0.88 (0.71, 1.10)
- Combined: 0.78 (0.69, 0.88)

**Cardiovascular Disease**
- Caerphilly Cohort Study (1996): 0.66
- ARIC Study (women) (1998): 1.32 (0.68, 2.56)
- ARIC Study (men) (1998): 0.69 (0.45, 1.05)
- Honolulu Heart Study (2003): 0.59 (0.39, 0.89)
- Health Professional Follow-up Study (2004): 0.86 (0.65, 1.13)
- Combined: 0.78 (0.60, 1.02)

**Hypertension**
- Nurses' Health Study (1989): 0.78 (0.62, 0.98)
- Health Professional Follow-up Study (1992): 0.89 (0.64, 1.25)
- ARIC Study (women) (1999): 0.99 (0.69, 1.43)
- ARIC Study (men) (1999): 0.98 (0.68, 1.41)
- Combined: 0.87 (0.75, 1.01)
<table>
<thead>
<tr>
<th>Student Project Topics</th>
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<tbody>
<tr>
<td><strong>Kristen Pagel</strong></td>
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<tr>
<td><strong>Rachelle Rodriguez</strong></td>
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<td><strong>Gina Wallar</strong></td>
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<td><strong>Lani Park</strong></td>
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<td><strong>Parinaz Lajevardi</strong></td>
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