Metabolically Healthy Obese:  
*Reality or Fantasy?*

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Feinberg School of Medicine at Northwestern University

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Women’s Health Research Institute at Northwestern University
Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1989

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1993

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1997

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI $\geq 30$, or $\sim 30$ lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Combined prevalence of overweight and obesity is over 80%
Body Mass Index (BMI)

• BMI is a tool for indicating weight status.

• It is a number that shows body weight adjusted for height.

• Used as an indicator of disease risk – not a true measure of BODY COMPOSITION or BODY FAT DISTRIBUTION.
Calculating BMI

\[
\text{BMI} = \frac{\text{Weight in Pounds}}{\left(\text{Height in Inches}\right)^2} \times 703
\]
What does “obesity” mean in men vs. women?

Gender differences in body composition

• Sex differences in fat mass vs. fat free mass (bone, muscle) beginning in adolescence
  − %BF is lower in boys (14.6%) than in girls (16.7%)
  − There is little or no change in %BF for girls from 10 to 18 years, although total fat mass increases at an annual rate of 1.14 kg per year.
  − For boys, %BF decreases annually by 1.15% across the age range.
  − Between ages 10 to 20, Fat Free Mass increases by 33 kg in boys, but only 16 kg in girls
Body Composition:

Sex Differences in Fat Free Mass by Age

Fat free mass in adult females is 72% of that in men

Shantz et al. 1983; Acta Physiologica Scandinavica 117: 219
Body Fat Distribution

• Obesity” refers to an excess of adipose (fat) tissue

• The distribution of the fat tissue through the body matters

• Central “abdominal” body fat poses greater health risks than fat stored in other areas

• Body fat distribution follows different patterns in women vs. men
Apple shape:
- Central deposition of adipose tissue
- Beer belly
- More common in men

Pear shape:
- Lower body deposition of adipose tissue
- Large hips and thighs
- More common in women

Jean Vague 1947
CAVEAT for today’s presentation

*BMI is not an accurate measure of body composition or body fat distribution*

- BMI can be misleading in terms of a person’s body fat as it solely depends on the net weight and height of a person
- It ignores the **distribution** of muscle and bone
- Does not differentiate between body fat and muscle mass (*body composition*)
- There is a potential risk of overestimating ‘fatness’ in individuals with high muscle mass and underestimating the fat deposit in those with less lean body mass
These men have the same height, weight, and BMI, but have very different body compositions.

<table>
<thead>
<tr>
<th>Height</th>
<th>Weight</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6'3&quot;</td>
<td>220 lbs</td>
<td>27.5</td>
</tr>
</tbody>
</table>

These men have the same height, weight, and BMI, but have very different body compositions.
Learning Objectives

• Describe the association of obesity with mortality
• Identify the contribution of gender to the relationship of obesity with mortality
• Discuss the plausibility of an inverse relationship between weight status and mortality
• List examples of diseases where leaner persons have worse health outcomes
Outline

• Evidence for an obesity paradox”
• Evidence against an obesity paradox
• Healthy obesity: fantasy or reality?
• Summary
Evidence in Favor of an Obesity Paradox
Definition of the obesity paradox

- Elevated mortality in normal weight adults as compared with overweight or obese adults
- U- or J-shaped association between weight status and mortality
Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories
A Systematic Review and Meta-analysis

Katherine M. Flegal, PhD
Brian K. Kit, MD
Heather Orpana, PhD
Barry I. Graubard, PhD

Importance Estimates of the relative mortality risks associated with normal weight, overweight, and obesity may help to inform decision making in the clinical setting.

Objective To perform a systematic review of cause mortality for overweight and obesity population.

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>RR</th>
<th>(95% CI)</th>
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<tbody>
<tr>
<td>Normal weight</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Overweight (BMI: &gt;25 to &lt;30)</td>
<td>0.93</td>
<td>(0.89 to 0.95)</td>
</tr>
<tr>
<td>Obese I (BMI &gt;30 to &lt;35)</td>
<td>1.13</td>
<td>(1.06 to 1.19)</td>
</tr>
<tr>
<td>Obese II (BMI &gt; 35)</td>
<td>1.25</td>
<td>(1.13 to 1.39)</td>
</tr>
</tbody>
</table>

Overweight men and women have lower mortality!

Estimates based on 89 studies
Findings persisted when taking into account adverse health behaviors and pre-existing disease

Flegal KM et al. JAMA 2013; 309: 71-82
“Obesity paradox” is present in women and men

Meta-analysis of 26 studies

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>1 (Referent)</td>
<td>1 (Referent)</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.97 (0.93-0.99)</td>
<td>0.97 (0.92-1.01)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.28 (1.18-1.37)</td>
<td>1.20 (1.12-1.29)</td>
</tr>
</tbody>
</table>

Summary

• Overweight women and men have a lower risk of mortality
• Obesity is associated with higher mortality

Obesity Paradox in Chronic Disease

- Obesity paradox has been observed in adults who have
  - Heart failure
  - Chronic kidney disease
  - Cancer
- Leaner weight in the setting of disease may reflect advanced disease
- Higher weight may reflect greater “metabolic reserve”
- Development of some diseases independent of obesity may reflect a unique, higher risk disease
  - Shared genes predisposing to disease and to mortality when disease occurs independent of obesity
Prevalence of Obesity and Diabetes among Adults Aged >20 years by County, 2007

Source: CDC Division of Diabetes Translation
Age-Standardized Trends in Diagnosed Diabetes by Race

Prevalence

Year

Prevalence
0 1 2 3 4 5 6 7 8 9 10

Legend:
- White Female
- Black Female
- Asian Female
Obesity Paradox in Diabetes

- Over 85% of persons with type 2 diabetes are overweight or obese
- Obesity is tied to the etiology of insulin resistance and diabetes
- Diabetes that develops independent of obesity may have a distinct etiology from “traditional” diabetes
  - Features of normal weight diabetes may be independently associated with higher mortality and contribute to an obesity paradox in diabetes
• Pooled 5 longitudinal cohort studies where BMI could be determined at the time of diabetes incidence
  - 2,625 incident diabetes/ 27,125 P-Y follow-up
  - 449 deaths

• Limitations of prior research to address this question included prevalent disease cohorts
  - Weight loss could have occurred secondary to the diagnosis of diabetes
  - Duration of diabetes was unknown
Mortality in Normal Weight vs. Overweight/Obese Incident Diabetes

SUMMARY

• Normal weight diabetes was associated with a doubling in the incidence of mortality as compared with overweight/obese diabetes

• Findings were similar for cardiovascular mortality

2.2 (95% CI: 1.4-3.4)

Carnethon et al JAMA 2012; 308: 581-590
Systematic Review of 18 Published Studies on the Obesity Paradox in Diabetes

Included studies published between 1991 and 2013 that tested the contribution of weight status on mortality in adults with diabetes and followed participants for mortality.

<table>
<thead>
<tr>
<th>Inverse</th>
<th>Direct</th>
<th>U-Shaped</th>
<th>No Association</th>
</tr>
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<tbody>
<tr>
<td>Carnethon</td>
<td>Cho</td>
<td>Ross</td>
<td>Church</td>
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<tr>
<td>Dallongeville</td>
<td>Eeg-Olofsson</td>
<td>Yano</td>
<td>Ford</td>
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<td>Doehner</td>
<td>Tobias*</td>
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<td>Landman</td>
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<td>Kokkinos</td>
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<td>Zoppini</td>
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Carnethon, Rasmussen-Torvik, Palaniappan *Current Cardiol Reports* 2014

*Not included in the review*
Summary of Plausibility of an Obesity Paradox

• Overwhelming majority of studies demonstrate an obesity paradox
  – Observed in “healthy” populations
  – Observed in the setting of chronic diseases
  – Numerous proposed alternative explanations were taken into account in the meta-analysis
Delaying mortality

• Is this our best strategy for delaying mortality?
Evidence Against an Obesity Paradox
Proposed Explanations for an Obesity Paradox

• Reverse causality
  - Pre-existing illness in normal weight persons
  - Prior study estimated the influence of this bias to be small (Flegal AJE 2011; 173: 1)
  - Excluding mortality in the first 2 years is one approach to try to account for this

• Older age
  - Sarcopenic obesity

• Smoking status
  - Leaner but higher mortality

• Heterogeneity of normal weight phenotypes in the referent arm
  - No data available to distinguish normal weight persons w/ and w/o risk factors
Body-Mass Index and Mortality among Adults with Incident Type 2 Diabetes

Deirdre K. Tobias, Sc.D., An Pan, Ph.D., Chandra L. Jackson, Ph.D., Eilis J. O’Reilly, Sc.D., Eric L. Ding, Sc.D., Walter C. Willett, M.D., Dr.P.H., JoAnn E. Manson, M.D., Dr.P.H., and Frank B. Hu, M.D., Ph.D.

Nurse’s Health Study (n=8,970) and Physicians Health Study (n=2,457) 3083 deaths over 15.8 years of follow up

• Finding from the full sample:
  – 3083 deaths over 15.8 years of follow up
  – J-shaped association with mortality
BMI at DM Diagnosis: All-Cause Mortality

The leanest men and women had higher mortality than normal weight

*p<0.05

**p<0.01
BMI and Mortality: By Age at DM Diagnosis

Elevated risk only present in older adults

A) Age <65 years

B) Age >=65 years

BMI prior to DM diagnosis
BMI at DM Diagnosis: by Smoking Status

BMI prior to DM diagnosis

adjusted for age, race, marital status, menopausal status (the NHS cohort only), family history of diabetes, smoking status, alcohol intake, and Alternate Health Eating Index dietary score.

*p<0.05
Conclusions

• J-shaped association in the total population, older adults and among smokers
  − No differences in the association between women and men
• Direct linear association among participants who had ever smoked
  − More young women are taking up smoking than young men in order to stay lean!!!

• Is this observation only relevant to adults with diabetes? What about everyone else?
Heterogeneity in Risk Factors by Obesity Phenotypes
## Four Obesity Phenotypes

<table>
<thead>
<tr>
<th>Weight Status</th>
<th>Normal weight</th>
<th>Overweight/Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Healthy&quot;</td>
<td>&quot;Healthy&quot;</td>
<td>Metabolically Healthy Obese (MHO)</td>
</tr>
<tr>
<td>Metabolically Obese Normal Weight (MONW)</td>
<td>Metabolically Obese Normal Weight (MONW)</td>
<td>Obese with RF</td>
</tr>
</tbody>
</table>
Who are the Metabolically Healthy Obese?

• Younger, non-Hispanic blacks, men, moderate alcohol drinkers and the physically active were more likely to be free from risk factors
  – Wildman RP. *Arch Intern Medicine* 2008; 168: 1617

• No differences in diet composition or self-reported activity between obese adults with and without risk factors

• Sleep duration was longer among MHO
  – Hankinson AL. *Obesity* 2013; 21: 102
Prevalence of Metabolically Healthy Obese in the US Population, by Age

National Health and Nutrition Examination Survey III

**BMI > 30 with 0 or 1 Metabolic Abnormality**

*Is this a persistent phenotype or a transitional state?*

Proportion of Obese Women Free From Risk Factors DECLINES Over 25 Years

Coronary Artery Risk Development in Young Adults: 1985-86 through 2010-2011

Obese adults do not stay free from risk factors over time

Unpublished data
Summary of Characteristics of the Metabolically Healthy Obese

- People who, although they are obese, are free from risk factors
- Few differences in healthy lifestyle behaviors
- Prevalence is inversely associated with age
- **MHO is a transitional state**
  - Initial “healthy” state gives way to the later development of risk factors
How do these non-traditional phenotypes contribute to mortality?

• If **metabolic** risk factors are driving mortality then obese without risk factors (MHO) should have lower mortality than obese with risk factors

• If **obesity** is driving mortality, then normal weight with risk factors will have lower mortality than MHO
<table>
<thead>
<tr>
<th>Weight Status</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>-</td>
</tr>
<tr>
<td>Overweight/Obese</td>
<td>+</td>
</tr>
</tbody>
</table>

**Lowest Risk**

**Intermediate risk?**

**Highest Risk**
• Meta-analysis of 8 studies describing overweight and obesity by the presence or absence of risk factors
• Participants followed longitudinally for cardiovascular events or mortality
  – Risk factor prevalence was defined by the presence of NCEP ATP III metabolic syndrome components

<table>
<thead>
<tr>
<th>Normal weight (BMI 18.5-&lt;25)</th>
<th>Overweight (BMI 25 - &lt;30)</th>
<th>Obese (BMI &gt; 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors (referent)</td>
<td>No risk factors</td>
<td>No risk factors</td>
</tr>
<tr>
<td>1+ risk factor</td>
<td>1+ risk factor</td>
<td>1+ risk factors</td>
</tr>
</tbody>
</table>
Metabolically Healthy Overweight vs. Metabolically Healthy Normal Weight

**All Studies**

Summary relative risk = 1.10 (0.9-1.24)

No difference between overweight and normal weight persons who are free from risk factors

**Restricted to studies with 10+ Y F-U**

Summary relative risk = 1.21 (0.91-1.61)

Non-significant elevation in risk of mortality among overweight vs. normal weight who are free from risk factors

Kramer CK. *Ann Intern Med* 2013; 159: 758
Metabolically Healthy Obese vs. Metabolically Healthy Normal Weight

All Studies

Summary relative risk = 1.19 (0.98-1.38)

Non significant elevated mortality in MHO vs. normal weight

Restricted to studies with 10+ Y F-U

Summary relative risk = 1.24 (1.02-1.55)

Elevated mortality in obese vs. normal weight who are free from risk factors when follow-up is at least 10 years

Kramer CK. Ann Intern Med 2013; 159: 758
Mortality risks in adults with risk factors across weight status

- Mortality and CVD risk is elevated in every weight status category
- The summary HR reported 3x higher mortality in MONW

Kramer CK. *Ann Intern Med* 2013; 159: 758
Summary of MHO and Mortality

- There is no such thing as "healthy obesity". All obese adults had elevated mortality vs. NW w/o RF.
- Differences emerged with at least 10 years of follow-up.
- Likely that risk factors develop over time.

- Evidence for elevated risk with overweight is not significant.
- Trend towards elevated mortality with borderline significance.
- Stronger effect with longer follow-up.

My observation based on longitudinal analyses in CARDIA:
- Adults do not stay overweight, but typically "track" into obesity.

Kramer CK. Ann Intern Med 2013; 159: 758
Implications
Obesity and Life Expectancy

• Previous generations saw a steady rise in life expectancy

• In the past 30 years these rates of slowed

• Obesity epidemic is expected to have a negative effect on life expectancy
  − Lifetime risk of diabetes is 30-40%
  − Diabetes has a life shortening effect of approx. 13 years

• Non-fatal conditions and disability also expected to rise

Olshansky SJ. NEJM 2005; 352: 111
Potential Gain in Life Expectancy if Obesity were Eliminated

Olshansky SJ et al. *NEJM* 2005; 11: 1138
Impaired QOL by Weight Status Results

• Obese
  – Lower overall health perception
  – Poorer physical functioning
  – Poorer social functioning (women only)

• Overweight
  – Impaired physical well-being (women only)

• Similar patterns of poor QOL reported by underweight persons

• Normal body weight important in older age
Summary

• Substantial burden of illness and death associated with overweight and obesity

• Cardiovascular disease incidence and death demonstrates strong association
  - Cancer deaths also associated with overweight

• Expected declines in life expectancy attributable, in part, to obesity epidemic

• Poor quality of life with obesity
What should scientists believe? What should the public believe?

**Today’s Random Medical News**

- Exercise
- Smoking
- Coffee
- Computer terminals
- Stress
- Red wine
- CAN CAUSE
- Hypothermia
- Dehydration
- Fatigue
- Anemia
- Headache
- Depression
- Spontaneous regression
- Glaucoma

- IN
- In families
- Two-income families
- 7 out of 10 men

- Twin
- Children
- Reduced weight
- Smoke

*According to a report released today...*

---

*Jim Borgman*

*The Cincinnati Enquirer*

*King Features Syndicate*
Future Directions: Addressing the Obesity Epidemic

- The public wants to believe in an obesity paradox
  - Studies which suggest that obesity is not a problem are covered heavily by the media
  - Studies with the opposite findings are not

- Rising rates of obesity in the population have shifted the public gaze towards normalizing obesity

- Rigorous and objective research needs to be carried out to describe the “reality”

- Public health messages about the findings must be non-judgmental

- Solutions that can be translated and disseminated must be proposed in order to reach the highest risk subpopulations
Acknowledgements

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  – NIDDK R21DK082903 2009-2012
  – CARDIA contracts

<table>
<thead>
<tr>
<th>Name and Affiliation</th>
<th>Affiliation</th>
</tr>
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<tbody>
<tr>
<td>Peter de Chavez, MS</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Alan Dyer, PhD</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Caroline Fox, MD</td>
<td>Framingham Heart Study</td>
</tr>
<tr>
<td>Kiang Liu, PhD</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>James Meigs, MD</td>
<td>Harvard Medical School</td>
</tr>
<tr>
<td>James Pankow, Ph.D.</td>
<td>University of Minnesota</td>
</tr>
</tbody>
</table>
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Thank You