Untangling the “Heavy” Cardiovascular Burden of Obesity and the "Obesity Paradox"

Carl J. Lavie, MD, FACC, FACP, FCCP
Professor of Medicine
Medical Director, Cardiac Rehabilitation and Preventive Cardiology
Director, Exercise Laboratories
John Ochsner Heart and Vascular Institute
Ochsner Clinical School-The UQ School of Medicine
New Orleans, La

Obesity and Obesity Paradox and CVD-Original Research

- Lavie CJ, Milani RV. Am J Cardiol 1997;79:397-401
- Lavie CJ et al. Am J Cardiol 2003;91:891-894
- Lavie CJ et al. Am J Cardiol 2007;100:1460-1464
- De Schutter A, Lavie CJ et al. PGM 2011;123(6):72-78
- Lavie CJ et al. JACC 2012; 60: 1374-1380
- De Schutter A, Lavie CJ et al. Am J Cardiol 2013; on-line

Obesity and Obesity Paradox and CVD-Major Reviews/Editorials

- Lavie CJ, Milani RV JACC 2003;42:677-679
- Lavie CJ et al. Eur Heart J 2005;26:5-7
- Artham SM, Lavie CJ et al. PGM 2008;120(2):34-41
- Lavie CJ et al. Heart 2013;99(9): 596-598
Weight Index Doesn’t Tell the Whole Truth

August 30, 2010

Why, when I weigh the same as or less than I did when I was younger, does my waist keep getting bigger? Phrased another way, the question could be “Why, when my body mass index (BMI) for height, is a crude measure of fatness in individuals. Calculated by dividing one’s weight in kilograms by the square of one’s height in meters, it doesn’t differentiate between fatty and lean tissue. ‘The BMI tables are excellent for identifying obesity and body fat in large populations, but they are far less reliable for determining fatness in individuals,” explained Dr. Carl Lavie, a cardiologist at the Ochsner Heart and Vascular Institute in New Orleans.

Fat Tissue, Lean Tissue

Fat takes up about four times the space of muscle tissue, for example, so it is quite possible to look and feel fatter even if your height and weight remain the same. This is particularly common among women past 50 and men past 60, and the results are likely to show around the middle. For children and the elderly, body mass values can be particularly misleading because the relationship of lean body mass to height changes as they get older. The maintenance of body fat in adults is determined by the rate of energy intake and expenditure. The degree of body fat can be estimated by determining if the body fat is under normal weight, overweight or obese. Thus, usually more than 25% of body fat is considered obese, 18% to 24% is normal, 16% to 21% is overweight, 13% to 15% is obese, and 11% to 12% is morbidly obese.

The New York Times

Obesity and Cardiovascular Disease

- Obesity increasing in epidemic proportions
- Body mass index (BMI) is primarily used
- Body fatness, waist circumference (WC), waist to hip ratio (WHR), and waist to height ratio may be superior

Lavie CJ et al. JACC 2009;53:1925-1932
Obesity and Cardiovascular Diseases

- 70% of adults in US are overweight or obese
- Morbid obesity especially increased
- Obesity is second to only tobacco abuse as the #1 cause of preventable death in US
- Due to obesity, we may soon see a reversal in the steady increase in life expectancy

Lavie CJ et al. JACC 2009;53:1925-1932

Adverse Effects of Obesity

- Increases in insulin resistance
  - Glucose intolerance
  - Metabolic Syndrome
  - Type 2 Diabetes Mellitus
- Hypertension
- Abnormal LV Geometry
  - Concentric Remodeling
  - LVH

Lavie CJ et al. JACC 2009;53:1925-1932

Adverse Effects of Obesity

**DYSLIPIDEMIA**
- Elevated total cholesterol
- Elevated VLDL and triglycerides
- Elevated LDL and small, dense particles
- Elevated non-HDL
- Elevated apolipoprotein B
- Reduced HDL and apolipoprotein A-1

Lavie CJ et al. JACC 2009;53:1925-1932
Adverse Effects of Obesity

- Abnormal endothelial function
- Abnormal systolic and diastolic LV function
- Increased systemic inflammation (eg CRP)
- Increased Pro-thrombotic state
- Albuminuria
- Obstructive sleep apnea / sleep disordered breathing

Lavie CJ et al. JACC 2009;53:1925-1932

Cardiovascular Diseases Associated With Obesity

- Hypertension
- Heart Failure
- Coronary Heart Disease
- Atrial Fibrillation
- Complex Ventricular Dysrhythmias
- Stroke
- Venous Thromboembolism
- OSA / SDB

Lavie CJ et al. JACC 2009;53:1925-1932

Obesity and CV Disease

BMI Associated Death Risk: General Population

Higher BMI → ↑ Risk of Development of Mortality in the General Population

Meta-Analysis of BMI and Survival

- 97 studies, 2.88 million individuals, >270,000 deaths
- Relative to normal weight, obesity (all grades combined) and grades 2 and 3 obesity were associated with higher all-cause mortality
- Grade 1 obesity was associated with a trend for lower mortality (HR 0.95; CI 0.88-1.01), and overweight had significantly lower mortality (HR 0.94; CI 0.91-0.96)

“Obesity Paradox” and Cardiovascular Diseases

Although obesity has been implicated as one of the major risk factors for most CV diseases, including HTN, HF, and CHD, evidence from clinical cohorts of patients with established CV diseases indicates an “obesity paradox” because overweight and obese with these diseases tend to have a more favorable short- and long-term prognosis.
**Obesity and Hypertension**

- Obesity increases levels of BP
- Obesity increases CR and LVH, independent of BP
- Obesity increases metabolic abnormalities in HTN
- Despite the increased prevalence, obese hypertensives have a favorable prognosis

Lavie CJ et al. JACC 2009;53:1925-1932

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**BMI and HTN Prognosis**

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**“Obesity Paradox” and Hypertension**

In aggregate, although obesity is a powerful risk factor for hypertension and LVH, obese hypertensive patients may paradoxically have a better prognosis, possibly due to low SVR and PRA

Lavie CJ et al. JACC 2009;53:1925-1932
Impact of Obesity and the Obese Paradox on Prevalence and Prognosis in Heart Failure


BMI and HF Prevalence

BMI and HF Prognosis

Kouchakchah SB et al. BMJ 2002;329:805-810

**Obesity Status and Heart Failure Mortality**

**Meta-Analysis of 9 Observational Studies**

The message from >28,000 CHF patients:
Once you have heart failure, bigger = live longer

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**BMI and HF Hospital Mortality**

- 108,927 decompensated HF patients
- Higher BMI associated with lower mortality
- For every 5-unit increase in BMI, HF mortality was 10% lower (p < 0.001)


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**Body Composition and HF Prognosis**

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Possible Reasons for Obesity Paradox in Heart Failure

- Advanced HF is catabolic state; obese may have more metabolic reserve
- Adipose tissue produces TNF-α receptors that may neutralize TNF-α
- Obese have lower ANP and PRA
- Obese have higher BP, so may tolerate more meds
- Higher circulating lipoproteins may detoxify lipopolysaccharides that effect inflammatory cytokines

Lavie CJ et al. JACC 2009;53:1925-1932

Obesity and CHD

- Obesity adversely affects most major CV risk factors (HTN, dyslipidemia, MetS/T2DM)
- Obesity probably an independent CHD risk factor
- Obesity strongly related with 1st premature MI at young age (Mandala MC et al. JACC 2008;52:979-985)

Lavie CJ et al. JACC 2009;53:1925-1932

Obesity Paradox and CHD

- 40 cohort studies of over 250,000 CHD patients followed for 3.8 years
- Overweight and obese had lower risk of total and CV mortality compared with underweight and "normal" weight patients
- Similar in stable CHD, PCI and CABG
- In BMI ≥ 35 kg/m², there was excess risk of CV mortality without an increase on total mortality

Obesity Paradox and CHD

- 529 consecutive CHD patients post events
- Overweight and obese (n = 393) had more adverse CHD risk profiles than leaner patients (n = 136)
- During 3-year follow-up, overweight/obese had significantly lower mortality

Obesity Paradox and CHD


The "Obesity Paradox" in CHD

The "Obesity Paradox" in CHD


Body Composition and CHD Mortality

De Schutter A, Lavie CJ et al. Am J Cardiol, online December,2012
Lean Mass Index and CHD Mortality

- Lavie CJ et al. JACC 2012;60: 1374-1380

Body Fat, Lean Mass Index and CHD Mortality

- Lavie CJ et al. JACC 2012; 60: 1374-1380

Obesity Paradox and CHD Mechanisms

- None of the studies accounted for non-purposeful weight loss
- Lower renin and ANP in obese
- Confounders
- COPD
- Impact of Fitness
- Baseline genetic differences

Obesity Paradox and CHD
Impact of Central Obesity and Fitness


Impact of Fitness on All-Cause Mortality in CHD

BMI
Waist Circumference
% Body Fat
Impact of Fitness on CVD Mortality in CHD

BMI

Waist Circumference

% Body Fat

Impact of Cardiorespiratory Fitness on the Obesity Paradox in Patients With Heart Failure

Low Fitness

Higher Fitness

Fitness, Mortality, Obesity Paradox in Heart Failure


Obesity Paradox and CVD Impact of Cardiorespiratory Fitness

- Goel K et al. Am Heart J 2011;16(3):590-597
- Lavie CJ et al. Circulation 2012; Nov, in press

Obesity and Mortality

Baseline Characteristics (n=35,607)

<table>
<thead>
<tr>
<th>Age</th>
<th>60 ± 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>53% female</td>
</tr>
<tr>
<td>BMI</td>
<td>29.2 ± 6.7 kg/m²</td>
</tr>
<tr>
<td>EF</td>
<td>60 ± 5 %</td>
</tr>
<tr>
<td>LVMI</td>
<td>82 ± 32 g/m²</td>
</tr>
<tr>
<td>RWT</td>
<td>0.43 ± 0.07</td>
</tr>
</tbody>
</table>

Lavie CJ et al. Am J Cardiol 2007;100:1460-1464

LV Geometry and Obese Mortality

* p<0.0001

3.9% Obese
7.8% Non-Obese

Lavie CJ et al. Am J Cardiol 2007;100:1460-1464
**BMI and Mortality**

- **BMI Category**
  - <18.5: 51P
  - 18.5-24: 9,857
  - 25-29: 13,450
  - 30-34: 6,788
  - 35+: 5,004

- **3-Year Mortality (%)**
  - <18.5: 17.9
  - 18.5-24: 8
  - 25-29: 5
  - 30-34: 3.9
  - 35+: 4

Lavie CJ et al. Am J Cardiol 2007;100:1460-1464

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**Obesity and Mortality**

**Multivariate Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chi-Square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher age</td>
<td>785</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lower BMI</td>
<td>32.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>10.3</td>
<td>0.0013</td>
</tr>
<tr>
<td>Higher RWT</td>
<td>7.6</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Lavie CJ et al. Am J Cardiol 2007;100:1460-1464

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**LV Geometry and Obese Mortality**

**Multivariate Predictors of Mortality**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chi-Square</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher age</td>
<td>198</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Higher RWT</td>
<td>22.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High BMI</td>
<td>14.4</td>
<td>=0.0001</td>
</tr>
<tr>
<td>Higher LVMI</td>
<td>13.5</td>
<td>=0.0002</td>
</tr>
<tr>
<td>Male gender</td>
<td>8.9</td>
<td>=0.03</td>
</tr>
</tbody>
</table>

Lavie CJ et al. Am J Cardiol 2007;100:1460-1464
Mortality Prevalence by BMI Categories in Females

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>10.2</td>
</tr>
<tr>
<td>18.5-25</td>
<td>7.4</td>
</tr>
<tr>
<td>25-30</td>
<td>6.2</td>
</tr>
<tr>
<td>30-35</td>
<td>5.4</td>
</tr>
<tr>
<td>≥35</td>
<td>5.8</td>
</tr>
</tbody>
</table>


Mortality in Four LV Geometric Patterns in Females with Preserved Systolic Function

<table>
<thead>
<tr>
<th>Geometric Pattern</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5.6</td>
</tr>
<tr>
<td>CR</td>
<td>12.3</td>
</tr>
<tr>
<td>EH</td>
<td>12.7</td>
</tr>
<tr>
<td>CH</td>
<td>18.6</td>
</tr>
</tbody>
</table>

P<0.001 compared with normal
P<0.01 compared to CR
P<0.001, non-obese vs. obese


Obesity and Atrial Fibrillation

- As with obesity, AF is also epidemic, and is expected to increase by 2.5-fold by 2050
- May be due to HTN, CHD, and HF
- Obesity appears to be a significant AF risk factor
- In a meta-analysis of 16 studies of 125,000 subjects, obesity increased the risk of AF by 49% ( Wanahita N, Messerli FH et al. Am Heart J 2008;155: 310-315.)

Lavie CJ et al. JACC 2009;53:1925-1932
Obesity Paradox in Atrial Fibrillation

**ARRIRM Study (n=4,060)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (continuous distribution)</td>
<td>0.95</td>
<td>0.93-0.98</td>
<td>.003</td>
</tr>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.03-1.06</td>
<td>.02</td>
</tr>
<tr>
<td>Consecutive heart failure</td>
<td>2.16</td>
<td>1.71-2.72</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.81</td>
<td>1.64-2.28</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.98</td>
<td>1.53-2.51</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.72</td>
<td>1.26-2.37</td>
<td>.007</td>
</tr>
<tr>
<td>Rhythm control arm</td>
<td>1.30</td>
<td>1.04-1.61</td>
<td>.02</td>
</tr>
</tbody>
</table>

BMI = body mass index; CI = confidence interval.
Male sex (P = .79), beta-blocker therapy (P = .04), and hypertension (P = .12) were removed on a priori stepwise selection.

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Obesity Paradox in Atrial Fibrillation

**ARRIRM Study (n=4,060)**

<table>
<thead>
<tr>
<th>Combined Endpoint</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight vs Normal</td>
<td>0.73 (0.64-0.82)</td>
<td>.0007</td>
<td></td>
</tr>
<tr>
<td>Obese vs Normal</td>
<td>0.63 (0.50-0.82)</td>
<td>.0004</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>0.96 (0.85-1.09)</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>Overweight vs Normal</td>
<td>0.96 (0.85-1.09)</td>
<td>.24</td>
<td></td>
</tr>
<tr>
<td>Obese vs Normal</td>
<td>0.65 (0.51-0.83)</td>
<td>.0005</td>
<td></td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>0.96 (0.86-1.04)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Overweight vs Normal</td>
<td>0.96 (0.86-1.04)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Obese vs Normal</td>
<td>0.66 (0.42-0.99)</td>
<td>.03</td>
<td></td>
</tr>
</tbody>
</table>

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Obesity Paradox in Atrial Fibrillation

**ARRIRM Study (n=4,060)**

Cumulative Hazard

- BMI 18.5-25.9
- BMI 26.0-30
- BMI >30

Days
Weight Loss in CV Diseases

• Obesity increases most CV risk factors and CV diseases
• However, an "obesity paradox" is present
• Weight loss improves risk factors
• Impact of weight loss on CV events remains controversial


Potential Adverse Effects of Weight Loss

• Obesity Paradox
• Prolonged QTc and increased ventricular dysrhythmias (starvation, very low calorie, liquid protein diets, and obesity surgeries)
• Pharmacologic agents have limited efficacy and considerable toxicity

Lavie CJ et al. JACC 2009;53:1925-1932

Weight Loss and Lifestyle Modifications

• Calorie restriction and exercise training is safe and is associated with 60% reduction in development of T2DM
  — Knowler WL et al. NEJM 2002;346:393-403
• CRET reduces MS by 37%
  — Milsan R, Lavie CJ. AJC 2003;92:35-34
• In 1,500 CHD patients, 6 month weight loss programs associated with lower CHD events in 4 years
• In 377 patients at Mayo Clinic, weight loss, even in those with BMI < 25 kg/m2, was associated with reduced mortality/CV events
**Weight Loss in CV Diseases**

- In HTN, weight loss reduces BP and LVH
- In HF, weight loss improves LVM, systolic and diastolic LV function, and functional class
- Obesity surgery improves CHD risk factors, T2DM, and short- and long-term mortality
- Obesity surgery in small studies is safe in CHD and HF

Lavie CJ et al. JACC 2009;53:1925-1932

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**Obesity, HF and Weight Loss**

**Guideline Statements**

- American Heart Association 40 kg/m²
- Heart Failure Society of America 35 kg/m²
- European Society of Cardiology 30 kg/m²
- Canadian Cardiovascular Society 30 kg/m²

- Vastly different cut-points due to minimal data by which to base these exact recommendations
- Clearly further research is needed to determine ideal BMI and body composition in CVD, including systolic and diastolic HF
Household Management Energy Expenditure in Women over 5 Decades

Archer E et al. PLOS ONE 2013;8(2): e 56620

Trends over 5 Decades in U.S. Occupation-Related Physical Activity and Their Associations with Obesity

Church TS et al. PLOS ONE 2011;6(5): e19657

Occupational METs over 5 Decades

Church TS et al. PLOS ONE 2011;6(5): e19657
Occupational EE and Obesity

Church TS et al. PLOS ONE 2011;6(5): e19657

Obesity and CV Diseases

Summary and Conclusions

- Overwhelming evidence supports the importance of obesity in the pathogenesis and progression of most CV diseases
- An Obesity Paradox exists
- At present, evidence supports purposeful weight reduction
- If the current obesity epidemic continues, we may soon witness an unfortunate end to the steady increase in life expectancy

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