You are serving as a delegate at the AMA House of Delegates. You are asked: Is obesity a disease?

1. Yes
2. No

Prevalence of Obesity (Adults)

- **Obesity:** 33.8%
  - Men: 32.2%  Women: 35.5%
- **Overweight + obesity:** 68%
  - Men: 72.3%  Women: 64.1%
- **Severe Obesity:** 6%
Prevalence of Obesity (Children)

- Severe obesity (97 percentile): 11.9%
- Obesity (95 percentile): 16.9%
- Overweight (85 percentile): 31%
- No increase from 1999 to 2008
  - (except severe obesity in boys)

Prevalence of Obesity and Trends in Body Mass Index Among US Children and Adolescents, 1999-2010

Obesity Disparities

- Women, 40-59
  - Black: 52%, Hispanic: 47%, Whites: 36%
- Teens
  - Black: 29%, Hispanic: 17.5%, Whites: 14.5%
- Mental illness
  - Overweight + obese: 83%
For a 40 yo woman, with normal BP, lipids, and FBS which BMI is associated with the lowest all-cause mortality?

1. 18
2. 24
3. 28
4. 34
5. 38

For a 40 yo woman, with normal BP, lipids, and FBS which BMI is associated with the lowest all-cause mortality?

1. 18
2. 24
3. 28
4. 34
5. 38

CLASSIFICATION OF OVERWEIGHT AND OBESITY BY BMI

<table>
<thead>
<tr>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight I</td>
<td>25.0 – 29.9</td>
</tr>
<tr>
<td>Obesity II</td>
<td>30.0 – 34.9</td>
</tr>
<tr>
<td>Extreme Obesity III</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Flegal, JAMA, 2005

BMI AND MORTALITY:

Combined NHANES I, II, and III data set

<table>
<thead>
<tr>
<th>BMI</th>
<th>25-59 y</th>
<th>60-69 y</th>
<th>≥70 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>1.38</td>
<td>2.30</td>
<td>1.69</td>
</tr>
<tr>
<td>18.5-&lt;25</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>0.83</td>
<td>0.95</td>
<td>0.91</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>1.20</td>
<td>1.13</td>
<td>1.03</td>
</tr>
<tr>
<td>≥35</td>
<td>1.63</td>
<td>1.63</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Flegal, JAMA, 2005

MORTALITY AND OBESITY

Meta-analysis of 97 studies of 2.8M people, 270,000 deaths

<table>
<thead>
<tr>
<th>BMI</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 25 (Normal)</td>
<td>1.0</td>
</tr>
<tr>
<td>25-30 (Overweight)</td>
<td>0.94</td>
</tr>
<tr>
<td>Above 30 (Obese)</td>
<td>1.18 ***</td>
</tr>
<tr>
<td>30-35 (Grade 1 Obesity)</td>
<td>0.95</td>
</tr>
<tr>
<td>Above 35 (Grade 2/3 Obesity)</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Flegal, JAMA, 2013
For a 40 yo woman, with normal BP, lipids, and FBS which BMI is associated with the lowest all-cause mortality?

1. 18
2. 24
3. 28
4. 34
5. 38

You are serving as a delegate at the AMA House of Delegates. You are asked: Is obesity a disease?

1. Yes
2. No

Epidemic of Inactivity

60% US adults don’t exercise regularly
25% are sedentary

**EXERCISE FOR OBESITY**

Meta-analysis of 43 RCTs: 3476 participants

- Exercise plus diet vs diet alone
  - -1.1 kg

- Increased intensity of exercise
  - -1.5 kg

- Exercise without weight loss
  - Reduced: BP, triglycerides, blood sugar

Shaw, Cochrane, 2006
**FITNESS AND MORTALITY**

Aerobics Center Longitudinal Study

25,714 men, 44 years old, 14 year observational study

<table>
<thead>
<tr>
<th>CV death (RR)</th>
<th>normal</th>
<th>overweight</th>
<th>obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit</td>
<td>1.0</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Not fit</td>
<td>3.1</td>
<td>4.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total death (RR)</th>
<th>normal</th>
<th>overweight</th>
<th>obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Not fit</td>
<td>2.2</td>
<td>2.5</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Relative Risk* of Death According to Body Mass and Physical Activity

<table>
<thead>
<tr>
<th>Physical activity level</th>
<th>1 – 3.4 hours/week</th>
<th>1 – 2 hours/week</th>
<th>&lt; 1 hour/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 – 29.9 BMI</td>
<td>2.42</td>
<td>1.91</td>
<td>1.64</td>
</tr>
<tr>
<td>&gt; 30 BMI</td>
<td>1.54</td>
<td>1.28</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* RR’s adjusted for age, smoking status, family history, menopausal status, hormone use, and other factors
** Reference group = women with 3.5 or > hours/week of physical activity and BMI of 25 or less


---

**Estimating Calorie Needs**

To estimate calories for weight maintenance:
- If you are moderately active, multiply current weight (pounds) x 15.

To estimate calories for weight loss:
- Subtract 500 calories to lose approximately 1.0 pound per week
- A pound of fat is about 3500 kcals
COMPARISON OF ATKINS, ORNISH, WEIGHT WATCHERS, AND ZONE

160 patients, randomly assigned

**Intention to treat at 1 year**

<table>
<thead>
<tr>
<th></th>
<th>Atkins</th>
<th>Ornish</th>
<th>WW</th>
<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt Loss (kg)</td>
<td>2.1</td>
<td>3.3</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Completers (%)</td>
<td>53</td>
<td>50</td>
<td>65</td>
<td>65</td>
</tr>
</tbody>
</table>

**Completers at 1 year**

<table>
<thead>
<tr>
<th></th>
<th>Atkins</th>
<th>Ornish</th>
<th>WW</th>
<th>Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt Loss (kg)</td>
<td>3.9</td>
<td>6.6</td>
<td>4.6</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Dansinger, JAMA, 2005

**Weight loss associated with adherence, but not diet type**

- Each group: 25% lost 5%, 10% lost 10% of initial weight
- Each diet reduced LDL/HDL by 10%
- No significant effects on BP or glucose

COMPARISON OF WEIGHT LOSS DIETS WITH DIFFERENT MACRONUTRIENTS

- RCT of 811 patients, 4 diets: fat/protein/carbs
  - 20/15/65, 20/25/55, 40/15/45, 40/25/35
- 6 months: 6kg, 7% weight; 2 years: completers lost 4kg; 15% lost 10% of weight
- Results similar for:
  - 15% pro v. 25% pro
  - 20% fat v. 40% fat
  - 35% carbs v. 65% carbs
- Attendance highly correlated with weight loss; satiety, hunger, lipids, insulin all equal

Sacks, NEJM, 2009

Heterogeneity of Response to Weight Loss Diets: Insulin Resistance

- Insulin sensitive: low carb and high carb both effective for weight loss
- Insulin resistant: low carb more effective
Very Low Calorie Diets (VLCD) vs Low Calorie Diets (LCD): Meta-analysis of 6 RCTs

- Trials with direct comparisons
- Short-term: mean 12.7 weeks
- Long-term: mean 1.9 years

Weight loss (as % of initial weight):

<table>
<thead>
<tr>
<th></th>
<th>short-term</th>
<th>long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCDs</td>
<td>9.7</td>
<td>5.0</td>
</tr>
<tr>
<td>VLCDs</td>
<td>16.1</td>
<td>6.3</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.001)</td>
<td>(0.2)</td>
</tr>
</tbody>
</table>

Tsai and Wadden, Obesity, 2006

WEIGHT LOSS DIET BOTTOM LINE

- The type of diet does not really matter for weight loss.
- Sticking to the diet does matter
- Calories “trump” macronutrients
- But, select healthy, nutrient rich foods

Weight Loss Diet Tips

- Ready to lose weight?
- Set realistic expectations.
- Choose diet that is easy to follow and compatible with lifestyle.
- Control portion size (plate method, etc).
- Vegetables, fruit and whole grains
- Maintaining the weight you lose is key.

BEHAVIORAL ASPECTS OF WEIGHT LOSS

- Goal setting
- Self-monitoring
- Stimulus control
- Cognitive skills
40 yo woman, BMI 36. Much to your surprise (and satisfaction), she has lost 35 pounds. In order to maintain her new weight, her lifelong daily calorie intake should be:

1. 2000 kcals
2. 1800 kcals
3. 1600 kcals
4. 1400 kcals
5. 1200 kcals

SUCCESSFUL WEIGHT LOSS MAINTENANCE
- 3000 subjects in National Weight Control Registry: 30-lb weight loss for 1-year
- Average weight loss 33 kg (10 BMI units less), average weight maintenance 5.5 years
- 45 years old, 80% women, 97% Caucasian
- 46% overweight as child, 46% one parent obese, 27% both parents

SUCCESSFUL WEIGHT LOSS MAINTENANCE
- High levels of physical activity
  - Women 2545 kcal/week, men 3293 kcal/week
  - (1-hour moderate intensity per day
  - Only 9% report no physical activity
- Diet low in calories
  - 1381 kcal day
  - 4.87 meals or snacks/day
  - Fast food 0.74/week
- Regular self-monitoring of weight
  - 44% weigh once per day; 31% once per week
40 yo woman, BMI 36. Much to your surprise, she has lost 35 pounds. In order to maintain her new weight, her lifelong daily calorie intake should be:

1. 2000 kcals
2. 1800 kcals
3. 1600 kcals
4. 1400 kcals
5. 1200 kcals

In the last year, I have prescribed a medication for weight loss.

1. Yes
2. No

The medication I have most commonly prescribed for weight loss is:

1. Phentermine
2. Orlistat (Xenical™, Alli™)
3. Bupropion (Wellbutrin™)
4. Exenatide (Byetta™, Bydureon™)
5. Phentermine/topiramate (Qsymia™)
6. Locaserin (Belviq™)
7. Other
MANAGEMENT OF OBESITY: A SYSTEMATIC APPROACH

Robert Baron, MD, MS

The Neuroendocrinology of Energy Balance

"LONG TERM" PHARMACOTHERAPY OF OBESITY
Review of all RCT's more than 36 weeks published since 1960
Weight loss in excess of placebo:

<table>
<thead>
<tr>
<th>Drug</th>
<th>% of Initial</th>
<th>kg's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phen-fen</td>
<td>11.0%</td>
<td>9.6 kg</td>
</tr>
<tr>
<td>Phentermine</td>
<td>8.1%</td>
<td>7.9 kg</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>5.0%</td>
<td>4.3 kg</td>
</tr>
<tr>
<td>Orlistat</td>
<td>3.4%</td>
<td>3.4 kg</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>3.0%</td>
<td>2.5 Kg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-0.4%</td>
<td>-0.4 kg</td>
</tr>
<tr>
<td>Diethypropion</td>
<td>-1.5%</td>
<td>-1.5 kg</td>
</tr>
</tbody>
</table>

James, NEJM 2010

SIBUTRAMINE AND CARDIOVASCULAR OUTCOMES (SCOUT)
- 9804 patients, over 55, with CV disease or diabetes
- Sibutramine vs. placebo, 3.4 year f/u
- Outcomes MI, stroke, cardiac arrest, CV death

Results
- Weight: -1.7 kg
- BP: 1.2 vs 1.4 mm Hg
- Combined outcome: 11.4% vs. 10.0% (HR 1.16; p = 0.02)
- Nonfatal MI: 4.1% vs. 3.1% (HR 1.28; p = 0.02)
- Nonfatal Stroke: 2.6% vs 1.9% (HR 1.36; p = 0.03)
- Death: No differences

Smith, NEJM, 2010

LORCASERIN
- Selective serotonin 2C receptor agonist
- RCT of 3,182 adults, 52 week study
- 45% vs. 55% drop-out (lorcaserin vs. placebo)
- 5.8 ± 0.2 kg vs. 2.2 ± 0.1 kg wt. loss
- Frequent adverse events: headache, dizziness, and nausea
- No increase in valvulopathy

Smith, NEJM, 2010
Weight Loss Medications: October, 2010

- Sibutramine (Meridia™): withdrawn by Abbott
  - Increased risk of stroke and MI

- Lorcaserin (selective serotonin receptor agonist, more specific than fenfluramine): not approved by FDA
  - Animals with increased mammary adenocarcinoma

- Phentermine/topiramate (Qnexa™): not approved by FDA
  - Psychiatric adverse events: sleep, anxiety depression: 21% vs 19% with placebo
  - Increased heart rate
  - Teratogenicity

Lorcaserin Update: May-June 2012

- FDA panel approved after new round of studies

- Industry sponsored study: 604 patients with type 2 diabetes
  - After 1 year, 3.1% more weight loss (criteria >5%)
  - 38% lost >5% weight vs. 16% on placebo

- Lingering uncertainty re breast tumors, valvular heart disease, psychiatric issues

- Approved June 2012. Trade name Belviq™

Lorcaserin Update (Belviq™): June 2013

- Classified as Schedule IV controlled substance

- Available as of June 7, 2013

Phentermine/Topiramate Update: February-July 2012

- FDA panel approved 20:2

- Industry sponsored study: 4323 subjects
  - 9.3% weight loss
  - Increased heart rate, increased cleft lip

- Recommend post-market monitoring for CV risk and recommendation against use in pregnancy

- Company plans larger trial (16,000 subjects)

- Approved July 2012. Trade name Qsymia™
Phentermine/Topiramate (Qsymia™) Side Effects

- Paraesthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth
- Fetal harm: cleft lip, cleft palate
- Mood disorders: anxiety and depression
- Suicidal thoughts or behavior
- Acute angle glaucoma
- Cognitive dysfunction: concentration memory, language
- Metabolic acidosis and renal failure
- Hypoglycemia (in association with diabetes meds)
- Interactions with alcohol and sedatives

Prescribing Phentermine/Topiramate (Qsymia™)

- Two prescriptions:
  - 14 days on 3.75/23 and
  - 30 days on 7.5/46
- Need DEA #
- Fax to certified pharmacy
- Pharmacy will call patient
- Drug delivered to patient’s home
- Local pharmacy availability soon

Other Investigational Drugs

- Buproprion/naltrexone (Contrave™): Approved by FDA panel 12/10; rejected by FDA 2/11 (concern re heart attacks and CV risk.)
- Buproprion/zonisamide (Empatic™): Phase 3
- Exenatide (Byetta™), Liraglutide (Victoza™): Phase 2/3
- Pramlintide/metreleptin: Phase 2/3
- Cetilistat: Phase 3 in Japan

Principles of Drug Therapy

- NIH: BMI ≥ 30 kg/m² or 27 kg/m² with co-morbidity (but in practice almost never)
- Motivated to begin structured exercise and low calorie diet
- Begin medications at completion of one month successful diet and exercise
- Continue medications only if additional weight loss achieved in first month with meds
Wouldn’t It Be Easier Just To Have Surgery?

Definition BMI
- Normal < 25
- Overweight 25-29.9
- Obese, class 1 30-34.9
- Obese, class 2 35-39.9
- Obese, class 3 40+
- “Superobese” 60+

Types of Surgery
- Restrictive
  - Horizontal Gastroplasties
  - Vertical Banded Gastroplasty (VGB)
  - Silastic Ring Vertical Gastroplasty (SRVG)
  - Adjustable Gastric Banding
  - Sleeve Gastrectomy
- Malabsorptive
  - Jejunooileal Bypass (JIB)
  - Biliopancreatic Diversion (BPD)
  - Duodenal Switch
  - Long Limb Gastric Bypass
- Restrictive with Malabsorptive Component
  - Roux-en-Y Gastric Bypass (RYGBP)

Restrictive and Mixed Procedures

- VBG Adjustable Gastric Banding Roux-en-Y GB
LONG-TERM OUTCOMES OF LAP BAND

- 151 patients, single center, 12 year f/u; 54.3% included (82/151)
- Operative mortality: 0
- Mean weight loss: 20.75 kg (BMI decreased from 41.6 to 33.8)
- 60% of patients satisfied; overall quality of life unchanged
- 39% major complications; 60% required re-operation

Conclusion: Lap band results in poor long-term outcomes

Sleeve Gastrectomy Indications

- Very high risk of co-morbidities
- BMI >60
- Possible non-compliance with meds (less risk of micronutrient deficiencies)
- IBD, IBS, abdominal pain, SBO, adhesions, other GI morbidities
Bariatric Surgery and Mortality
Swedish Obese Subjects Study

- 4047 subjects, surgery vs. matched control. 10.9 years f/u

<table>
<thead>
<tr>
<th></th>
<th>Max weight loss %</th>
<th>Final weight loss %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Vertical banded</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Gastroplasty</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Banding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Resolution of Comorbidities

35 yo woman, BMI 42 in good health, asks about bariatric surgery. Her surgeon suggests a laparoscopic roux-n-y. Her risk of mortality, DVT, reintervention, or prolonged hospital stay is:

1. 1 in 200
2. 1 in 100
3. 1 in 50
4. 1 in 25
5. 1 in 10

BARIATRIC SURGERY OUTCOMES

- Ten sites, 4776 patients. 3/4 roux-en-y (87% lap); 1/4 lap band
- 30 Day overall mortality: 0.3%
  - lap band 0.0%
  - roux-en-y (lap) 0.2%
  - roux-en-y (open) 2.1%
- Composite (death, DVT, reintervention, 30 + days in hosp): 4.1%
  - lap band 1.0%
  - roux-en-y (lap) 4.8%
  - roux-en-y (open) 7.8%
35 yo woman, BMI 42 in good health, asks about bariatric surgery. Her surgeon suggests a laparoscopic roux-n-y. Her risk of mortality, DVT, reintervention, or prolonged hospital stay is:

1. 1 in 200
2. 1 in 100
3. 1 in 50
4. 1 in 25
5. 1 in 10

57 yo woman, BMI 42 with diabetes, hypertension, and creatinine 1.4 asks about bariatric surgery. Her risk of mortality 30 days post-op is

1. 1 in 200
2. 1 in 100
3. 1 in 50
4. 1 in 25
5. 1 in 10

Mortality After Surgery
Community Medicare Data: 55-64 year old

<table>
<thead>
<tr>
<th></th>
<th>30 days</th>
<th>90 days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.0%</td>
<td>2.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bariatric Surgery and Mortality
Swedish Obese Subjects Study

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>HR Rate</th>
<th>MI deaths</th>
<th>Cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>129</td>
<td>0.003</td>
<td>25</td>
<td>47</td>
</tr>
<tr>
<td>Surgery</td>
<td>101</td>
<td>0.76</td>
<td>0.050</td>
<td>13</td>
</tr>
</tbody>
</table>

NNT 77 over 11 years (approx 850 per year)
MANAGEMENT OF OBESITY: A SYSTEMATIC APPROACH

BARON’S FACTS ABOUT OBESITY

- Environmental changes work: YES
- Diets work, but not for long in most people: YES, BUT THEY DO FOR SOME
- Exercise improves health independent of weight change and aid in weight maintenance: YES
- Continuation of conditions that promote weight loss promotes weight maintenance: YES

BARON’S FACTS ABOUT OBESITY

- For children, programs that involve parents and home promote greater weight loss: MAYBE
- Provision of meals and meal replacement products promote greater weight loss: IN THE SHORT TERM
- Medications can help achieve meaningful weight loss for as long as agents can be used: BUT WHAT ABOUT LONGER TERM CLINICAL OUTCOMES?
- Surgery results in long term weight loss and reductions of diabetes and mortality: WITH COMPLICATIONS IN SOME/MANY AND A HIGH NNT

Weight Loss Before Bariatric Surgery

881 patients with gastric bypass; 6 month program to achieve 10% weight loss; 2/3 lost 5%; 1/2 lost 10%

<table>
<thead>
<tr>
<th>Weight Change</th>
<th>Complications %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain 5%</td>
<td>28.4</td>
</tr>
<tr>
<td>Gain 0-5%</td>
<td>27.9</td>
</tr>
<tr>
<td>Loss 0-5%</td>
<td>23.5</td>
</tr>
<tr>
<td>Loss 6-10%</td>
<td>14.2</td>
</tr>
<tr>
<td>Loss 10%</td>
<td>18.0</td>
</tr>
</tbody>
</table>

(p for trend = 0.004)

Nutrition after Bariatric Surgery

<table>
<thead>
<tr>
<th>Gastric Bypass</th>
<th>Lap Band</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin 2 daily</td>
<td>Multivitamin 1 daily</td>
</tr>
<tr>
<td>(400 mcg folate)</td>
<td></td>
</tr>
<tr>
<td>Omeprazole 20 mg daily</td>
<td>Omeprazole 20 mg daily</td>
</tr>
<tr>
<td>Calcium (500mg TID)</td>
<td>Calcium (500mg TID)</td>
</tr>
<tr>
<td>Vitamin D (200 IU TID)</td>
<td>Vitamin D (500 IU TID)</td>
</tr>
<tr>
<td>Iron sulfate 325mg daily (women)</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 500mcg SL daily</td>
<td></td>
</tr>
</tbody>
</table>
GOALS OF MANAGEMENT

- Be as fit as possible at current weight
- Prevent further weight gain
- If successful at 1 and 2, begin weight loss

The Magic Formula

"Eat less and exercise more? That's the most ridiculous fad diet I've heard of yet!"