Medical Approach To Obesity

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Disclosures

• No financial investment/ownership in pharmaceutical/health companies

• I have received speaker honoraria from MSD, Novartis, Sanofi, AstraZeneca, Boehringer-Ingelheim, Eli Lilly

Conflict of interest - not a sugar-sweetened beverage fan.
My dislike of SSB, not as problematic as industry influence on scientific research

Conflicts to Food Industry

With financial conflicts to the food industry
- 83.3% found insufficient support of a positive association between sugar-sweetened beverage consumption and weight gain

Without conflicts to the food industry
- The same percentage (83.3%) found that
- Sugar-sweetened beverage consumption reporting a positive association for weight gain

<table>
<thead>
<tr>
<th>Conflict of Interest with Food Companies</th>
<th>Grading of SR Conclusion</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number (Percent) Reporting Positive Association</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (16.7%)</td>
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<tr>
<td>No</td>
<td>0 (83.3%)</td>
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Is Obesity ‘Medical’?
Is it a debatable point?

Still debate within medical circles.
## Is obesity a disease?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
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</table>
| **WHO**
Obesity is a chronic disease, prevalent in both developed and developing countries, and affecting children as well as adults... one of the most significant contributors to ill health | **Australian Government** |
| **American Medical Association**
"The suggestion that obesity is not a disease but rather a consequence of a chosen lifestyle... equivalent to suggesting that lung cancer is not a disease because it was brought about by individual choice to smoke cigarettes" | **Australian Medical Association** |

Obesity, not just 1, but 2 diseases

Sick Fat disease

- Metabolic syndrome
- Pro-inflammatory
- Pro-thrombotic
- Pro-cancer

Fat mass disease

- Tissue compression
- Musculoskeletal wear & tear
- Tissue friction
- Immobility, loss of function
Fat inflammation leads to metabolic dysfunction

Liver fat is sick fat, leading to inflammation and ultimately fibrosis/cancer

Multiple organs are involved in obesity. Brain is a major organ.

There are 9 gut hormones that make us full, only 1 gut hormone that makes us hungry

Common obesity is polygenic, but what genes?

Two commonest gene variants associated with obesity

- **FTO** (fat mass and obesity-associated protein) gene. *Hypothalamus hunger*
  - 15% of Europeans have this.

- **MC4R** (melancortin receptor-4)
  - *Hypothalamus energy balance*
  - Found in 1-2.5% of people with BMI >30
But there are also environmental/epigenetic factors

Rosenquist, J.N. et al., Cohort of birth modifies the association between FTO genotype and BMI. pnas.org.
Can microbiome play a role in obesity?

Transplanting microbiota from obese/lean twin to mice

Metabolic effects of fructose


- Increase liver & visceral fat
- Increase fat inflammation
- Westernise gut microflora
- Increase uric acid level
- Decrease liver insulin sensitivity
- Decrease satiety
- Decrease incretin effect
- Increase triglycerides
Trans fat + High-Fructose Corn Syrup = American Lifestyle Induced Obesity syndrome

![Graph showing weight gain over weeks for different diets: ALIOS, Lard + HFCS, Trans-fat, no HFCS, Control. The graph indicates a significant increase in weight gain for ALIOS compared to the other diets. The figure is labeled with * P< 0.05 compared to ALIOS.]


• Metabolically healthy obese is hard to define¹
• Obesity paradox only applies for BMI 30-34.9²


The relative importance of various measures of obesity in prediction of myocardial infarction was assessed in several different ways. First, we compared the odds ratios (ORs) across various quintiles; second, we estimated the OR for 1 SD change in the measure, (using both overall and subgroup specific SD); third, we adjusted for age, sex, smoking, and region. Which is better for MI prediction?

80% of people have inappropriate hyperinsulinemia on OGTT

The 5 dynamic patterns of insulin (80% with hyperinsulinemia):

- #1
- #2 — HYPERINSULINEMIA
- #3 — HYPERINSULINEMIA
- #4 — HYPERINSULINEMIA
- #5

Diabetes in-situ?

Detection of Diabetes Mellitus, In Situ (occult diabetes), Kraft, Joseph R., Laboratory Medicine, Volume VI, #2, pages 10–22, February 1975.
BMI class not great at predicting survival, Edmonton Obesity Staging is.

Edmonton Obesity Staging System

Stage 0
- Medical: absent
- Mental: absent
- Functional: absent

Stage 1
- Medical: absent
- Mental: absent
- Functional: absent

Stage 2
- co-morbidity
- moderate
- mild

Stage 3
- end-organ damage
- severe end-stage

Stage 4
- end-stage

Obesity


**EOSS works across all BMI in predicting survival**

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- Time since examination, mo
- Proportion surviving
- Stage 0
- Stage 1
- Stage 2
- Stage 3
So how do we treat obesity?
Lifestyle modification
Pharmaceutical agents
Surgical/procedures

Monotherapy (treat to failure) vs. Multimodality
In pre-diabetes, every 1 kg weight loss leads to relative risk reduction of diabetes by:

A. 2%
B. 5%
C. 8%
D. 10%
E. 16%

New!
Miracle Cure!
Truly amazing!
Works in minutes!
Guaranteed!
Why weight rebound? gut hormones are perturbed

Figure 2. Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

Registry data for bariatric surgery

Rodent models still helpful in obesity drugs


Correlation $R^2 = 0.82$
Rimonabant (withdrawn from Europe due to severe depression/suicidality)

Sibutramine (withdrawn due to CV risk)
FDA approved drugs, with potential to break the 10% weight loss ceiling

Brain continues to be a therapeutic target organ

Liraglutide 3.0mg FDA approved

Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg


## Conclusion

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<tr>
<td><strong>1</strong></td>
<td><strong>Obesity</strong></td>
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<tr>
<td><strong>2</strong></td>
<td><strong>Risk factors</strong></td>
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<tr>
<td><strong>3</strong></td>
<td><strong>Treatment</strong></td>
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Any Questions? Or follow me [Twitter](https://twitter.com/dr_kevinlee)