Overnutrition: reversing obesity and insulin resistance

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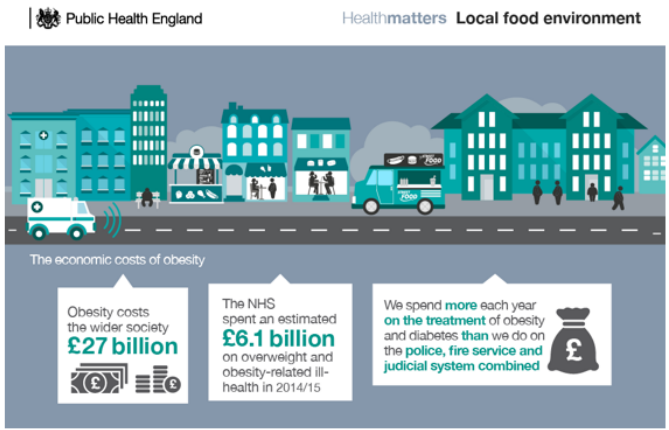
Understanding the impact of the obesity epidemic

Issues with gravity ➡
- Sleep apnoea
- Arthritis
- Difficulty with mobility

However real problems are with a host of related illnesses

➡
- Type II Diabetes
- Heart disease
- High blood pressure
- Certain cancers



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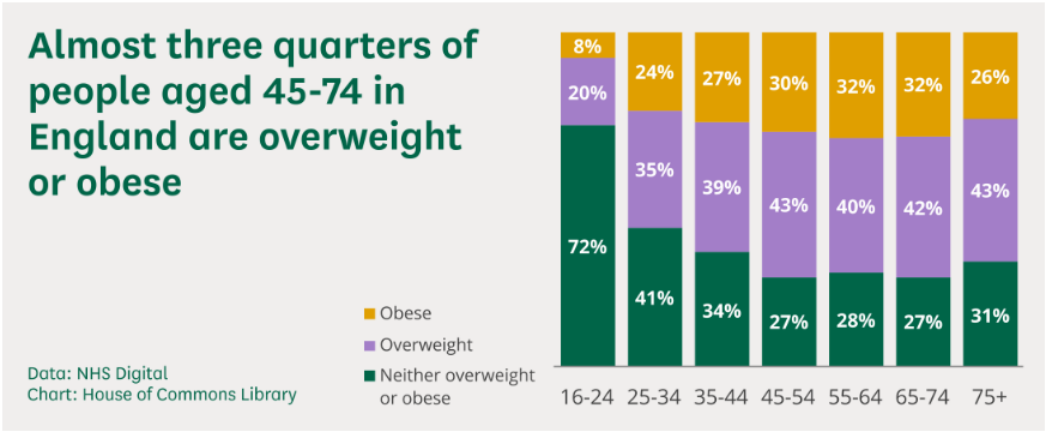
Understanding the impact of the obesity epidemic



Obesity is a leading risk factor for type II diabetes, cancer, cardiovascular disease and dementia

Understanding obesity from a food supply perspective

- Driven by chronic overnutrition i.e. calorie excess
- Excess calorie intake is rarely deliberate
- Weight gain is often seen as inevitable, especially with age

What is driving chronic calorie overconsumption?

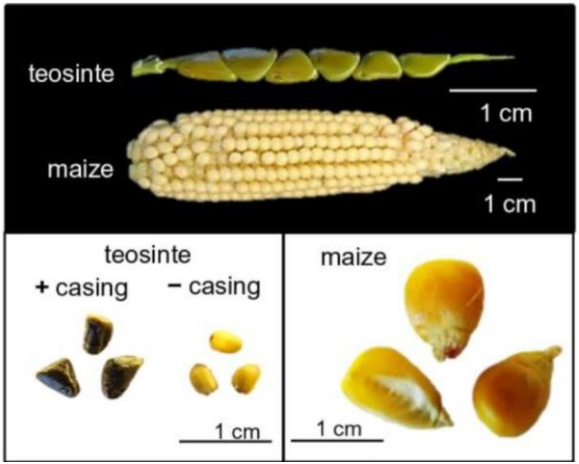
Calories are now much more accessible per volume of food

Calories are more accessible per volume of food

Teosinte (6-10,000 years ago) vs modern domesticated maize

Calories are more easily accessed through loss of kernel and other undigestible material

Larger kernel size therefore more calories accessed with less effort



Guan et al. Maize domestication phenotypes reveal strigolactone networks coordinating grain size evolution with kernel-bearing cupule architecture, *The Plant Cell*, Volume 35, Issue 3, March 2023, Pages 1013–1037, https://doi.org/10.1093/plcell/koac370

Calories are more accessible per volume of food

https://lubacommoditytrading.com/products/maize-grain

Caloric load is buffered by fiber, protein and undigestible cellulose

UK's top breakfast cereal according to *The Sun*

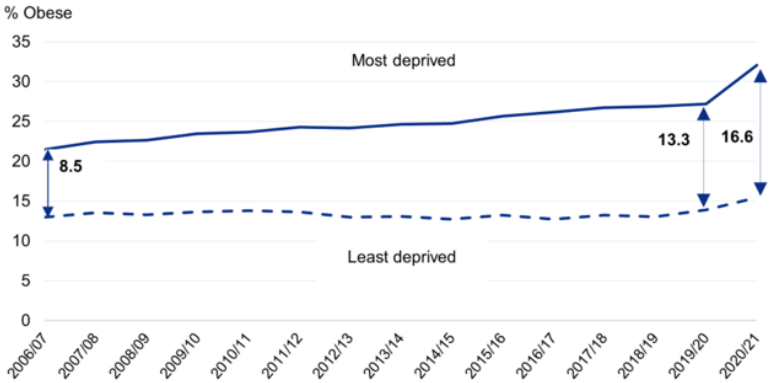
Calories are more easily absorbed through digestion due to milling, removal of fiber and addition of sugar

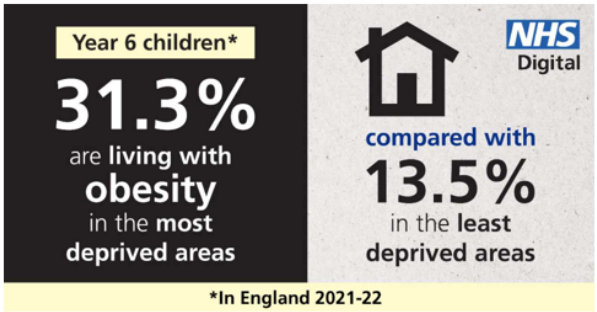
Obesity and nutrition cannot be divorced from socioeconomic inequality

- "Healthy foods" cost an average of £8.51 for 1,000 calories
- "Unhealthy foods" cost an average just £3.25 for 1,000 calories (Food Foundation, 2022)

- **One in five households would spend 43% of income on food to achieve the government-recommended healthy diet**

Obesity rates in English children 10-11y





https://digital.nhs.uk/data-and-information/publications/statistical/national-child-measurement-programme

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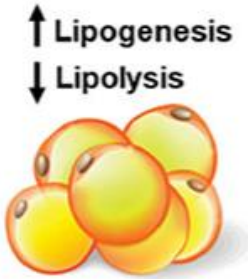
How does obesity exert negative impacts on health?

- Negative health consequences of obesity are largely exerted through **insulin resistance**
- This is the process by which tissues in the body become insensitive to the actions of insulin
- In a healthy context, insulin promotes the uptake and storage of glucose after eating, and controls the release of stored fat

Normal function of insulin



Muscle: Facilitate uptake of glucose and storage as glycogen

Adipose tissue (fat): Facilitate uptake of glucose to be converted and stored as fat

Prevent unnecessary breakdown of stored fat

Liver: Facilitate uptake of glucose to be converted and stored as fat in other tissues

Prevent unnecessary breakdown of stored glycogen

Tyagi, Anit, and Subbiah Pugazhenthi. 2021. "Targeting Insulin Resistance to Treat Cognitive Dysfunction." *Molecular Neurobiology* 58(6): 2672–91. doi:10.1007/s12035-021-02283-3.

Understanding insulin resistance & consequences

Elevated blood lipids due to elevated synthesis and uncontrolled breakdown of stored fats

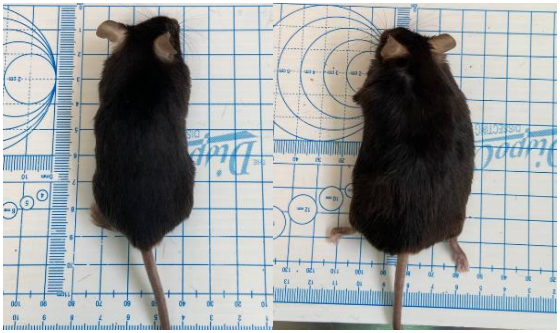
>> Leads to cardiovascular disease

Elevated blood sugar due to inability of muscle and adipose tissue to absorb glucose

>> Leads to type II diabetes

The complete mechanism by which tissues become resistant to insulin is incompletely understood. This question is a core focus of the Savage Lab.

How do we study insulin resistance?



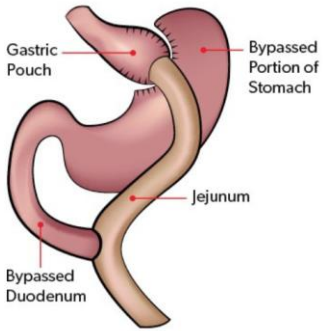
Chow diet vs High Fat Diet

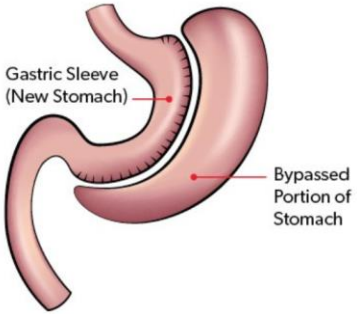
How do we study insulin resistance?

How do we study insulin resistance?

Insulin Tolerance Test

Bariatric surgery as a treatment insulin resistance and type II diabetes





Arkansas Heart Hospital, 2023

"Within 7 days of instituting a substantial negative calorie balance by either dietary intervention or bariatric surgery, **fasting plasma glucose levels can normalize."**

Roy Taylor; Type 2 Diabetes: **Etiology and reversibility**. *Diabetes Care* 1 April 2013; 36 (4): 1047–1055. https://doi.org/10.2337/dc12-1805

Mouse model of bariatric surgery

8wks
High Fat Diet

8wks
Chow Diet

Lean control

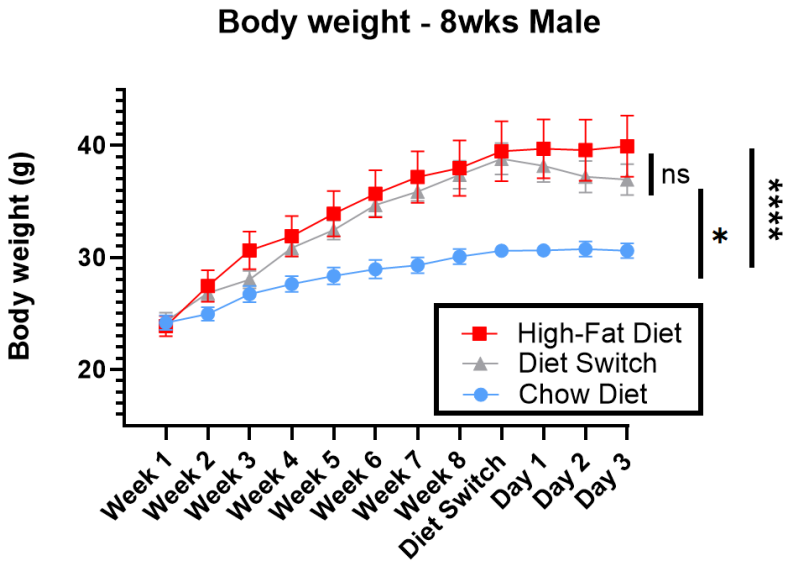
8wks
High Fat Diet

Obese control

3 days
Chow Diet

Treatment group
Models the calorie restriction associated with bariatric surgery

Insulin sensitivity is restored in the absence of significant weight loss



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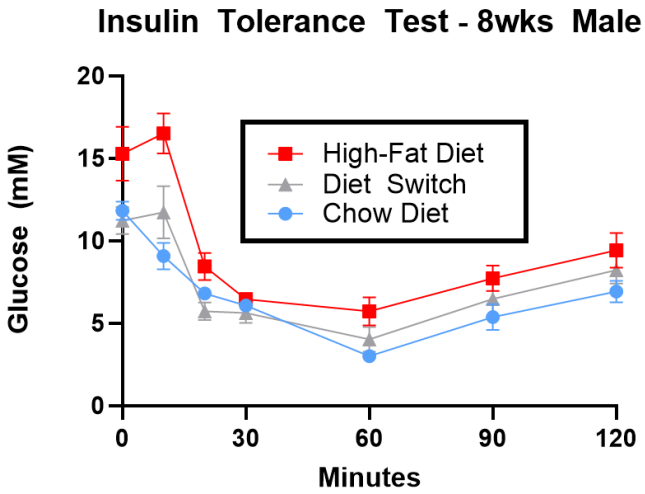

NHS soup and shake diet can beat type 2 diabetes

The soups and shakes contain the right balance of nutrients

Michelle Roberts
Digital health editor, BBC News

6 August 2024 · 1153 Comments

People can put their type 2 diabetes into remission by going on a strict 900-calorie-a-day liquid diet offered by the NHS.

Institute of Metabolic Science

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Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

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"The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months….co-primary outcomes were weight loss of 15 kg or more, **and remission of diabetes**"

Insulin resistance can be rapidly reversed when obesogenic environment is removed and calories are restricted

Sex specific effects

Mechanisms of estrogen protection in diabetes and metabolic disease

Andrea Cignarella* and Chiara Bolego

Department of Pharmacology and Anesthesiology, University of Padua, Padua, Italy

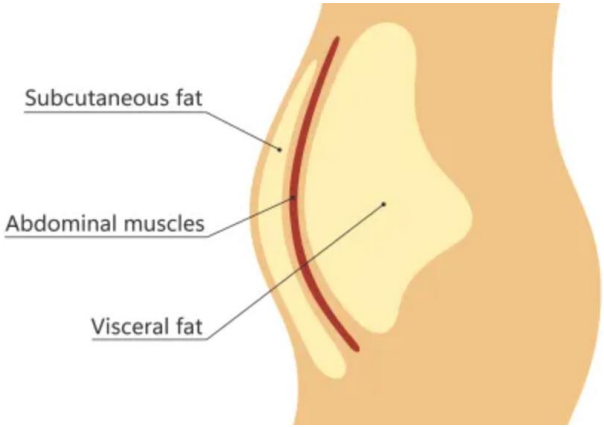
Abstract

Until menopause, women are largely protected against several metabolic disorders, implicating a role for sex hormones. Adiposity and insulin resistance are fundamental features in the pathogenesis of type 2 diabetes mellitus. Emerging data suggest that sex-steroid hormones and adipocyte-derived hormones and cytokines could be associated with type 2 diabetes risk and that some of these novel markers can exhibit a sexual dimorphism with regard to this risk. Evidence suggests that the female hormone, 17β-estradiol protects insulin a role. Indeed, ovariectomy in rodents leads to visceral obesity which is prevented by estrogen supplementation [4, 5]. Moreover, menopausal hormone therapy (MHT) with combined estrogen-progestins can reduce weight gain and elicit adipose tissue redistribution in postmenopausal women [6, 7]. Lack of estrogen results in the development of a metabolic syndrome in humans and rodents, including excess adiposity, hepatic steatosis, and insulin resistance. By contrast, estrogen replacement results in a prompt reversal of the energy imbalance symptoms associated with estrogen deficiency. A variety of metabolic actions of estrogens are exerted on skeletal muscle, pancreas, adipose tissue, and the central nervous system. Estrogen has profound effects on body fat distribution and fat accumulation, promoting peripheral adipose tissue distribution, reducing appetite and increasing

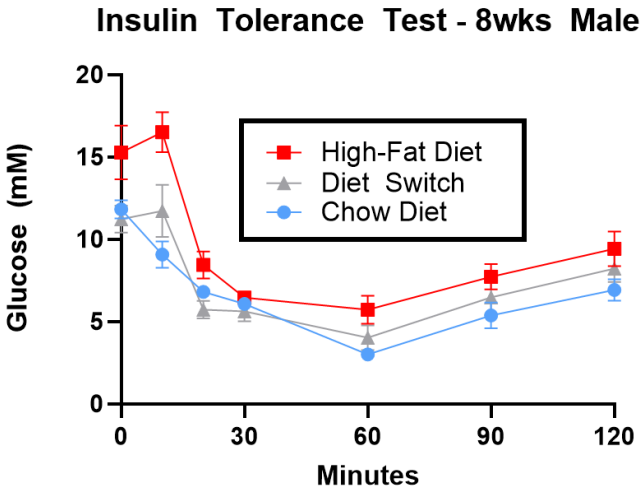
- Females are protected against type II diabetes prior to menopause
- Mechanism is unclear but likely related to fat distribution

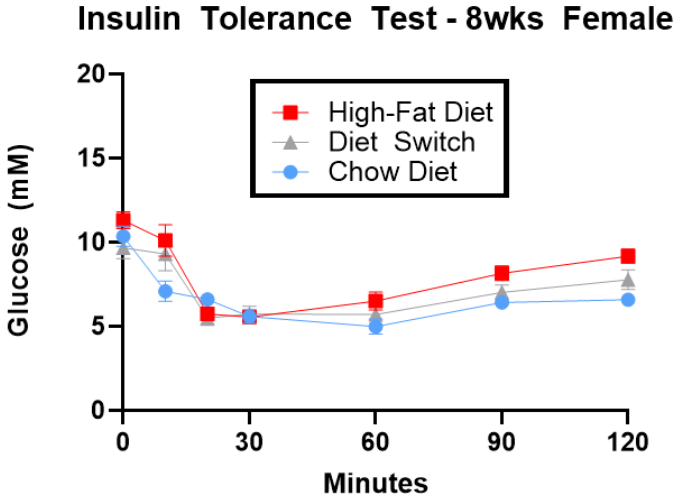
Subcutaneous vs. visceral fat

- “Healthy” vs “unhealthy” fat
- Subcutaneous = stored under the skin and usually in the lower body, hips and buttocks
- Visceral = centrally stored belly fat, accumulates between organs

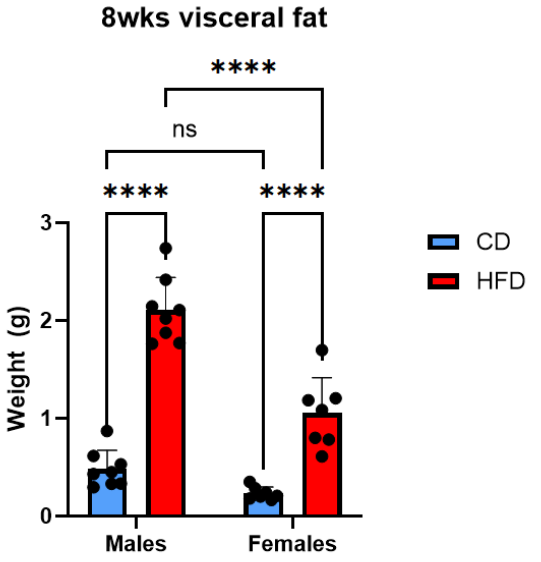


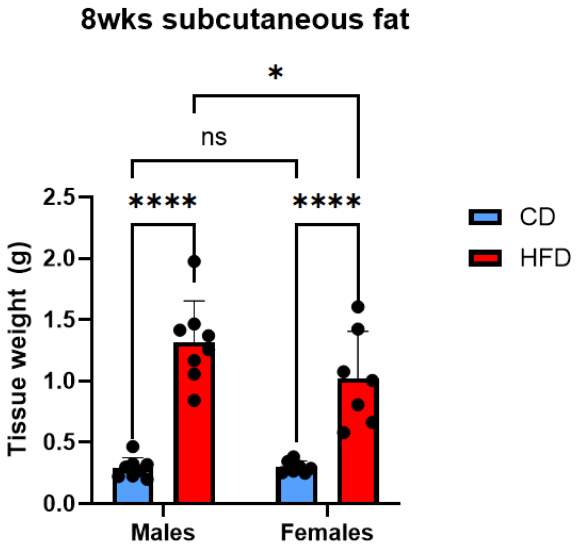
Insulin resistance is sexually dimorphic – females are protected





Fat distribution plays a role in protection





Hormonal status plays a role in metabolic risk

- Estrogen helps to contribute to healthier fat distribution
- Women post-menopause or with hormonal imbalances (e.g. polycystic ovary syndrome) are therefore at greater risk of metabolic health issues

Summary

- Food is more abundant now that it has been historically, with higher calorie density
- The lower cost of refined, processed food contributes to an obesogenic environment particularly for lower income earners
- Obesity is harmful because it is correlated with insulin resistance, which leads to elevated blood sugar and blood lipids, and eventually type II diabetes and cardiovascular disease

Summary

- Our data show that in mouse models, insulin resistance can be rapidly reversed following a diet switch
- Clinical studies mirror this result in humans; full diabetes remission can be achieved on a low-calorie diet or with bariatric surgery
- Females are protected compared to males prior to menopause due to estrogen. Hormonal health changes such as PCOS and menopause can impact metabolic risk for females

Nutritional environment has profound impact over health outcomes. Ensuring the supply and accessibility of nutrient dense, low-calorie food is the most important factor in preventing obesity and comorbidities.

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