The Cardiometabolic Consequences of Obesity and Nutritional Strategies for Prevention

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Prevalence of Self-Reported Obesity Among U.S. Adults 2014

† Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

Prevalence of obesity: 35% in men and 40% in women

Class 3 obesity: 6% in men and 10% in women

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.
Global trends in obesity: 1980-2013

**Adults**

A. Overweight and obesity (BMI ≥ 25 kg/m²)

B. Obesity (BMI ≥ 30 kg/m²)

**Children**

A. Overweight and obesity (based on IOTF cutoffs)

B. Obesity (based on IOTF cutoffs)

Ng et al. Lancet 2014; 384: 766-81
After ‘The Biggest Loser,’ Their Bodies Fought to Regain Weight

Contestants lost hundreds of pounds during Season 8, but gained them back. A study of their struggles helps explain why so many people fail to keep off the weight they lose.

GINA KOLATA

MAY 2, 2016

- Decreased leptin (satiety hormone)
- Increased ghrelin (hunger hormone)
- Decreased metabolism
- Genetic predisposition

http://www.nytimes.com/2016/05/02/health/biggest-loser-weight-loss.html
Atherogenic factors in metabolic syndrome

- Type 2 diabetes and glycemic disorders
- Dyslipidemia
  - Low HDL
  - Small, dense LDL
  - Hypertriglyceridemia
- Hypertension
- Endothelial dysfunction/inflammation (hsCRP)
- Impaired thrombolysis
  - ↑ PAI-1

Insulin resistance
Glucotoxicity
Lipotoxicity
↓ Adiponectin

Courtesy of Selwyn AP, Weissman PN.
97 studies were included in the analysis (2.88 million individuals and 270,000 deaths).

**Normal weight (18.5-<25):** reference group  
**Overweight (25-<30):** 0.94 (95% CI, 0.91-0.96)  
**Class 1 obesity (30-<35):** 0.95 (95% CI, 0.88-1.01)  
**Class 2 & 3 obesity (≥35):** 1.29 (95% CI, 1.18-1.41)
Methodological Issues in BMI-mortality Studies

- Reverse causation (weight loss due to preexisting diseases)
- Residual confounding by cigarette smoking (Smokers tend to be leaner but have higher mortality rates)
- Over-adjustment for intermediates (e.g., blood pressure, lipids, glucose)
  - High prevalence of comorbid conditions & illness-weight loss
  - Body mass index (BMI) less reliable measurement of adiposity
  - Depletion of susceptibles
  - High baseline mortality risk dilutes individual risk factors

Elderly populations

Obesity researchers must distinguish between two issues

• Role of excess body fat (high BMI) in causing illness and premature death. (Here BMI is a cause of disease)

• Role of chronic illness in causing involuntary weight loss (low BMI). (Here low BMI is a consequence of disease)
Three Approaches to Minimize Bias In This Situation

- Restrict analyses to healthy never-smokers
- Exclude initial years of follow-up
- Consider disease incidence & risk factors as well as mortality
The Global BMI Mortality Collaboration

- **Goal**
  - Provide valid estimates of the associations of overweight and obesity with all-cause mortality across populations in major global regions
  - Conduct individual-level meta-analysis using the same protocol for data analysis

- **Who we are**
  - 500 investigators, 300 institutions, 32 countries, 4 continents
  - 239 prospective studies, 10.6 million participants

Lancet 2016
HRs for all-cause mortality by pre-defined categories of BMI

<table>
<thead>
<tr>
<th></th>
<th>HR† (95% CI)</th>
<th>Studies</th>
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<tbody>
<tr>
<td>Overall</td>
<td>1.31 (1.29, 1.33)</td>
<td>189</td>
</tr>
<tr>
<td>European cohorts</td>
<td>1.39 (1.34, 1.43)</td>
<td>89</td>
</tr>
<tr>
<td>North American cohorts</td>
<td>1.29 (1.26, 1.32)</td>
<td>40</td>
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<tr>
<td>East Asian cohorts</td>
<td>1.39 (1.34, 1.44)</td>
<td>46</td>
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<tr>
<td>Australia/New Zealand cohorts</td>
<td>1.31 (1.27, 1.35)</td>
<td>11</td>
</tr>
<tr>
<td>South Asian cohorts</td>
<td>1.13 (0.97, 1.30)</td>
<td>3</td>
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</tbody>
</table>

Denotes reference category
Summary and Conclusions

1. After accounting for residual confounding by smoking and reverse causation as well as possible, the lowest mortality is at BMI less than 25 in the general population.

2. One likely explanation for the “obesity paradox” is that chronically ill patients who lose weight and become frail are the ones who tend to die early.

3. Associations were substantially higher at younger than at older ages of baseline assessment
   - Policies to curb obesity to start early in life

4. Associations were higher in males than females
   - Greater insulin resistance, ectopic (e.g., liver) fat levels and type 2 diabetes prevalence at equivalent BMI levels
Associations of Weight Gain From Early to Middle Adulthood With Major Health Outcomes Later in Life

Yan Zheng, MD, PhD; JoAnn E. Manson, MD, DrPH; Changzheng Yuan, MD, ScD; Matthew H. Liang, MD, MPH; Francine Grodstein, ScD; Meir J. Stampfer, MD, DrPH; Walter C. Willett, MD, DrPH; Frank B. Hu, MD, PhD
In the meta-analysis of data from women and men, per 5 kg weight gain was associated with
30% higher risk of type 2 diabetes,
14% higher risk of hypertension,
8% higher risk of cardiovascular disease,
6% higher risk of obesity-related cancer,
5% higher risk of deaths in never-smokers,
17% lower likelihood of achieving healthy aging in later life.
The average adult gains about 1 lb (0.45 kg) per year.

Subtle, but adds up: 20 lbs over 20 years!

This gradual pace makes it very difficult for individuals to perceive specific causes or remedies.

Many RCTs have tested short-term weight loss strategies in obese/overweight persons. Such findings may have little relevance to determinants of long-term, gradual weight gain in non-obese populations.

Courtesy of Mozaffarian
Lifestyle Changes and Long-Term Weight Gain

Nurses’ Health Study (121,701 women)
Diet Diet Diet Diet Diet Diet Diet Diet Diet Diet

Health Professionals Follow-up Study (51,529 men)
Diet Diet Diet Diet Diet Diet Diet Diet

Nurses’ Health Study II (116,686 young women)
1989 1991 1993 1995 1997 1999 2001 ....... 2011
Diet Diet Diet Diet Diet Diet Diet

Every Two Years: Weight, smoking, physical activity, CVD risk factors, diseases.
Every Four Years: Detailed dietary habits.
Among 120,877 men and women followed for 20 years, adjusted every 4-years for age, baseline BMI, sleep, and changes in activity, smoking, TV watching, and all dietary factors simultaneously.

Weight Change Each Four Years (lbs)

Weight Change Associated with Each Increased Daily Serving of:

Foods
- Potato chips
- Potatoes/fries
- Processed meats
- Unprocessed red meats
- Butter
- Sweets and desserts
- Refined grains
- Cheese
- Vegetables
- Nuts
- Whole grains
- Fruits
- Yogurt

Beverages
- Sugar-sweetened beverages
- Alcohol
- 100% fruit juice
- Low fat or skim milk
- Whole fat milk
- Diet (zero calorie) soda
Diet quality is likely to influence diet quantity. → not simply “eat less”, but also “eat better.”

Current emphasized metrics based on total amounts of fat or carbohydrates may not be very helpful.

Carbohydrate quality and extent of food processing appear to be potentially key metrics.

Weight gain is very gradual → Difficult to detect/combat.

Small diet and lifestyle changes can make big difference → Tremendous opportunity for prevention!

Take Home Messages

Courtesy of Mozaffarian
Prospective Urban Rural Epidemiology (PURE) Study

- 135,000 participants, 18 countries
- 7 years of follow up
- Findings
  - Highest fat intake (35% daily calories) 23% lower mortality risk than lowest intake (10% daily calories)
  - Highest carbohydrate intake (77% daily calories) 28% higher mortality risk than lowest intake (46% daily calories)

Dehghan et al. Lancet 2017

Conclusions: Carbs are bad and fats are good.
Methodological Problems

• “Total carbohydrates” is over-simplified
  • High quality vs. low quality carbs

• Very high carbohydrate intake may indicate poverty diet
  • Confounding from poverty and undernutrition

• Assessment and analysis of types of fat
  • No trans fat data
  • Did not examine replacing saturated fat with polyunsaturated fat

• Reliability of data
  • Fat intake in Chinese cohort 17.7% vs. 30% in other surveys
Beyond the Headlines and Abstract

- Large studies assessing diet in developing countries are needed
- Interpret findings with caution
- Dietary guidance:
  - Enjoy whole grains and unsaturated fat
  - Limit saturated fat and refined grains/added sugars
Types of Fats and Mortality

Diagram showing the relationship between different types of fat and change in total mortality. The fat types include Trans Fat, Saturated Fat, Monounsaturated Fat, and Polyunsaturated Fat.
Dietary Pattern Analysis: A New Direction in Nutritional Epidemiology

Frank B. Hu

Current Opinion in Lipidology 2002; 13:3-9

Conceptually, dietary patterns represent a broader picture of food and nutrient consumption, and may thus be more predictive of disease risk than individual foods or nutrients.
Establishing a robust evidence base for the dietary patterns described by national guidelines is essential to test the public health relevance of these guidelines.
The DGAC recommends 3 healthy dietary patterns

- Healthy U.S.-style Pattern
- Healthy Mediterranean-style Pattern
- Healthy Vegetarian Pattern

Common components of healthy dietary patterns:

- Rich in vegetables, fruit, whole grains, seafood, legumes, and nuts
- Moderate in low-/non-fat dairy products and alcohol
- Lower in red/processed meat
- Low in sugar sweetened foods/beverages and refined grains
- Low in saturated fat, added sugars, and sodium
Changes in Diet Quality and Total and Cause-Specific Mortality

Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, Willett WC, Rimm EB, Hu FB.

New England Journal of Medicine (July 2017)
The Alternate Healthy Eating Index-2010 (AHEI) score

- Based on recommendations for food and nutrient consumption with
- Current scientific evidence of beneficial health effects

The Alternate Mediterranean diet (AMED) score

- Comprised of foods and nutrients characteristic of the Mediterranean Pattern

The Dietary Approach to Stop Hypertension (DASH) score

- Developed from the DASH dietary recommendations aiming to reduce blood pressure

Shorter- and longer-term changes in diet quality

<table>
<thead>
<tr>
<th></th>
<th>Alternate Healthy Eating Index-2010 (range 0-110)</th>
<th>Alternate Mediterranean Diet (range 0-9)</th>
<th>DASH (range 8-40)</th>
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<tbody>
<tr>
<td></td>
<td>8y Changes</td>
<td>12y Changes</td>
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<td>8y Changes</td>
<td>12y Changes</td>
<td>16y Changes</td>
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<tr>
<td></td>
<td>Hazard Ratio (95%CI) for total mortality</td>
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The association was strengthened when longer changes were evaluated.
**Translating the Public Health Message**

- Even a modest improvement in diet quality (i.e. ~22 points or 20%) out of 110 for the AHEI score over a 12-year lower the risk of total mortality by 17%

- This change can be achieved by swapping out just one serving of red or processed meat for one daily serving of nuts or legumes

- Underscore the importance of promoting dietary changes as part of nutrition and public health policies.
Plant-based diets and risk of type 2 diabetes and coronary heart disease

Satija et al. PloS Medicine 2016

Satija et al. J Am College of Cardiology 2017
Plant-based diets are not equivalent to “vegetarian” diets

Foods excluded in different types of dietary patterns

<table>
<thead>
<tr>
<th></th>
<th>RED MEAT &amp; POULTRY</th>
<th>FISH &amp; SEAFOOD</th>
<th>EGGS</th>
<th>DAIRY</th>
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<tr>
<td>NON-VEGETARIAN</td>
<td><img src="image" alt="Red Meat" /></td>
<td><img src="image" alt="Fish" /></td>
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<td>PESCO-VEGETARIAN</td>
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<td>LACTO-OVO-VEGETARIAN</td>
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The three plant-based diet indices

**Overall Plant-based Diet Index (PDI)**
- High animal, low plant food intake
- High plant, low animal food intake

**Healthful Plant-based Diet Index (hPDI)**
- High animal, high unhealthy plant, and low healthy plant food intake
- High healthy plant, low unhealthy plant, and low animal food intake

**Unhealthful Plant-based Diet Index (uPDI)**
- High animal, high healthy plant, and low unhealthy plant food intake
- High unhealthy plant, low healthy plant, and low animal food intake
Results

Associations with T2D

Pooled HRs (95% CI) for T2D according to deciles of the plant-based diet indices

HR for extreme deciles: 0.80 (95% CI: 0.74-0.87)

Multivariable model. P trend<0.001 for all analyses
Results

Associations with T2D

Pooled HRs (95% CI) for T2D according to deciles of the plant-based diet indices

HR for extreme deciles:
0.80 (95% CI: 0.74-0.87)

HR for extreme deciles:
0.66 (95% CI: 0.61-0.72)

Multivariable model. P trend<0.001 for all analyses
Results

Associations with T2D

Pooled HRs (95% CI) for T2D according to deciles of the plant-based diet indices

Multivariable model. P trend<0.001 for all analyses

HR for extreme deciles:
1.16 (95% CI: 1.08, 1.25)

HR for extreme deciles:
0.80 (95% CI: 0.74-0.87)

HR for extreme deciles:
0.66 (95% CI: 0.61-0.72)
Results

Associations with CHD

Pooled HRs (95% CI) for CHD according to deciles of the plant-based diet indices

Multivariable model. P trend=0.003 for PDI, and <0.001 for hPDI and uPDI

HR for extreme deciles:
0.92 (95% CI: 0.83-1.01)
Results

Associations with CHD

Pooled HRs (95% CI) for CHD according to deciles of the plant-based diet indices

Multivariable model. P trend=0.003 for PDI, and <0.001 for hPDI and uPDI

HR for extreme deciles:
0.92 (95% CI: 0.83-1.01)

HR for extreme deciles:
0.75 (95% CI: 0.68-0.83)
Results

Associations with CHD

Pooled HRs (95% CI) for CHD according to deciles of the plant-based diet indices

<table>
<thead>
<tr>
<th>Deciles of the plant-based diet indices</th>
<th>HR (95% CI)</th>
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<tr>
<td>D1</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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<td>D2</td>
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<tr>
<td>D3</td>
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<tr>
<td>D4</td>
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<tr>
<td>D5</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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<tr>
<td>D6</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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<tr>
<td>D7</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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<tr>
<td>D8</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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<tr>
<td>D9</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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<tr>
<td>D10</td>
<td>1.00 (95% CI: 0.83-1.01)</td>
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</table>

Multivariable model. P trend=0.003 for PDI, and <0.001 for hPDI and uPDI
Polyphenols

Phenolic acids
- Chlorogenic acid
- Caffeic acid
- Ferulic acid
  - Food sources: coffee, corn flour, blueberry, kiwi

Lignans
- Seco-isolariciresinol
- Matairesinol
  - Food sources: linseed, lentile, cereal

Flavonoids

Stilbenes
- Resveratrol
  - Food sources: red wine

Anthocyanins
- Cyanidin
- Peonidin
  - Food sources: blueberry, blackberry, grapes, strawberry

Isoflavones
- Genistein
- Daidzein
- Glycitein
  - Food sources: soy foods

Flavonols
- Quercetin
- Kaempferol
- Isorhamnetin
  - Food sources: onion, leek, kale

Flavanones
- Hesperetin
- Naringenin

Flavanols
- Catechin
- Epicatechin
  - Food sources: green tea, chocolate, beans
Diet alters human gut microbiome

The similarity of each individual’s gut microbiota to their baseline communities (B diversity) decreased on the animal-based diet (dates with q,0.05 identified with asterisks; Bonferroni-corrected, two-sided Mann–Whitney U test).

Ab libitum ‘plant-based diet’ and ‘animal-based diet’ for five consecutive days by six male and four female.

Bacterial cluster response to dietary arm

The similarity of each individual’s gut microbiota to their baseline communities (B diversity) decreased on the animal-based diet (dates with q,0.05 identified with asterisks; Bonferroni-corrected, two-sided Mann–Whitney U test).

David LA et al. Nature 2013; 500(7464): 585-8
Conclusions & Implications

- An overall plant-based diet score was associated with lower risk of T2D & CHD.
- This inverse association became substantially stronger for a healthier version of the diet, but was positive for an unhealthful version.
- Not all plant-based diets are created equal.

Increasing intake of healthy plant-foods, while reducing intake of less healthy plant foods and certain animal foods, may be beneficial for T2D and CHD prevention.
Increasing intake of healthy plant-foods, while reducing intake of less healthy plant foods and certain animal foods (e.g. red and processed meats), is also beneficial for the health of the planet.
Acknowledgements

• Shilpa N Bhupathiraju
• Lea Borgi
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