

Obesity and Cardiovascular Disease

Steven E. Nissen MD MACC

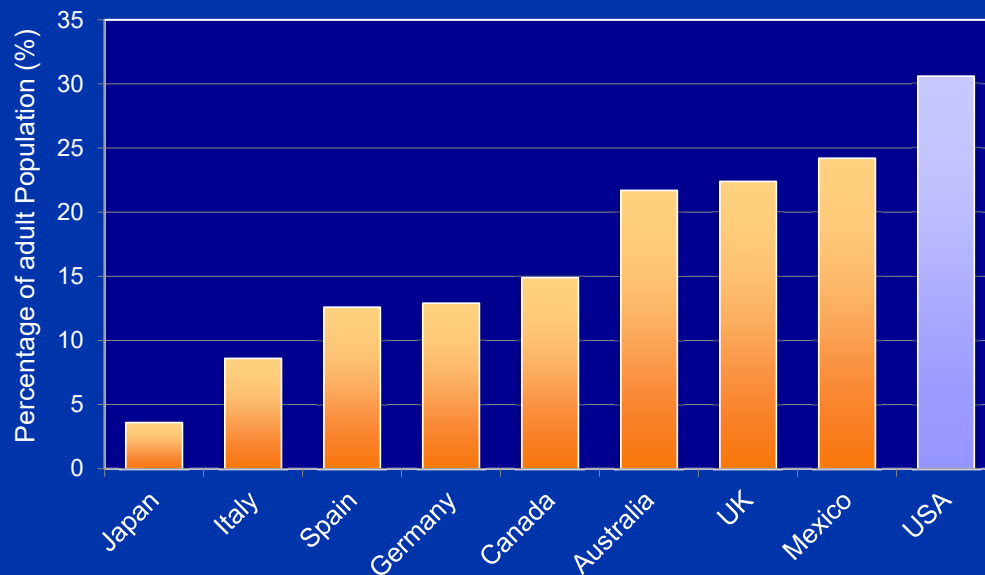
Disclosure

Clinical Trials: AbbVie, Amgen, Arrowhead, AstraZeneca, Bristol Myers Squibb, Esperion, Eli Lilly, New Amsterdam, Novartis, Ethicon, Medtronic, Mineralys, Silence Therapeutics, and Pfizer.

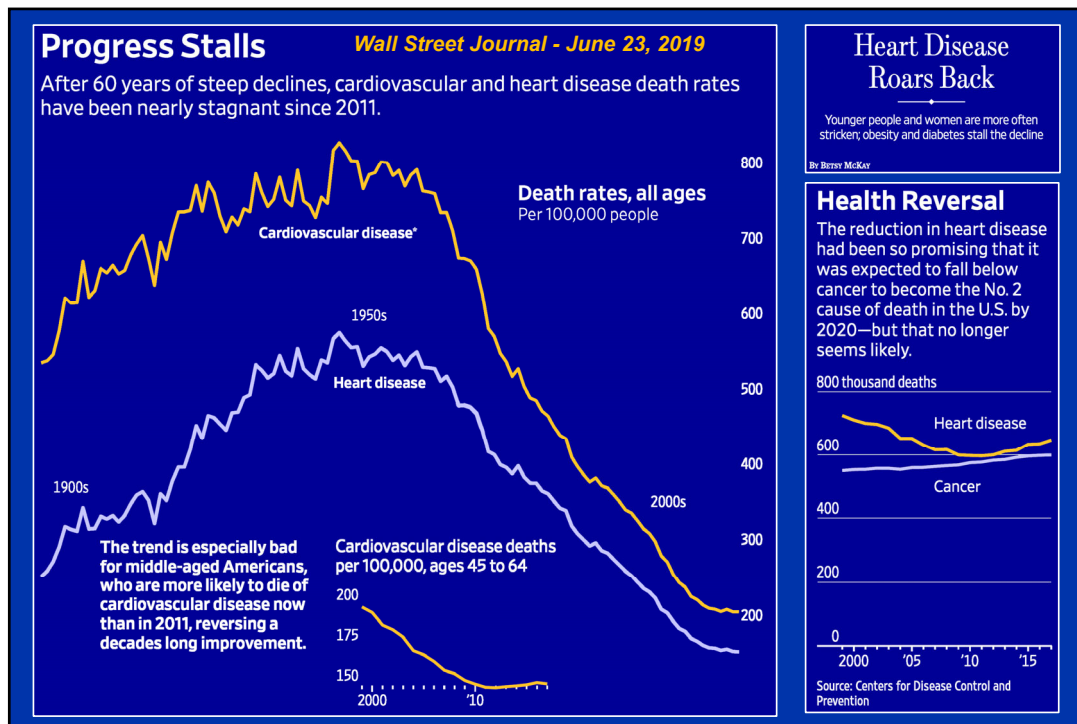
Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

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Projections: Adults with BMI >30 in 2030 (%)



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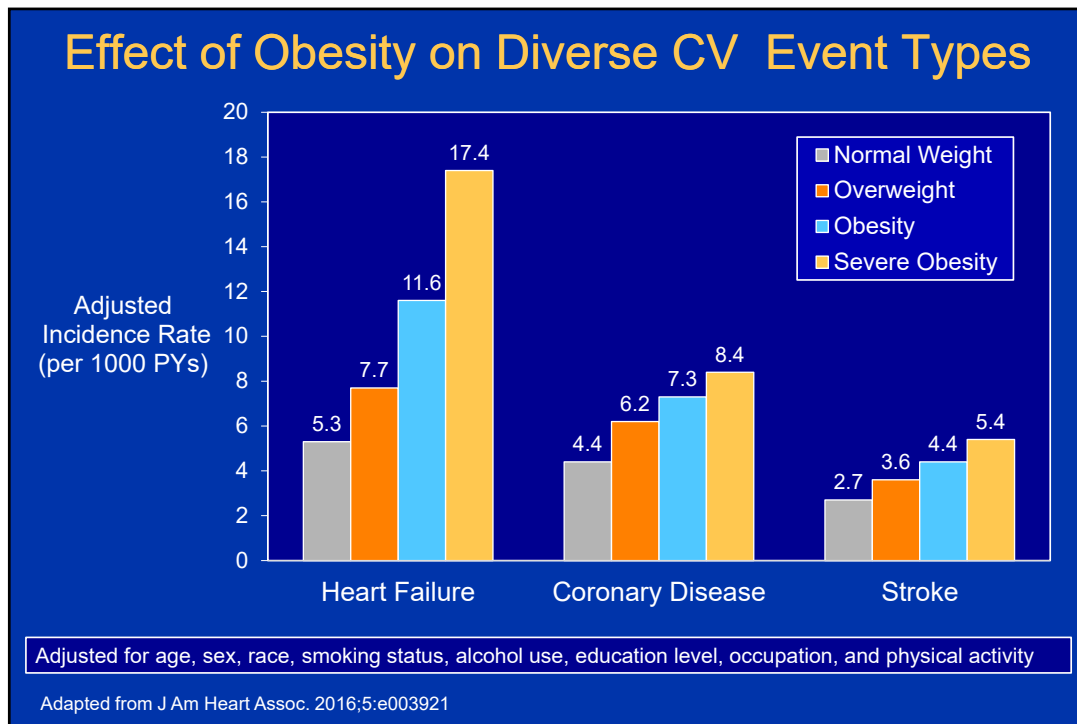
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Effect of Obesity on Life Expectancy at Age 40

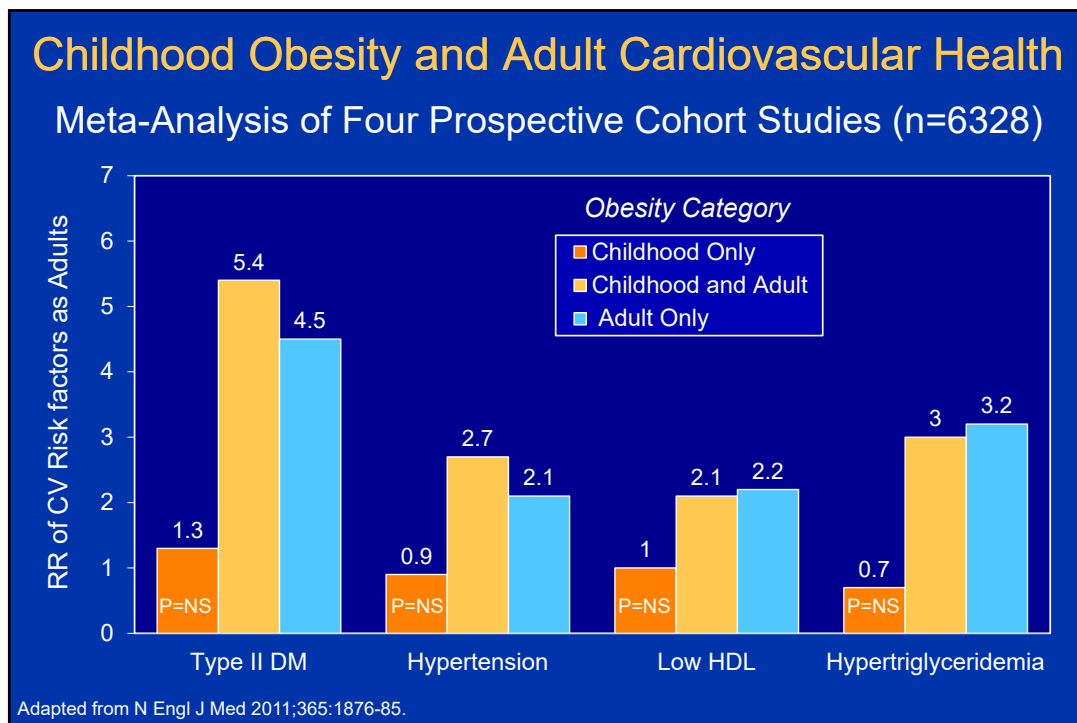
	Men		Women	
BMI (kg/m ²)	Life expectancy at age 40	Reduction in life expectancy	Life expectancy at age 40	Reduction in life expectancy
<18.5	77.9	4.3	79.8	4.5
18.5-24.9	82.2	referent	84.3	referent
25.0-29.9	81.2	1.0	83.5	0.8
30.0-34.9	78.7	3.4	81.9	2.4
35.0-39.9	76.2	5.9	79.6	4.7
≥40	73.1	9.1	76.6	7.7

Lancet Diabetes Endocrinol 2018

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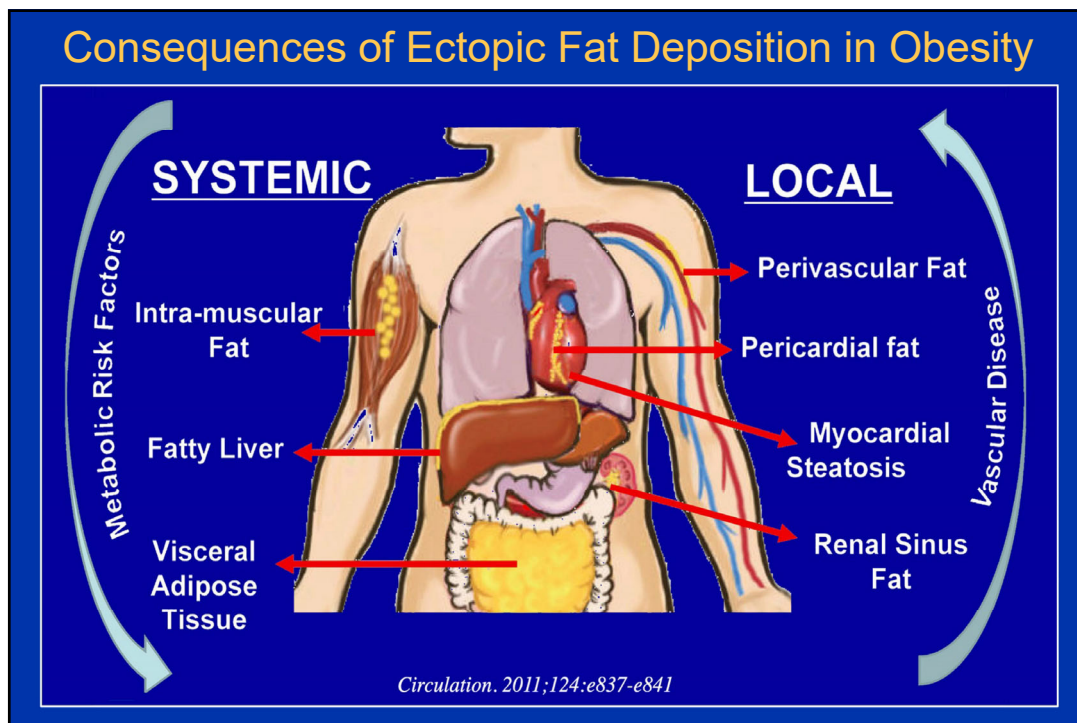
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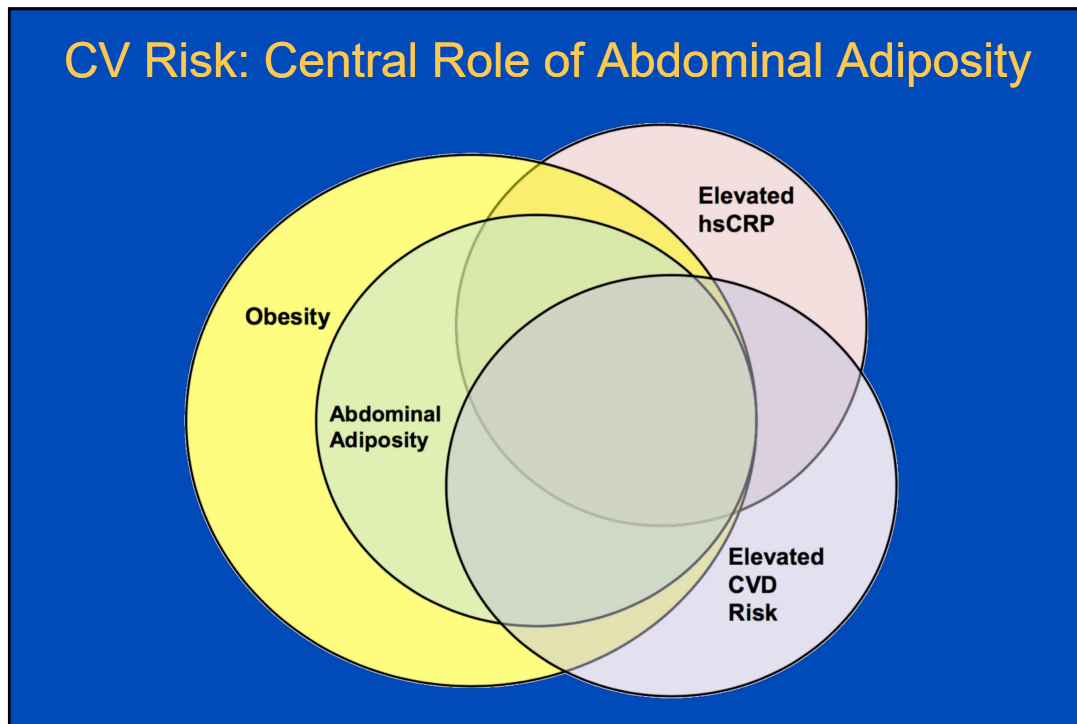
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How Does Obesity Cause Cardiovascular Disease?

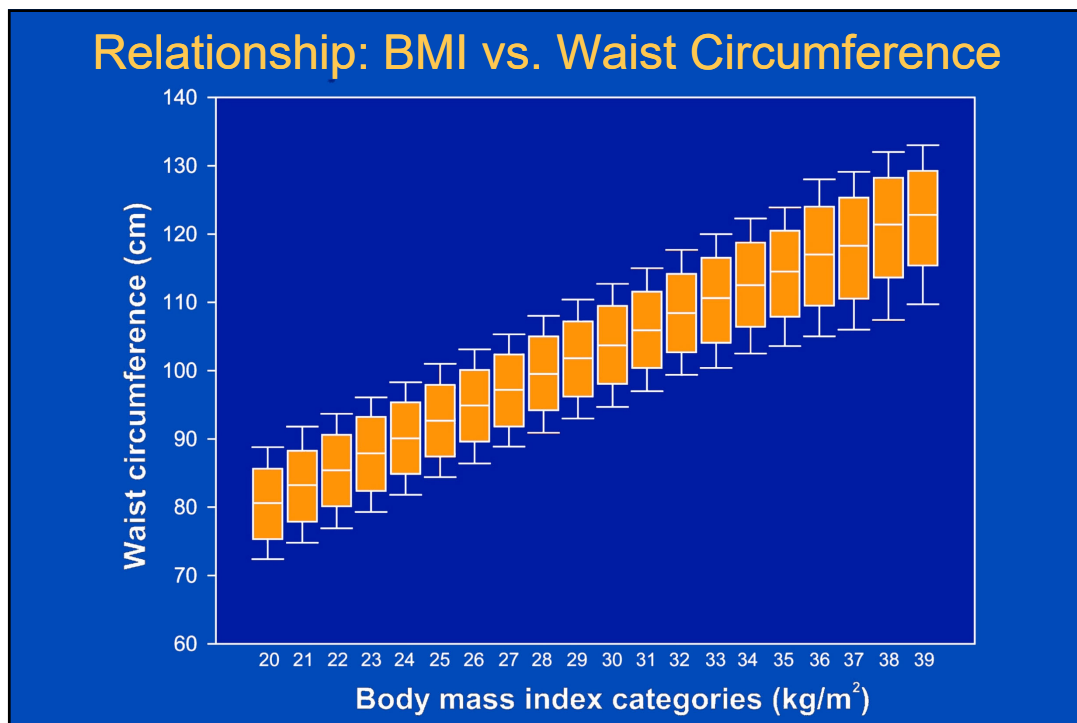
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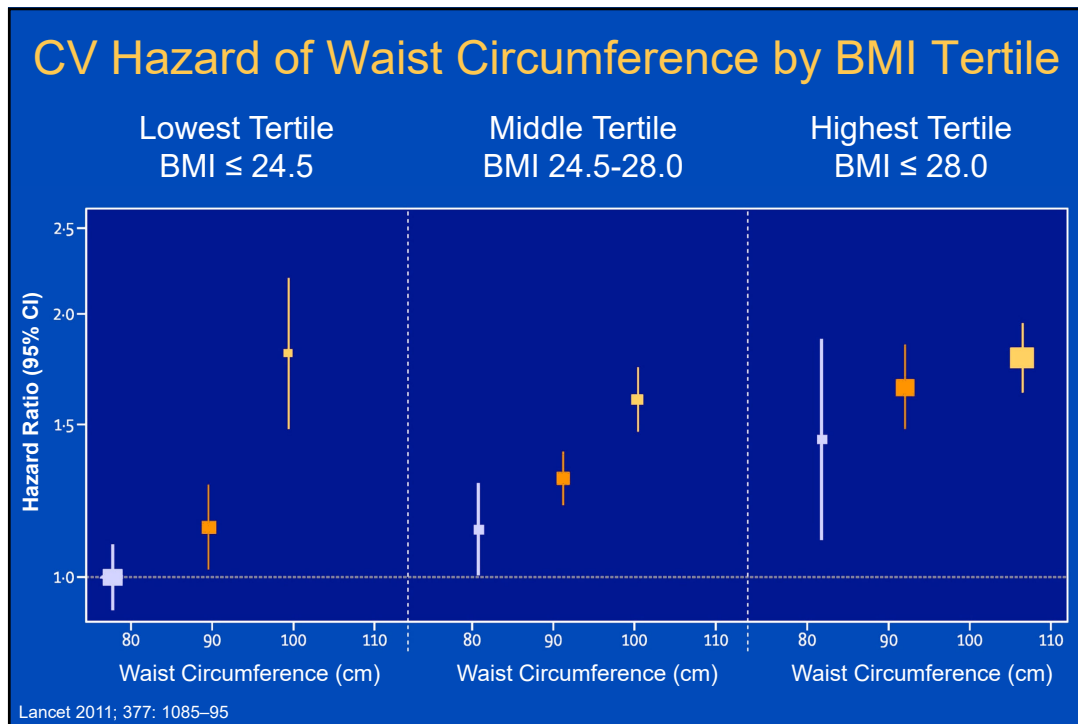
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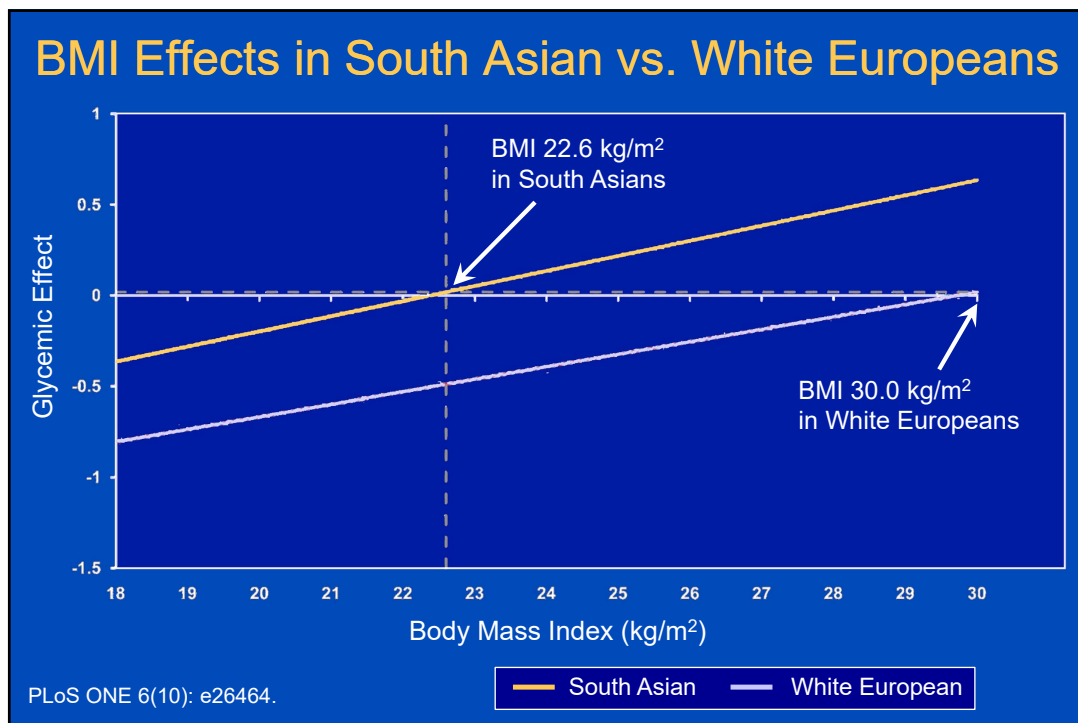
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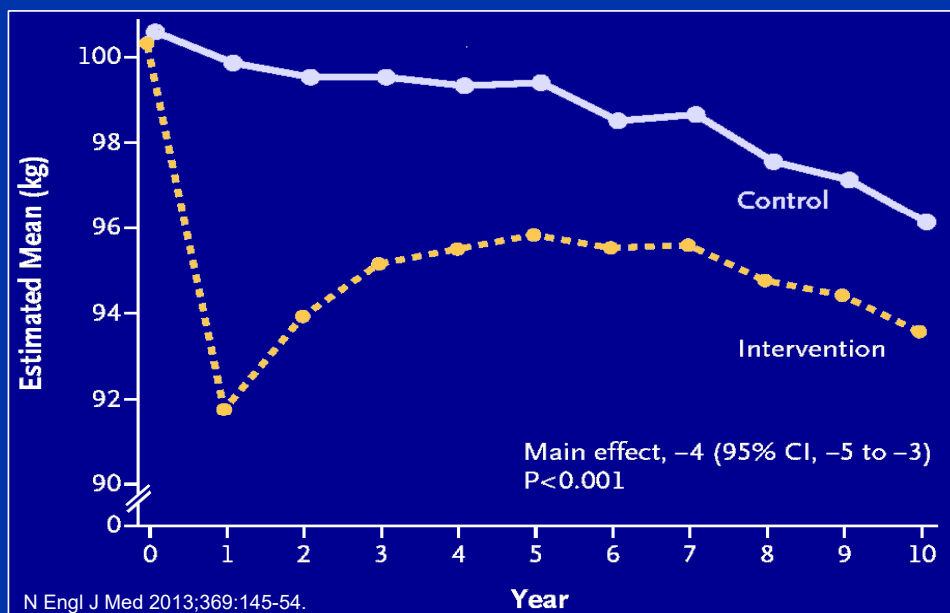


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We Know What Doesn't Work:
Diet or Conventional Drug Therapy
to Improve Cardiovascular Outcomes.

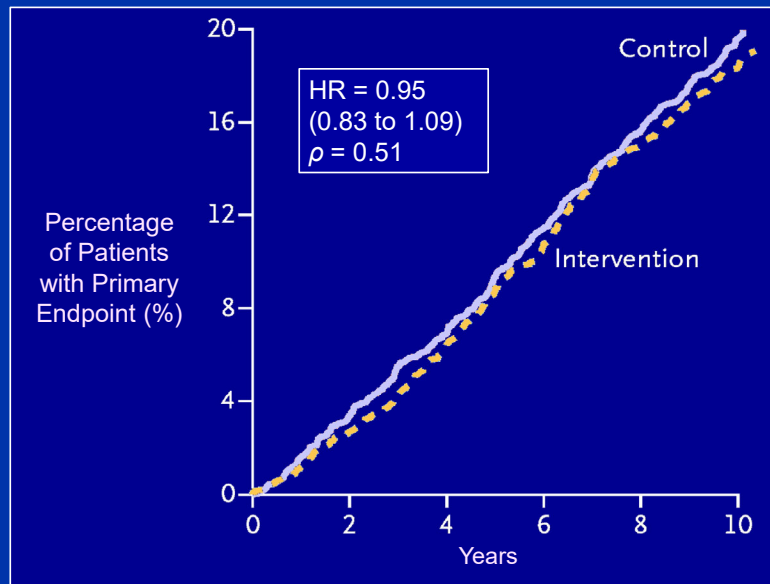
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Look Ahead: Weight Loss over 10 Years



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Look Ahead: Primary Endpoint over 10 Years



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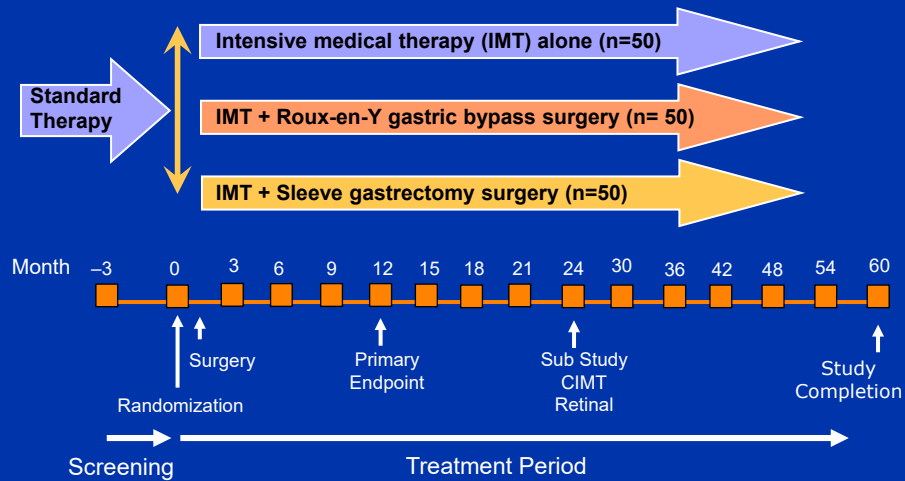
The Sad History of Conventional Drugs to Treat Obesity

- Amphetamines - high abuse potential, hypertension
- Fenfluramine - fatal pulmonary hypertension (**withdrawn**)
- Fenfluramine/phentermine - valvular heart disease (**withdrawn**)
- Sibutramine – hypertension, arrhythmias, sudden death, increased CV morbidity/mortality (**withdrawn**)
- Orlistat – Anal leakage, deficiency in fat soluble vitamins
- Rimonabant – Suicide and other psychiatric effects (**withdrawn**)
- Lorcaserin – Malignancy (**withdrawn**)
- Bupropion-naltrexone (No CV benefit)

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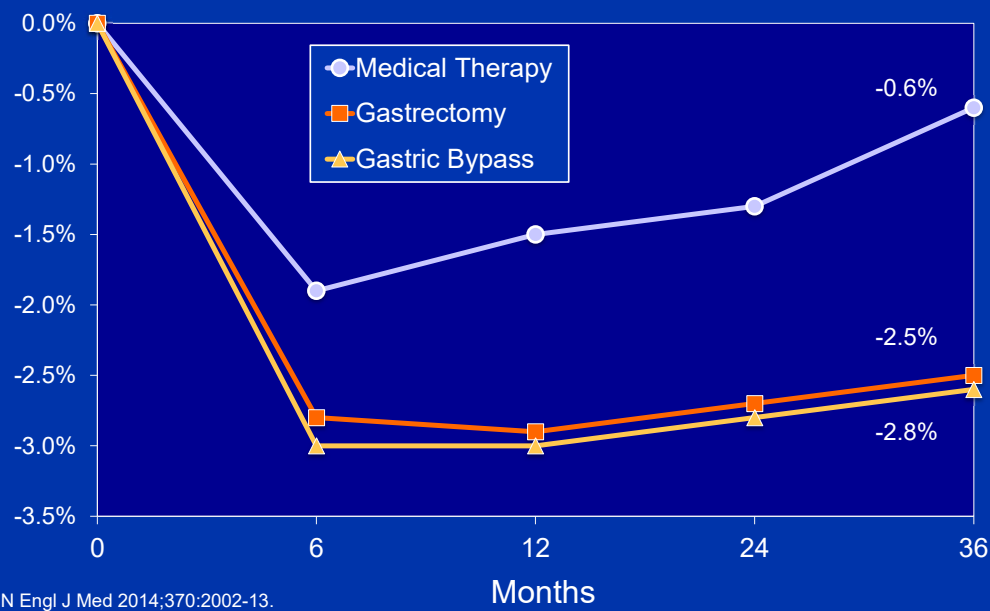
Stampede: Study Design

150 T2DM patients (HbA1c > 7.0%, BMI 27- 43 kg/m²)



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Change in Glycohemoglobin Through 36 Months



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Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity

Ali Aminian, MD; Alexander Zajichek, MS; David E. Arterburn, MD, MPH; Kathy E. Wolski, MPH; Stacy A. Brethauer, MD; Philip R. Schauer, MD; Michael W. Kattan, PhD; Steven E. Nissen, MD

IMPORTANCE Although metabolic surgery (defined as procedures that influence metabolism by inducing weight loss and altering gastrointestinal physiology) significantly improves cardiometabolic risk factors, the effect on cardiovascular outcomes has been less well characterized.

OBJECTIVE To investigate the relationship between metabolic surgery and incident major adverse cardiovascular events (MACE) in patients with type 2 diabetes and obesity.

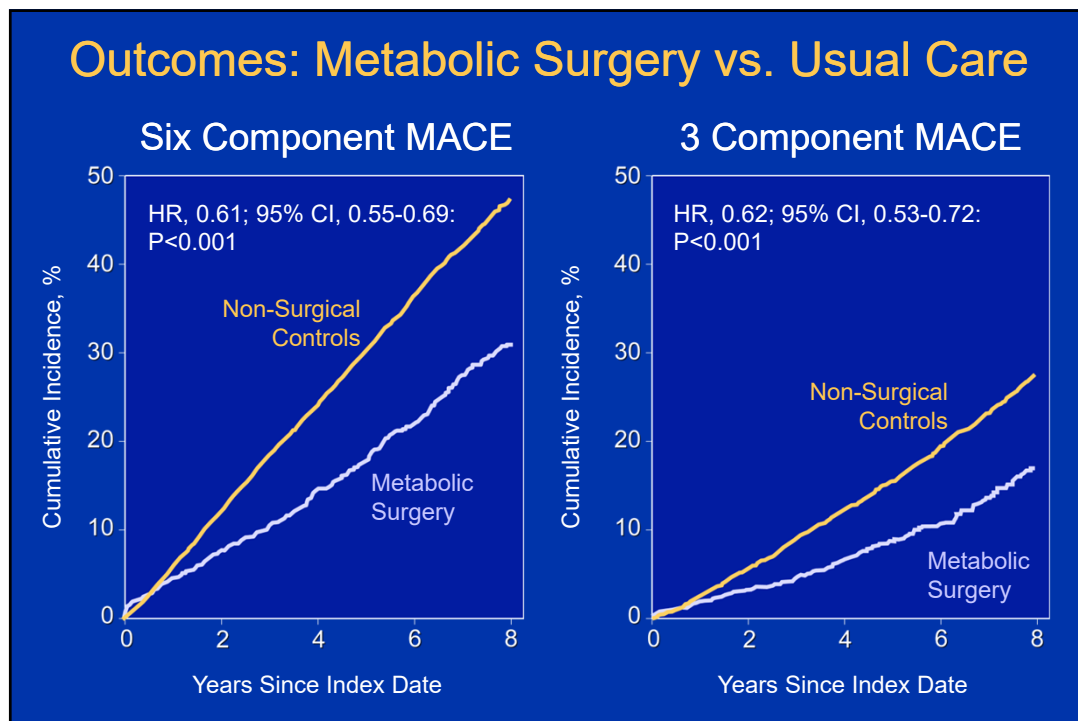
DESIGN, SETTING, AND PARTICIPANTS Of 287 438 adult patients with diabetes in the Cleveland Clinic Health System in the United States between 1998 and 2017, 2287 patients underwent metabolic surgery. In this retrospective cohort study, these patients were matched 1:5 to nonsurgical patients with diabetes and obesity (body mass index [BMI] ≥ 30), resulting in 11 435 control patients, with follow-up through December 2018.

EXPOSURES Metabolic gastrointestinal surgical procedures vs usual care for type 2 diabetes and obesity.

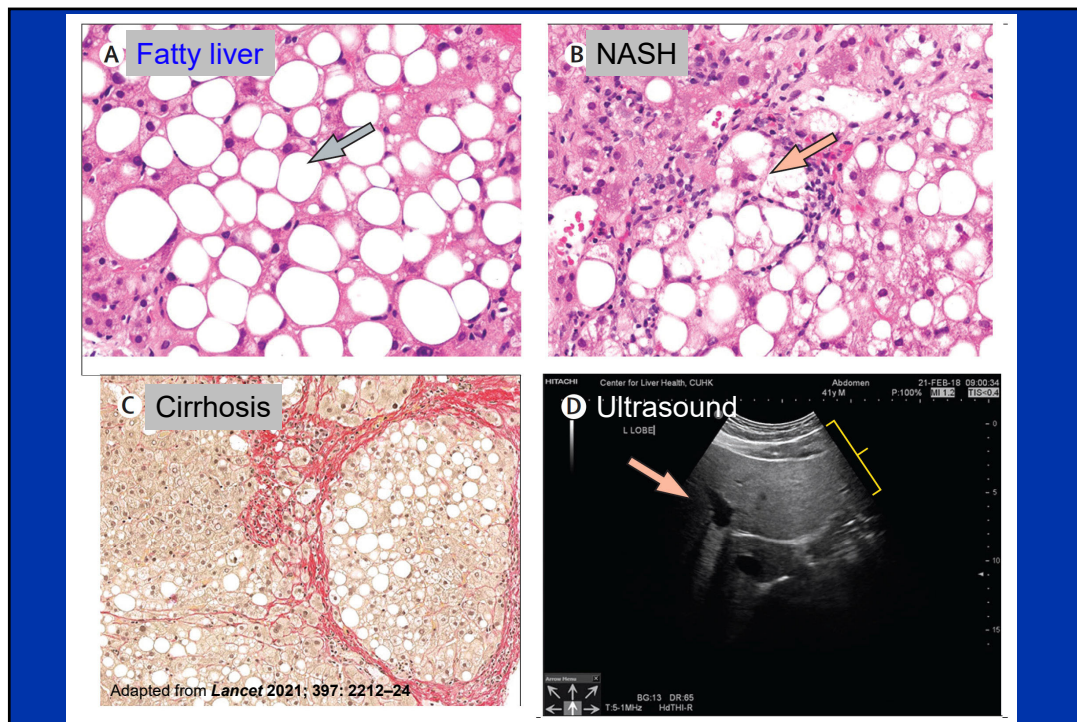
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Interventions Required Following Metabolic Surgery

Intervention	Years Since Metabolic Surgery			
	1	2	5	8
Total Parenteral Nutrition	1.5%	1.8%	2.1%	2.9%
Endoscopy	23.9%	30.1%	44.2%	52%
Interventional Radiology	2.6%	3.3%	6.8%	10.4%
Abdominal Surgical Procedure	5.9%	8.1%	12.1%	13.8%
Repair Abdominal wall hernia	2.8%	5.7%	8.7%	11.1%
Cholecystectomy	1.4%	3.5%	6.5%	9.7%

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Can Newer Pharmacological Therapies Achieve the Benefits Shown for Bariatric Surgery?

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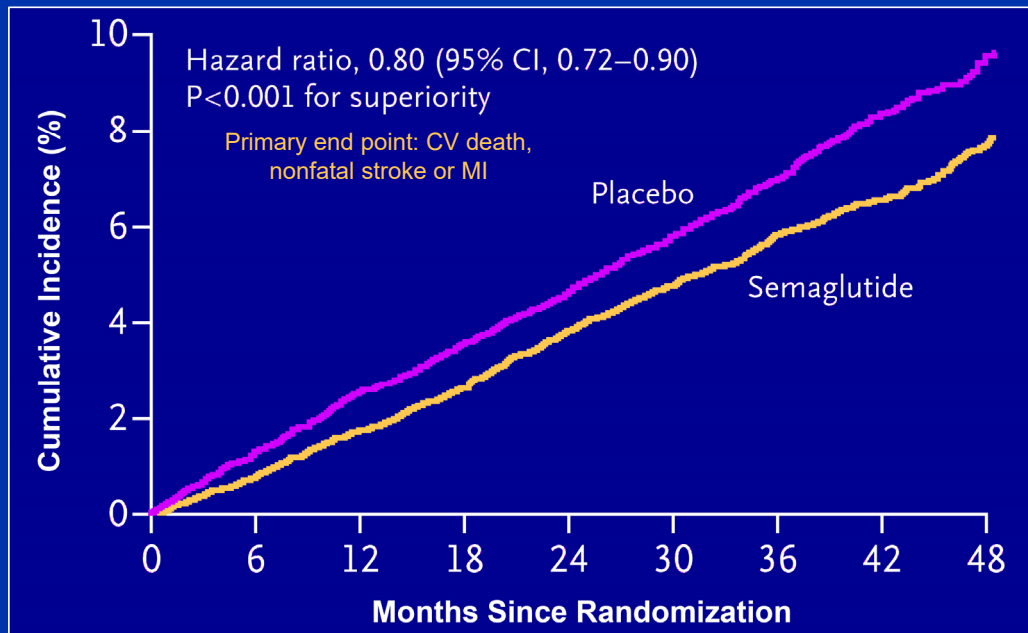
Incretins and Glucagon: Three Potential targets

- GLP-1 - Glucagon-like peptide-1
- GIP - Glucose-dependent insulintropic polypeptide
- Glucagon receptors

Designers of drugs can target any of these three receptors, potentially with single peptides, enabling multifunctional drugs

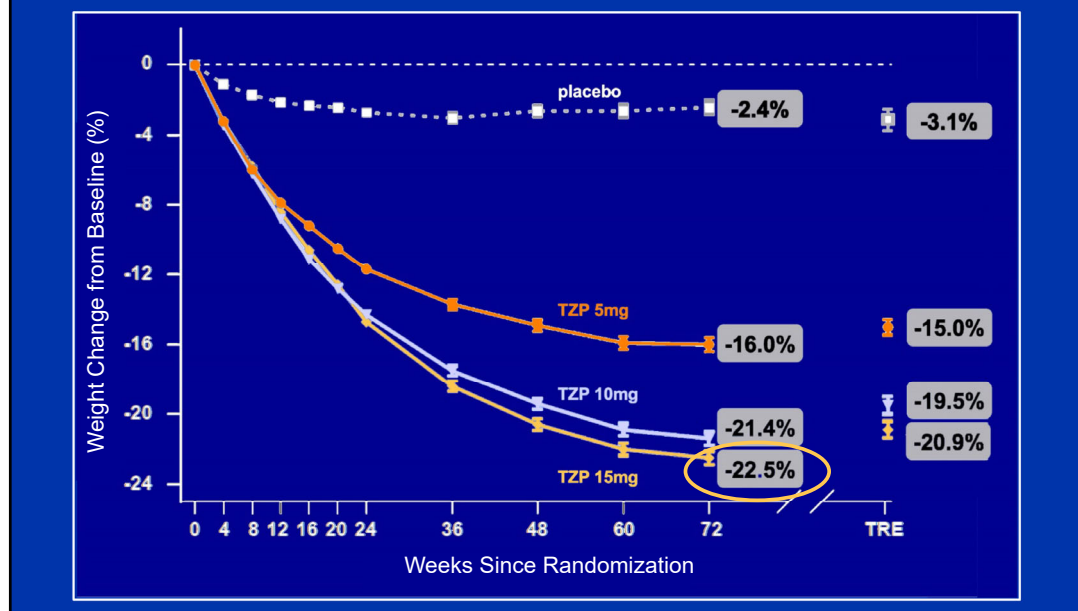
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SELECT: Semaglutide and Cardiovascular Outcome



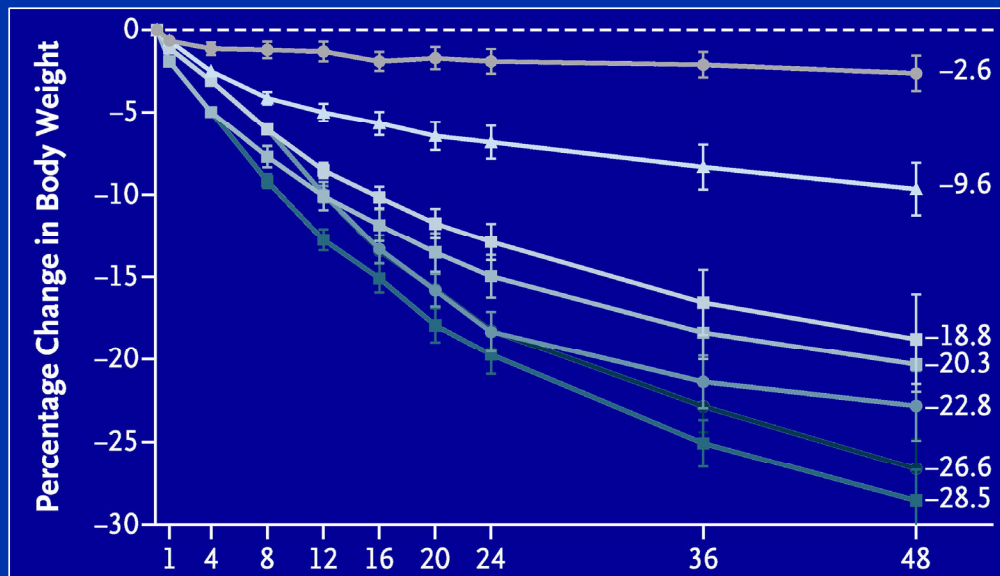
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Tirzepatide: Dual GLP & GIP Agonist Effect on Weight Loss



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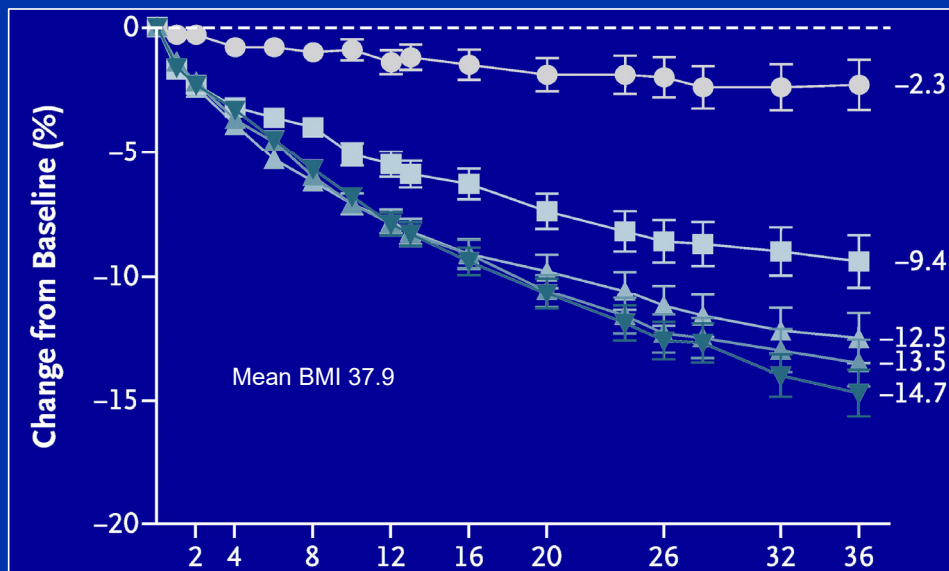
Retatrutide: Triple Agonist Effect on Weight in Females



DOI: 10.1056/NEJMoa2301972

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Orforglipron: Effect on Weight through 36 Weeks



DOI: 10.1056/NEJMoa2302392

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Know The Enemy: Billions and Billions Served



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The Essential, Toxic, American Fast-Food Diet

Percent Daily Values: Calories (68%), Fat (73%), Sugar (168%)

Nutrition Calculator



1360 Cal.
Calories

57g
Total Fat (73 % DV)

188g
Total Carbs (69 % DV)

32g
Protein (0 % DV)

Saturated Fat:	14g (72 % DV)	Total Sugars:	86g	Vitamin D:	0mcg (0 % DV)
Dietary Fiber:	9g (32 % DV)	Added Sugars:	84g (168 % DV)	Potassium:	1405mg (28 % DV)
Calcium:	149mg (12 % DV)	Iron:	6.0mg (33 % DV)	Sodium:	1530mg (66 % DV)
Trans Fat:	1g	Cholesterol:	85mg (28 % DV)		

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