Management of Overweight and Obesity: Clinical Considerations

Primary Care Essentials webinar 9/11/2020

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Disclosures

1. Champion 2020 VA/DoD CPG Screening and Management of Obesity and Overweight. https://www.healthquality.va.gov/guidelines/CD/obesity/

2. Research funding NovoNordisk (Sub-PI SELECT) August 2019–March 2020.

→OFF FDA label prescribing practices to consider will be discussed.

Objectives

- Epidemiology of the Obesity Epidemic
- Culprits underlying Obesity: Multifactorial
- Treatment Considerations
  - Iatrogenic (Is your prescribing practice making it harder on your patients?)
  - Motivational Interviewing and Behavioral Change
  - Brief Dietary Considerations
  - Pharmacologic Therapy Considerations
  - Surgical Approaches
- Patient case and Pearls from an endocrinologist's perspective

AMA Recognized Obesity as a Disease 5/16/2013

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 420
(A-13)

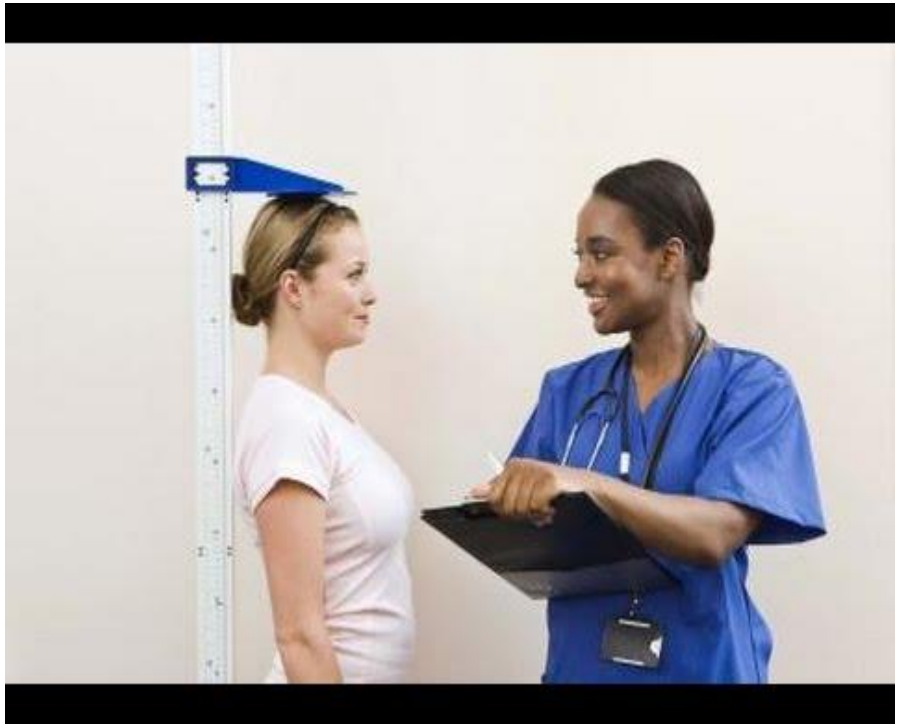
Introduced by: American Association of Clinical Endocrinologists
American College of Cardiology
The Endocrine Society
American Society for Reproductive Medicine
The Society for Cardiovascular Angiography and Interventions
American Urological Association
American College of Surgeons

Subject: Recognition of Obesity as a Disease

Referred to: Reference Committee D
(Douglas W. Martin, MD, Chair)

Defining Obesity: Body Mass index (kg/m²) (Adults)

BMI classification	
Underweight	< 18.5
Normal range	18.5 - 24.9
Overweight	⩾ 25.0
Preobese	25.0 - 29.9
Obese	⩾ 30.0
Obese class I	30.0 - 34.9
Obese class II	35.0 - 39.9
Obese class III	⩾ 40.0

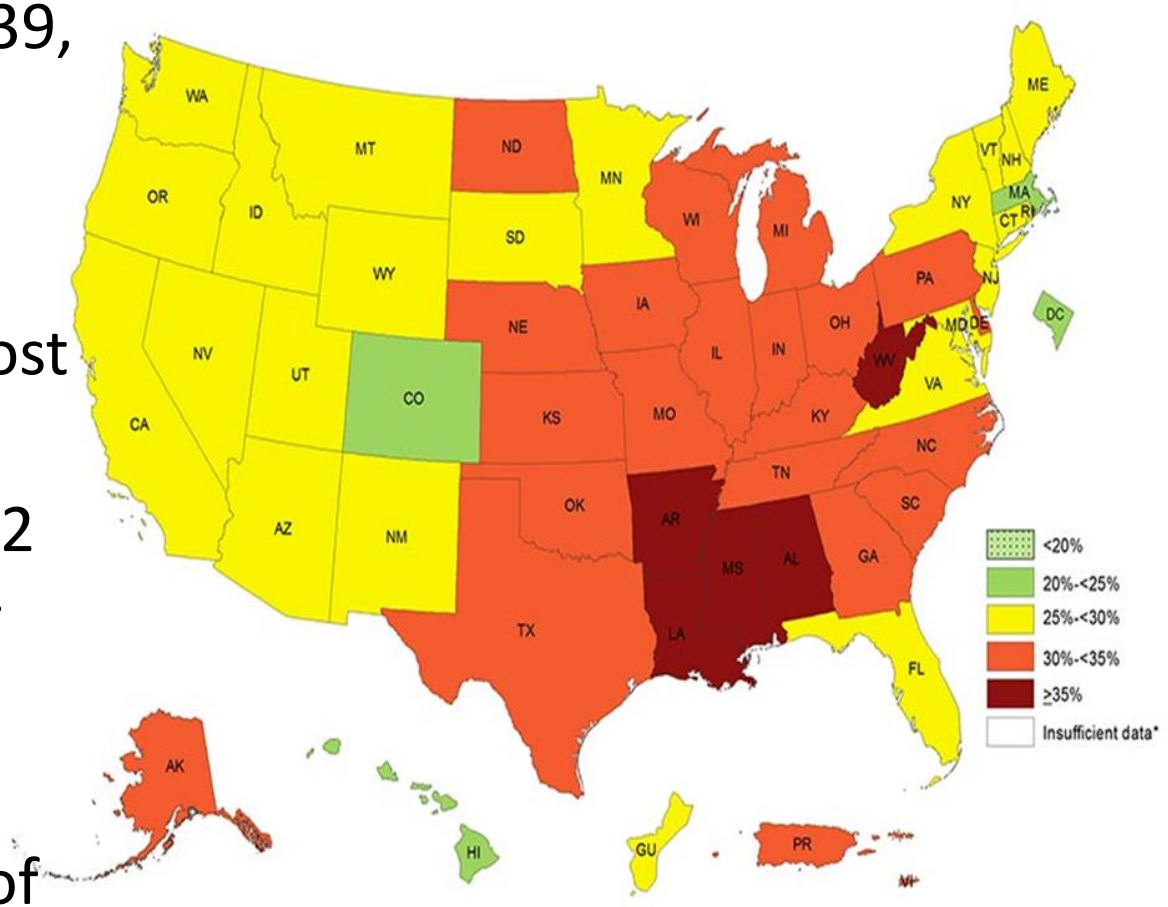


- Both healthcare providers and patients routinely underestimate BMI.

1. Steinsbekk, S. et al. *Front Psychol*. 2017; 8: 2038
2. Sun, Q. et al., 2010. *Am. J. Epidemiol.*, 172(12), pp.1442–1454

Epidemiology of Obesity

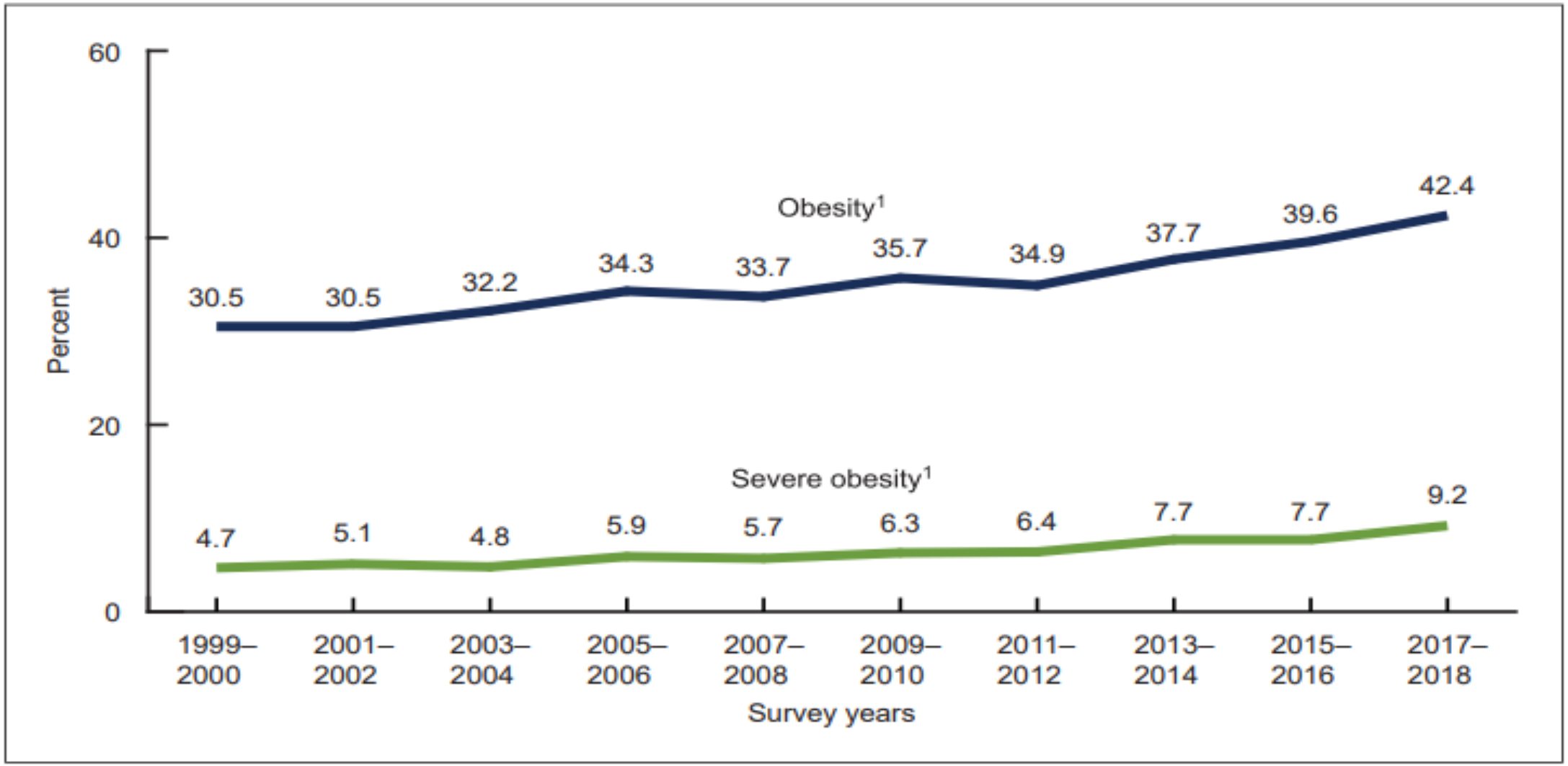
- **Common**: 40.0% among adults aged 20–39, 44.8% among adults aged 40–59, and 42.8% among adults aged 60 and over
- **Morbid**: associated with 13+ types of cancer; 40% of all cancers diagnosed (most particularly colon, breast and prostate)
- **Costly**: 2012 IOM report estimated $190.2 Billion (estimated annual cost of Obesity-related Illness)



- Affected by ethnicity, age, sex, and level of education

1. NHANES 2017-2018
2. U.S. Department of HHS CDC National Center for Health Statistics
3. Flegal, K.M. & Graubard, B.I., 2009. *Am. J. Clin. Nutr.*, 89(4), pp.1213–1219

Obesity Trends US adults (>20 yrs) 1999-2018



SOURCE: NCHS, National Health and Nutrition Examination Survey, 2017–2018.

Causes of Obesity – Multifactorial

- Intrauterine environment
- Genetic factors in obesity
- Both Food deserts and Food overabundance
- Aggressive marketing and food engineering in the food industry
- Reduced job and daily activity
- Climate controlled temperature regulation (less thermogenesis/ brown fat)
- Associative sorting – cultural/family environment
- Multi-hormonal/neural control of body weight
- Gut signals affect feeding
- Gut microbiome
- Clock genes and sleep regulation may play a role; Sleep hygiene / debt
- (Mal)adaptive biological responses to weight loss: fall in energy expenditure + increase in appetite after weight loss
- Secondary causes – screen IF PE and Hx suggest
- Iatrogenic: use of medications that promote weight gain (antiglycemics, anticonvulsants, antipsychotics, SSRIs, BB, OCPs)

1. McAllister EJ, et al. Crit Rev Food Sci Nutr. 2009; 49(10):868-913
2. Apovian et al. *J Clin Endocrinol Metab*, February 2015, 100(2):342–362

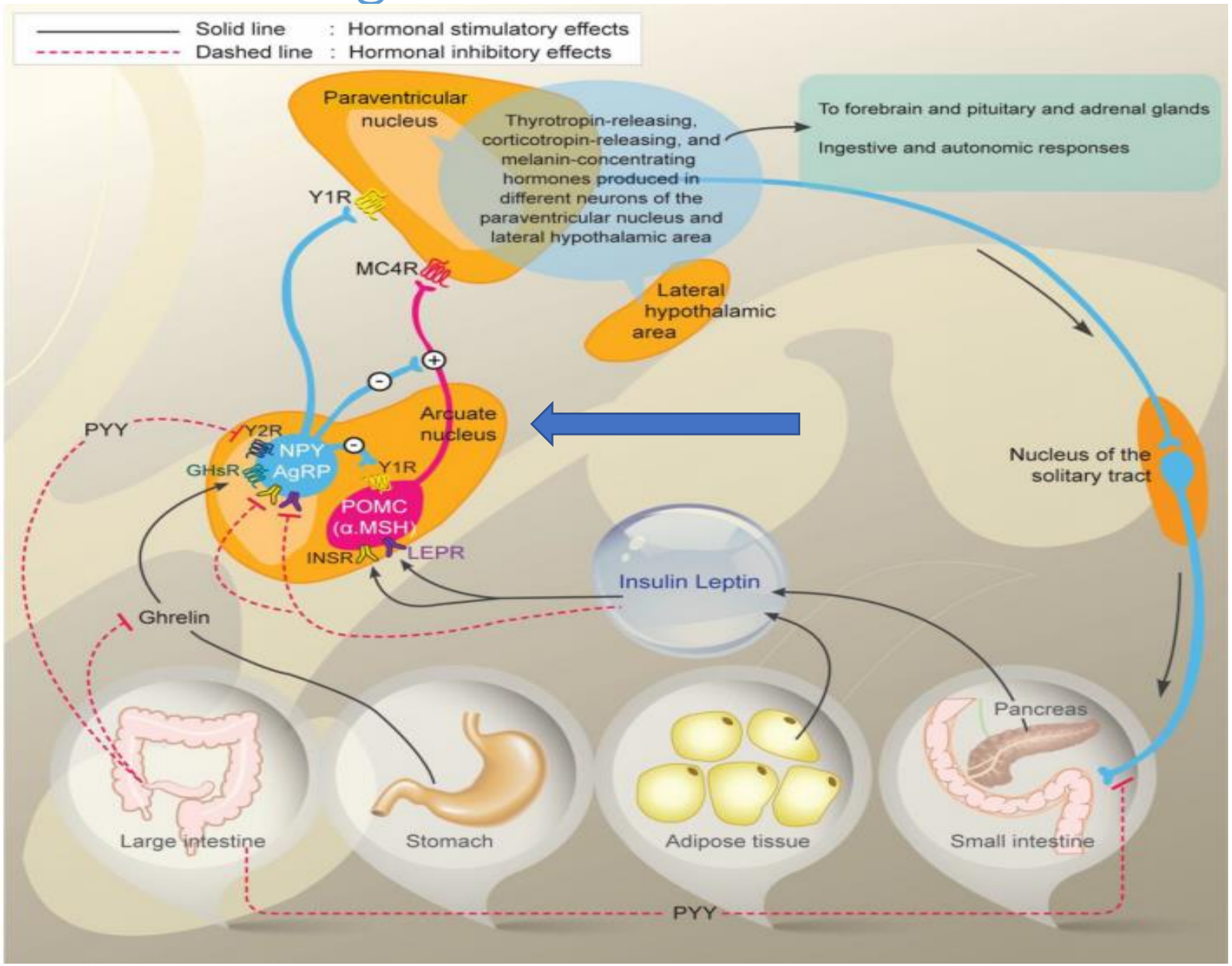
Food Intake Regulation Inputs
(+) hunger/orexigenic; (-) satiety/anorexigenic

- Peripheral organs:
  - GI tract (stomach, pancreas, intestine)
  - Adipose tissue
  - Adrenal glands
- Peripheral signals:
  - PYY (-) secreted ileum and colon
  - Glucose (-)
  - CCK (-) duodenum
  - GIP (-) K cells duodenum and jejunum
  - GLP-1 (-) L cells of ileum
  - Vagal afferents (-)
  - Ghrelin (+) stomach
  - Leptin (-) adipose tissue
  - Cortisol (+) adrenal glands
  - Insulin (+) pancreas

- Central signals:
  - NPY (+) arcuate nucleus
  - AGRP (+) arcuate nucleus
  - Cannabinoids (+)
  - Orexin-A (+)
  - Dynorphin (+)
  - alpha-MSH (-)
  - CRH/UCN (-)
  - GLP-1(-)
  - POMC/CART (-) arcuate nucleus
  - NE (-)
  - 5-HT (-)

Bray, George A. Handbook of Obesity: Clinical Applications (Hardcover), 2003

Neural and Hormonal Regulation of Food Intake and Body Fat Mass



Apovian et al. *J Clin Endocrinol Metab*, February 2015, 100(2):342–362

Secondary Causes of Obesity

- Screen IF physical exam and history warrant:
  - Depression
  - Binge eating disorder
  - Hypothyroidism
  - Hypercortisolism (Cushing's disease or syndrome)
  - Acromegaly
  - Traumatic brain injury
  - Brain tumor
  - Cranial irradiation

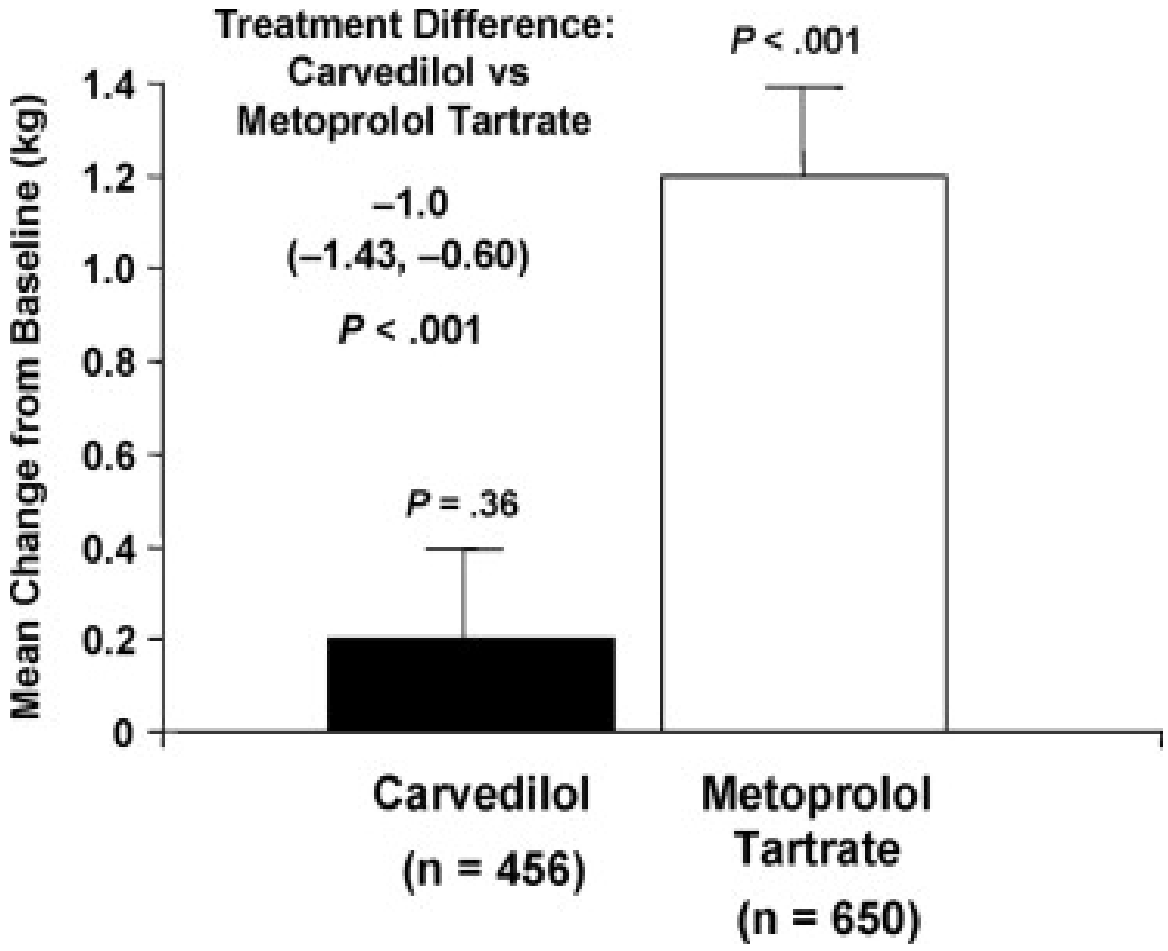
  Always look for most common culprit: PRESCRIBED MEDICATIONS!!

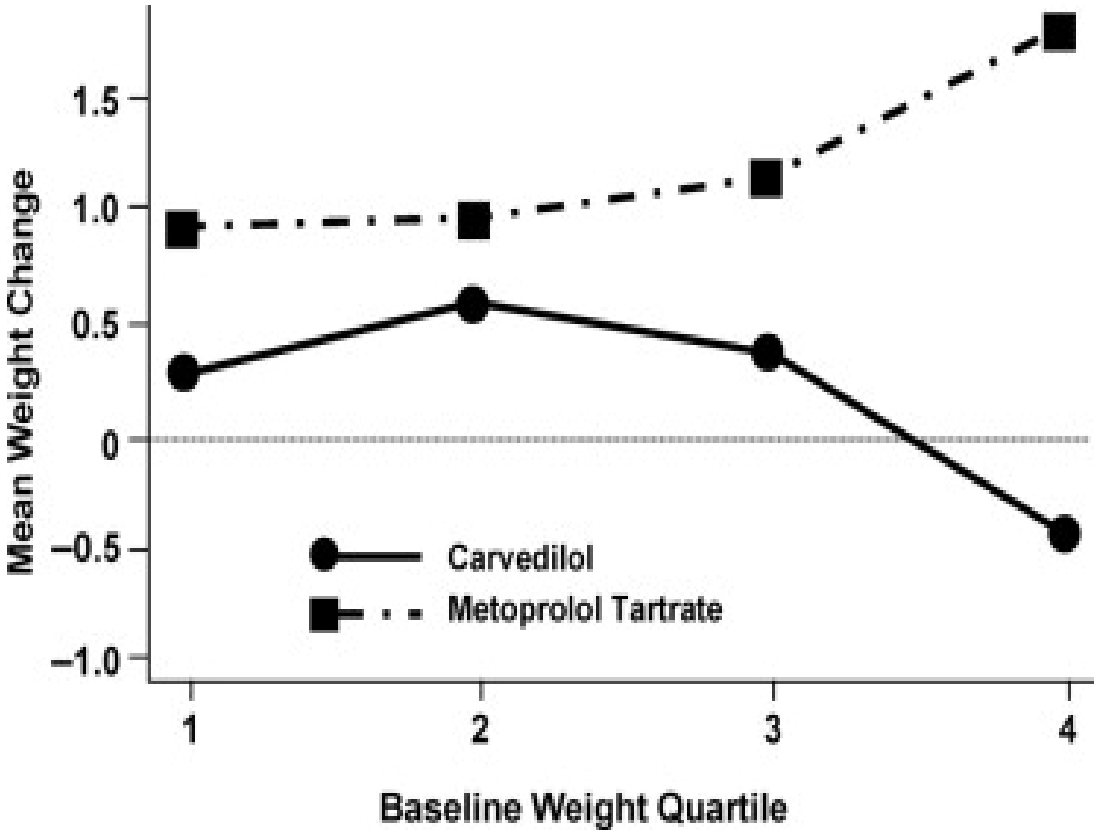
Iatrogenic: Don’t Make it Harder than it Already is!

Category	OBESOGENIC – CAUSE WEIGHT GAIN	Alternative to Consider
Antidepressants	TCAs (amitriptyline, nortriptyline, clomipramine, imipramine, doxepin, protriptyline*); Mirtazipine SSRIs (paroxetine, sertraline, citalopram*, escitalopram*, fluoxetine*) ; MAOIs (phenelzine)	Bupropion Desvenlafaxine Venlafaxine Duloxetine
Antipsychotics	Olanzipine; Quetiapine; Risperidone; Clozapine; Thioridazine	Aripiprazole; Haloperidol; Ziprasidone
Antiepileptics/ Mood Stabilizing	Gabapentin; Pregabalin; Divalproex; Valproic acid; Vigabatrin; Lithium; Carbamazepine	Topiramate; Lamotrigine; Zonisamide
Antiglycemics	Insulin Sulfonylureas (glipizide, glimepiride, glyburide etc) Thiazoledinediones (pioglitazone, rosiglitazone) Meglitinides (nateglinide, repaglinide)	Biguanides (metformin) SGLT2i (empagliflozin, canagliflozin, dapagliflozin etc.) GLP-1 (semaglutide, liraglutide, dulaglutide etc.) DPP4i (sitagliptin, saxagliptin, alogliptin etc.) alpha glucosidase inhibitors (acarbose or miglitol) Amylin analogs (pramlintide)
Antihypertensives	α Adrenergic Blocker (terazosin) β Adrenergic Blockers (especially nonselective metoprolol, propranolol, atenolol)	ACEi (lisinopril, ramipril etc) ARB (losartan, valsartan etc) CCB (amlodipine, verapamil, diltiazem) Diuretics
Steroid Hormones	Glucocorticoids (prednisone, hydrocortisone, methylpred) Contraceptives injectables >oral; any Progesterone based	NSAIDs; biologics; non-traditional therapies Copper IUD
Antihistamines	Cyproheptadine, Cetirizine, Fexofenadine	Decongestants, inhalers, nasal irrigation system

https://www.healthquality.va.gov/guidelines/CD/obesity/

Prespecified secondary analysis of GEMINI study (n=1106) evaluated change in body wt. after 5 mos. in DM2.





Messerli et al. Am J of Med (2007) 120, 610-615.

UKPDS (N=1,148) RCT in patients with DM2 and HTN

Atenolol gained more weight > Captopril

- (3.4 kg (7.5 lbs) *vs.* 1.6 kg (3.5 lbs)over nine years, p=0.020).

Atenolol required additional antiglycemic treatment > captopril

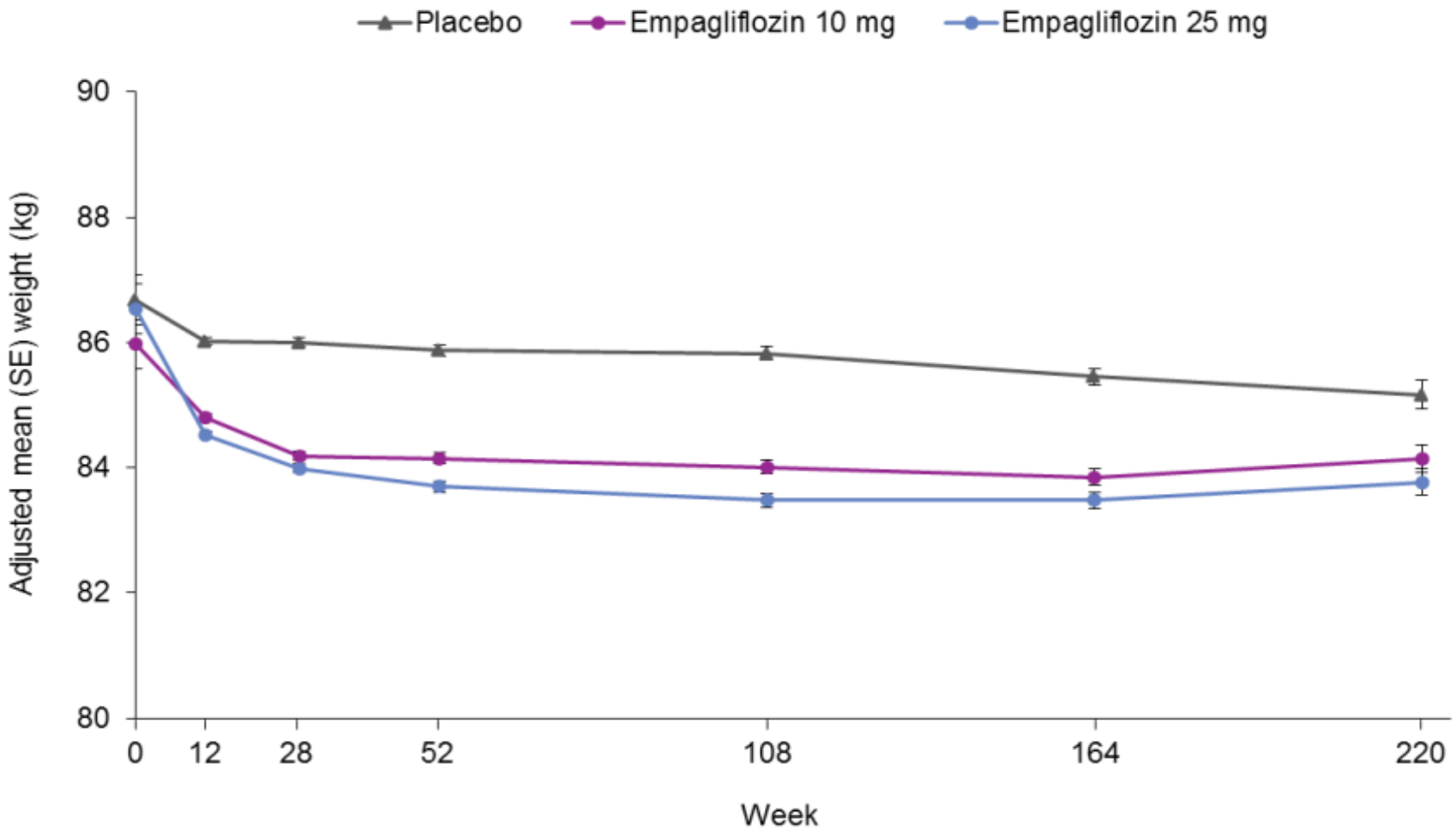
- (81% vs 71%, p=0.029)

Atenolol had worse Hemoglobin A_{1c} over the first 4 years

- (7.5% vs 7.0%, p=0.0044)

UK Prospective Diabetes Study Group. BMJ 1998 Sep 12; 317(7160): 713-720.

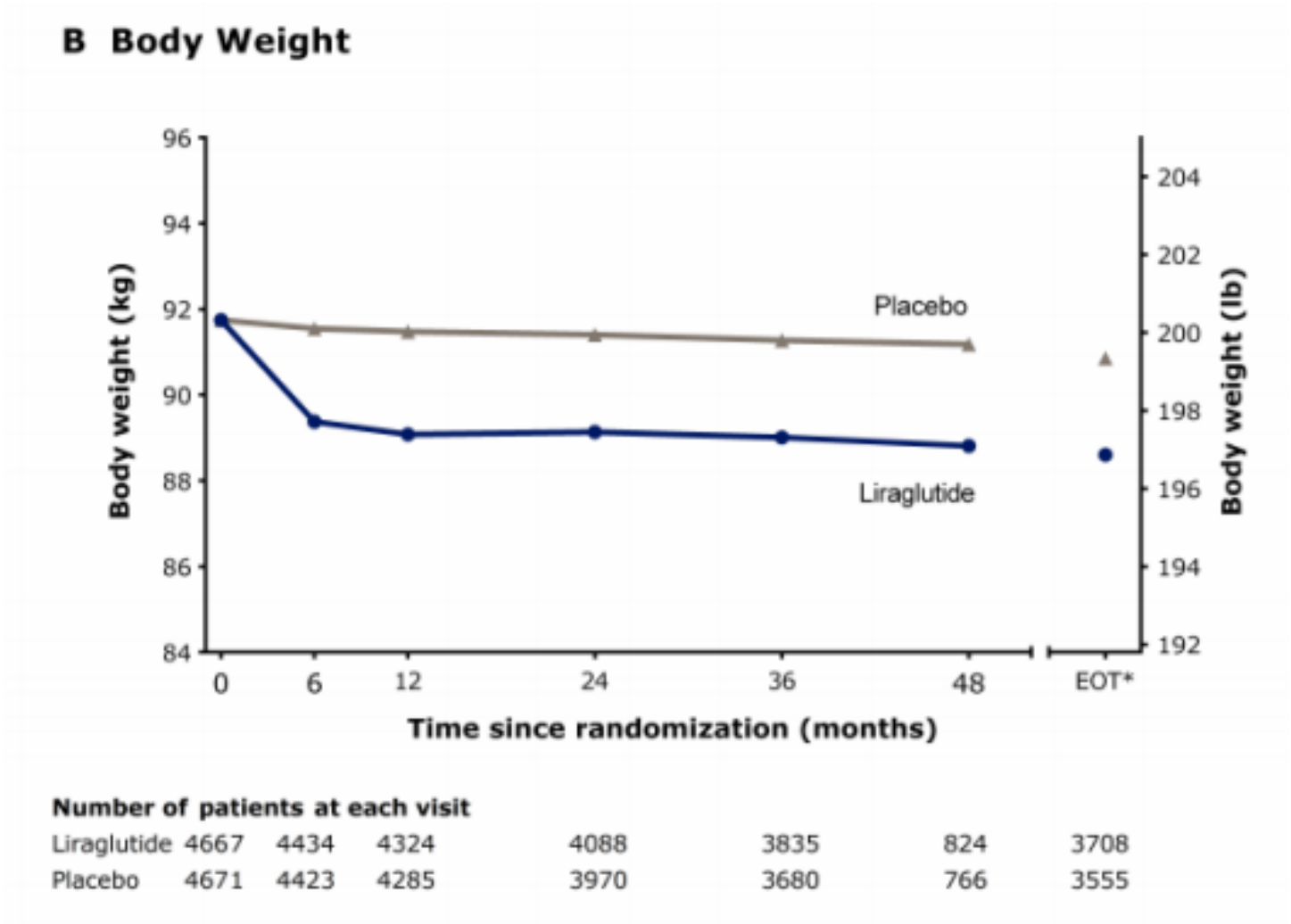
2015 EMPA-REG OUTCOME study – Weight in kg, (n=7020)



Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

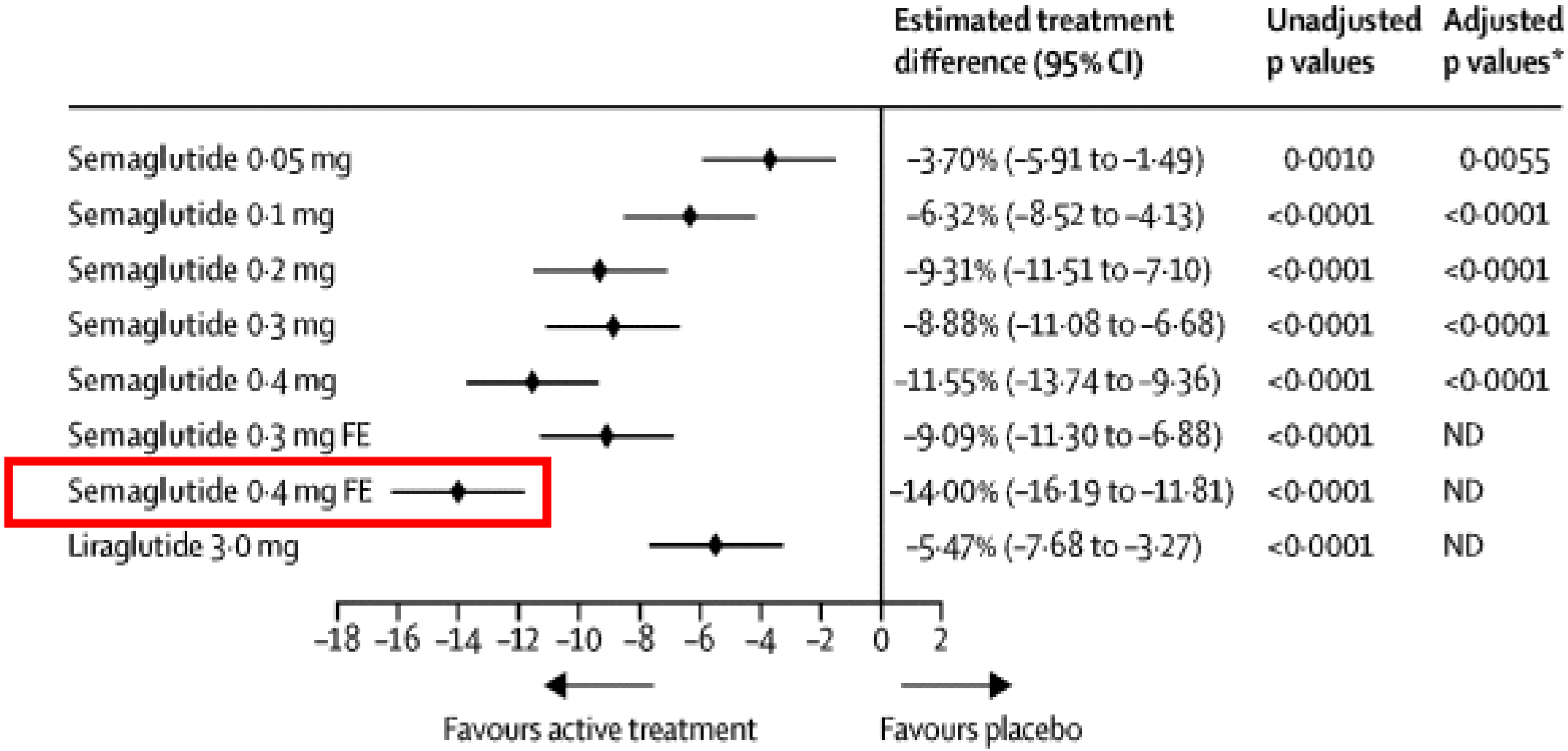
Zinman et al. N Engl J Med 2015. 373; 22.

2016 LEADER Trial RCT n=9,340 (A1c ≥7%)



LEADER Trial New Engl J Med 2016; 375:311-322 July 28, 2016

2018 Semaglutide vs. Liraglutide vs. Placebo for Weight Loss (n=957).



O'Neil et al. Lancet, 2018-08-25, Volume 392, Issue 10148, Pages 637-649

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

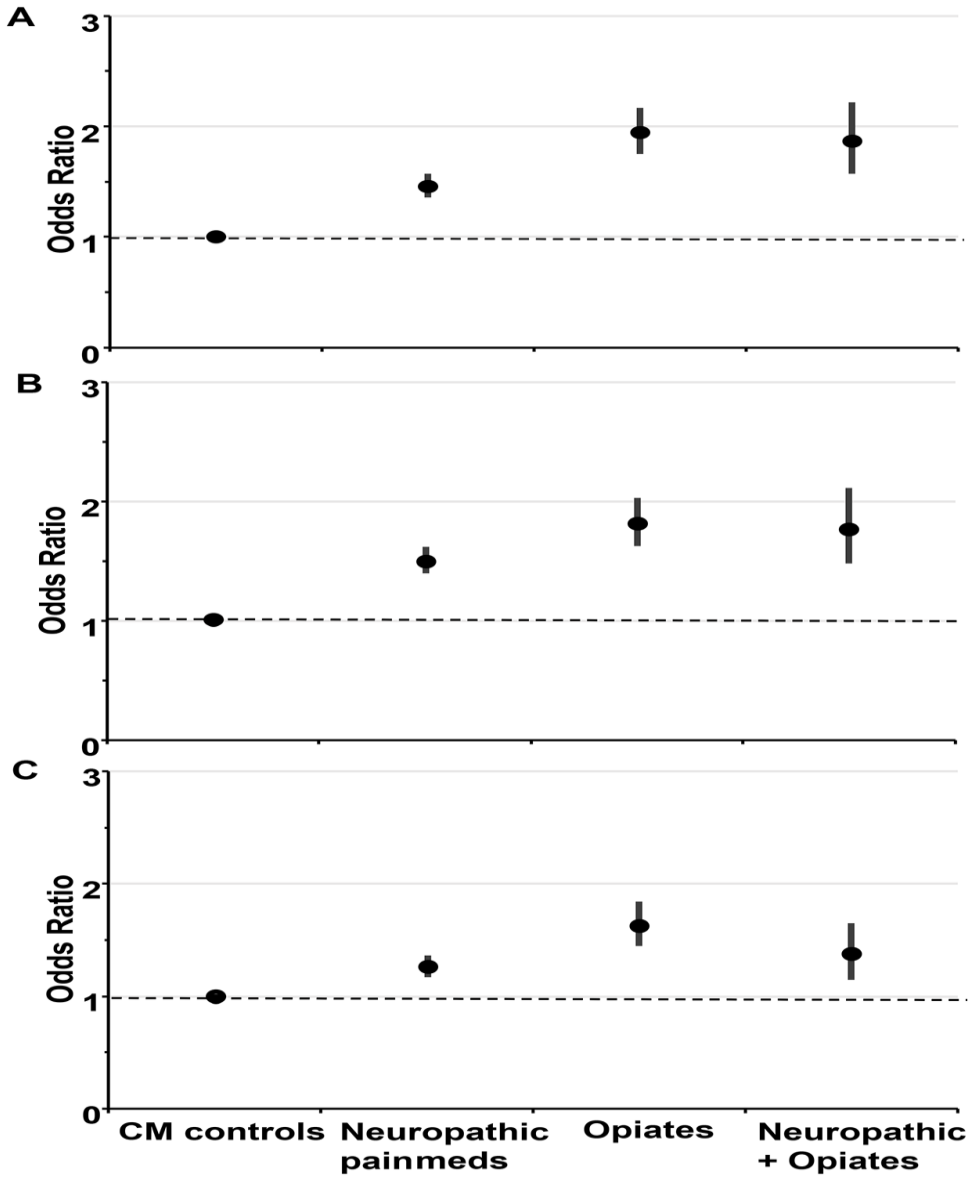
FDA label update 4/8/2016: Metformin

- Check eGFR Before starting metformin
- Contraindicated with eGFR <30 mL/minute/1.73 m2
- Not recommended new start if eGFR between 30-45 mL/minute/1.73 m2
- If eGFR falls after starting to between 30-45 mL/minute/1.73 m2, reassess continuing treatment.
- Obtain an eGFR at least annually, more frequently in the elderly or those at risk for loss of renal function.
- Discontinue metformin at the time of or before an iodinated contrast imaging if eGFR between 30 and 60 mL/minute/1.73 m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf

Neuropathic pain Meds + Opiates and Obesity

N=133,401
UK Cohort:
Biobank participants



(A) being obese

(B) having a 'very high risk' waist cm

(C) being hypertensive

Cassidy et al. PLOS ONE 2017

Dr. Mayer's approach to Neuropathy; Treatment Options that are NON-Obesogenic

1. Topiramate (OFF label; Avoid if CI: nephrolithiasis and acute closed angle glaucoma, teratogenic)

OR (sometimes AND)

2. Duloxetine (FDA indication for diabetic neuropathy)

+ 3. Capsaicin cream (usually not monotherapy)

4. Alpha Lipoic Acid (OTC antioxidant) 600mg daily

5. Lidocaine patches / cream

6. NSAID gel /cream ex. Voltaren

- All of the above + improving BG control with a more narrow SD, can refer to VA diabetes clinic

- Referral to pain clinic +/- neurologist

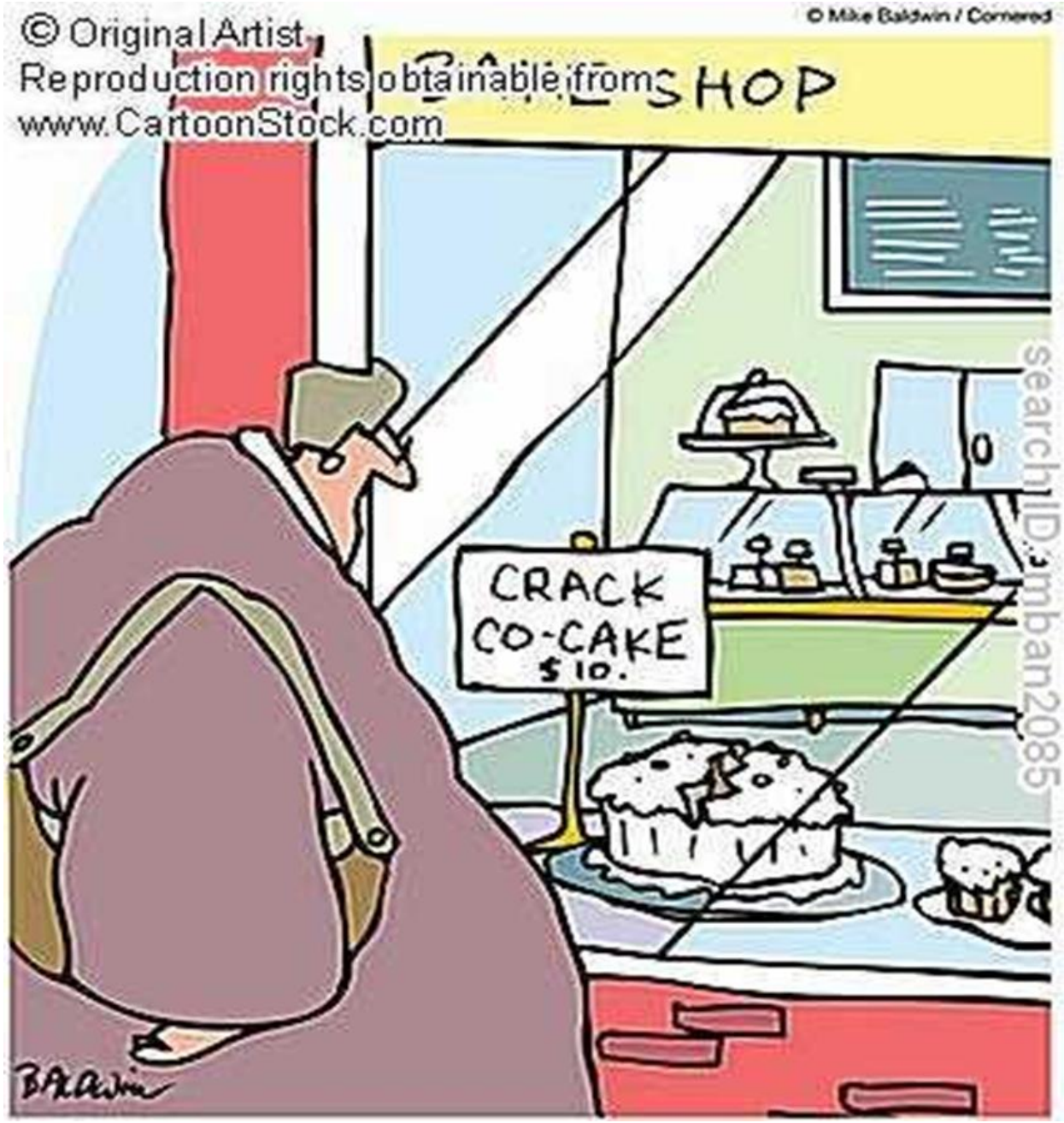
Recommendations for Obesity

1. Screen for obesity.

2. BMI ≥30 kg/m²→refer to intensive, multi-component behavioral intervention program, a **Comprehensive Lifestyle intervention**

TAKE OFF POUNDS SENSIBLY

http://uspreventativeservicestaskforce.org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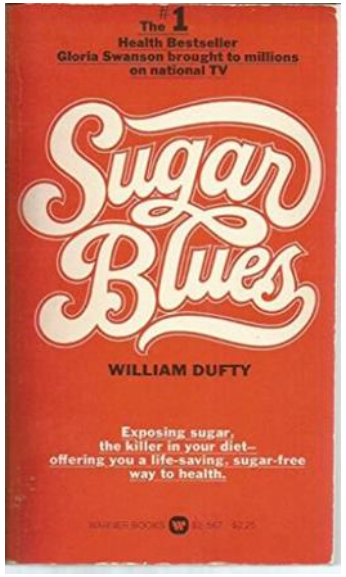
Behavior Modification Therapy



- Goal of long-term changes
- Identification and control of stimuli that trigger eating
- Setting SMART goals (specific, measurable, action-oriented, realistic, time-sensitive)
- Modification and then monitoring (emphasis on self-monitoring) eating behavior and activity level
- Mindful eating, slowing down the process, eating with intent
- Social support, encourage family engagement
- Cognitive restructuring, problem solving, assertiveness training, behavioral contracting, reinforcement of success and stress reduction also may be helpful

1. Voils et al. Trials. 2009 Feb 6;10.10.
2. Apovian et al. *J Clin Endocrinol Metab*, February 2015, 100(2):342–362

Diet: Goal of Negative Energy Balance

- Many dietary programs studied: Low carbohydrate/ketogenic (modified-Atkins), DASH, Mediterranean, low fat (LEARN or Ornish), low glycemic index (South Beach, Zone), and intermittent fasting
- Meal replacement (shake or bar) can be helpful
- Low carbohydrate more effective than low fat: 6 mos only, not different 12 mos.
- Meta-analysis of 48 RCTs comparing dietary programs (low carb, moderate macronutrient, or low fat) to comparator: all resulted in 6-8 kg weight loss at 6 months (nadir) and 4-7 kg at 12 months
- Degree of adherence, and perhaps frequency of intervention, key
- CHOICE study: opportunity to choose did not improve weight loss
- DIETFITS neither 3 SNPs multilocus genotype responsiveness patterns or insulin secretion determined degree of weight loss on either a HLF or HLC diet.

1. Johnston et al. JAMA 2014 Sep;312(9):923-33.
2. Yancy et al. CHOICE Ann Intern Med. 2015;162(12):805-814

Dietary Recommendations: Good for ALL!

- NO liquid sugar (NO juice –including cranberry, no smoothies, no sweet tea, no Gatorade, no Koolaid, no Lemonade, no soda/ginger ale)
- MORE non-starchy vegetable servings per day
- MORE lean proteins
- Minimize or avoid alcohol –diuretic, calories, brain misinterprets thirst for hunger

Sugar synonyms:

- Agave syrup
- Maple syrup
- Molasses
- Brown sugar
- Sugar in the raw
- Honey

http://theoriesofconspiracy.com/wp-content/uploads/2011/11/jabba-hfcs.jpg

Pharmacologic Management of Obesity

FDA cites indicated for:

- BMI ≥ 27 kg/m^2 + an obesity related comorbidity: type 2 DM, HTN, dyslipidemia, OA and OSA (consider with NAFLD, and GERD)

- BMI ≥ 30 kg/m^2

FDA Approved Obesity Medications (more in pipeline)

1. Phentermine (short term only)
2. Diethylpropion (short term only)
3. Orlistat
4. Qsymia (Topiramate ER + Phentermine)
5. Saxenda (Liraglutide)
6. Contrave (Bupropion + Naltrexone)

- Weight loss in general is contraindicated in pregnancy. Most are Pregnancy class X.

Phentermine (Adipex-P, Lomaira)

- Approved 1960's for short term "few weeks"
- Somewhat effective: -3.6kg 2-24 wks
- MOA: Sympathomimetic amine, norepinephrine releasing agent = CNS stimulant
- No CVOT data (lack of safety data); one study since 1975
- Side effects include mean blood pressure elevation and pulse rate, restlessness, headache, dry mouth, impotence

- Contraindicated: anxiety disorders, CVD, HTN, seizure disorder, MAOi use, hyperthyroidism, glaucoma, hx of drug abuse, pregnancy and breastfeeding

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Diethylpropion (Tenuate)

- Approved 1960's for short term use 3 months only
- Somewhat effective: -3.0 kg 6-52 wks

- MOA: Sympathomimetic amine, norepinephrine releasing agent = CNS stimulant
- IR 25mg 3xD AC; CR 75mg 1xD
- No CVOT data (lack of safety data)
- Side effects include arrhythmia, HTN, tachycardia, restlessness, headache, dry mouth, impotence

- Contraindicated: anxiety disorders, CVD, severe HTN, pulmonary HTN, seizure disorder, within 14 days of MAOi use, hyperthyroidism, glaucoma, hx of drug abuse, pregnancy and breastfeeding

Orlistat (Rx Xenical; OTC Alli)

- FDA approved 1999 for chronic weight management
- Somewhat effective -2.9 – 3.4kg at 1 year
- MOA: inhibits pancreatic lipase, limiting fat absorption,
- Blocks 25-30% of fat calorie
- Minimal systemic absorption
- SE: decreased absorption of fat soluble vitamins (K,A,D,E), flatulence with discharge, steatorrhea, fecal incontinence

- CI: cyclosporine 3hrs before or after orlistat, malabsorption syndromes, avoid use with LT4, warfarin or antiepileptic agents; pregnancy and breastfeeding

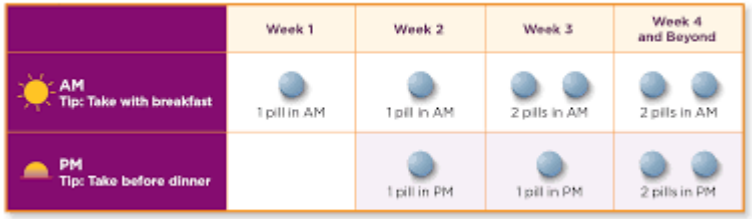
Qsymia:
combination of Phentermine + Topiramate ER

- FDA approved 2012 for chronic weight management
- Effective: -6.6 - 8.6 kg at 1 year
- MOA: Topiramate: antiepileptic (GABA receptor modulation?) + Phentermine: sympathomimetic amine
- Requires dose titration
- SE: inc heart rate, suicidal ideation, angle closure glaucoma, nephrolithiasis, decreased serum bicarbonate, insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia
- CI: hyperthyroidism, glaucoma (closed angle), concomitant MAO inhibitor, caution if nephrolithiasis ≤3%
- Pregnancy: X (cleft lip/palate), requires REMS to prescribe

Qsymia (phentermine and topiramate ER) package insert. Mountain view CA: Vivus, Inc:2012

Contrave (combination of bupropion + naltrexone)

- FDA approved 2014 for chronic weight management
- Moderately effective -4.8% body weight loss at 1 year
- MOA: Bupropion: dopamine and norepinephrine reuptake inhibitor that stimulates POMC neurons + Naltrexone opioid antagonist potentiates the feedback inhibition of POMC neurons (promoting satiety)
- SE: nausea, constipation, headache, vomiting, dizziness
- CI: uncontrolled HTN, seizure disorder, anorexia nervosa or bulimia, drug or ETOH withdrawal, use of MAO inhibitors
- Pregnancy: X



Liraglutide (Saxenda brand)

- FDA approved 2014 for chronic weight management
- Effective: -5.8kg at 1 year
- MOA: GLP-1 agonist–>binds to GLP-1 receptors in many tissues (β cells and brain) inc glucose-dep insulin secretion, dec glucagon sec, inc ß cell growth, slows gastric emptying, receptors dorsal vagal complex centrally promote satiety.
- Injection only, requires dose escalation
- SE: nausea (40-50%), diarrhea, headaches, dizziness, URI, increased serum lipase, hyperbilirubinemia
- Caution: gastroparesis
- CI: medullary thyroid cancer in pt or family, MEN2A or B (family hx of pancreatic cancer?)

Reassess Response

- “Effective” is often defined as 5% loss of body weight at 3 months.
- Ineffective = < 5% weight loss at 3 mos, or if side effects →discontinue (may need to taper back down) consider switch or referral
- Weight loss effects are sustained only while taking these agents.
- Cross-over trials demonstrate weight regain once off of the obesity treatment agent.

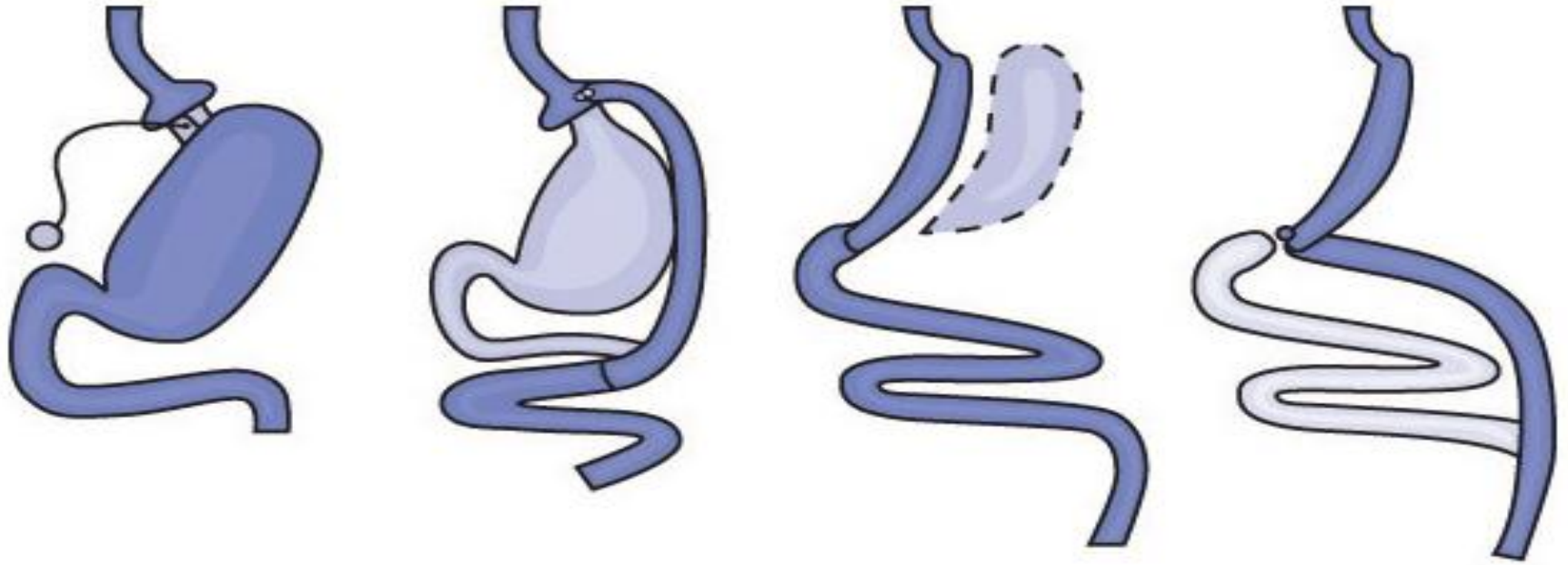
Surgical Treatment Options for Obesity

Bariatric surgery is indicated:

- BMI ≥30 kg/m^2 with type 2 Diabetes
- BMI ≥35 kg/m^2 + an obesity-related comorbidity (could include HTN, OSA, OA, GERD)
- BMI ≥ 40 kg/m^2

1. https://www.healthequality.va.gov/guidelines/CD/obesity/
2. Horwitz et al. Surg Obes Relat Dis. 2016
3. Liang et al. Diabetes Res Clin Pract. 2013

Surgical Treatments for Obesity



Adjustable Gastric Band (AGB)

Roux-en-Y Gastric Bypass (RYGB)

Vertical Sleeve Gastrectomy (VSG)

Biliopancreatic Diversion With a Duodenal Switch (BPD-DS)

http://win.niddk.nih.gov/publications/gastric.htm

Space Occupying Systems for weight loss

- Endoscopically placed balloons

Short-term 6 month use only

Patient Case: Broaching the Topic of Weight

- Ms. M. is a 62 year-old woman
- PMHx: type 2 diabetes complicated by neuropathy, high blood pressure
- BMI is 36 kg/m^2

First step: Ask for permission!

"I am concerned about how your weight might be affecting your health. Is this something you feel comfortable discussing today?"

Look for Culprit Obesogenic Meds

Next: Review medication list

→Look for culprits making weight loss harder

Med list:

1. Glipizide 10mg twice daily
2. Metformin 1000mg twice daily
3. Metoprolol tartrate 25 mg twice daily
4. Lisinopril 5mg daily
5. Gabapentin 600mg three times daily
6. Cetirizine 10mg daily

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Don’t make it Harder than it already is!

Select Medications and Potential Effects on Weight		
Category	Potential for Weight Gain	Alternative to Consider
Antidepressants	Tricyclic antidepressants (amitriptyline, nortriptyline); mirtazapine; SSRIs (paroxetine); Monoamine oxidase inhibitors	bupropion; desvenlafaxine; venlafaxine
Antipsychotics	quetiapine; clozapine; olanzapine; risperidone; thioridazine	aripiprazole; haloperidol; ziprasidone
Antiepileptics or mood stabilizers	gabapentin; pregabalin; carbamazepine; divalproex; lithium; valproic acid; vigabatrin	topiramate; lamotrigine; zonisamide
Antihyperglycemic agents	Insulin; Sulfonylureas; Meglitinides; Thiazolidinediones	GLP-1 agonists; SGLT2 inhibitors; metformin; Alpha-glucosidase inhibitors; pramlintide; DPP-4 inhibitors
Beta-Blockers	metoprolol; atenolol; propranolol	carvedilol; nebivolol Other drug classes available (ACEIs, ARBs, CCBs, diuretics) per indication
Alpha-Blockers	terazosin	BPH: doxazosin, alfuzosin, tamsulosin
Glucocorticoids	prednisone; methylprednisolone; hydrocortisone	NSAIDs, biologics/DMARDs, nontraditional therapies
Hormonal agents	Progestins	For contraception, consider alternative methods (e.g., copper IUD)
Antihistamines	cetirizine; cyproheptadine	Depending on symptoms, consider decongestants, inhalers, nasal irrigation

Obesogenic Agent Alternatives

- Consider regimen that does not include a beta blocker if no CV event history
- Consider SWITCH from glipizide (sulfonylurea) to alternative hypoglycemic agent (SGLT2i or GLP-1 agonist associated with weight loss; DPP4i weight neutral)
- Trial nasal sprays and daily nasal irrigation system (Netti Pot) to minimize use of antihistamines
- Suggest WEAN DOWN on gabapentin while adding one or more alternative agents:
  - Topiramate (OFF label; Warnings/Precautions include: nephrolithiasis and acute closed angle glaucoma, teratogenic)
  - Duloxetine (FDA indication for diabetic neuropathy)
  - Capsaicin cream (usually not monotherapy)
  - Topical lidocaine
  - Topical NSAID

Weight Management Options

- Ask about weight history: “When do you feel you started struggling with your weight? What has worked the best for you in the past? What makes it easier, what makes it harder?”
- Ask if she would be interested in considering referral to a comprehensive weight loss program (ex: TOPS)
- Simultaneously, is she interested in considering starting a medication for weight loss?
- Would she be interested in more information regarding bariatric surgery option?

PE: Look for signs of Insulin Resistance →check a HgbA1c

BMI >30kg/m² consider screening: diabetes mellitus, dyslipidemia, HTN, CVD, OSA, NAFLD, OA, major depression, and cancer screening as indicated.

Weight Management Pharmacotherapy Considerations

Obtain history:

- Kidney stones
- Seizure
- Acute closed angle glaucoma
- Any current or future need for opiates
- Conception goals
- Uncontrolled HTN
- Diarrhea or constipation/GI concerns, gastroparesis
- Medullary thyroid cancer, pancreatitis, MEN
- On SSRI's or SNRI's
- Mental health history

-Trying to quit smoking
-Insomnia
-Migraine headaches

Prescribing Information for Chronic Weight Management Medications[a]

Phentermine/Topiramate ER (Qsymia®) C-IV [3.75 mg/23 mg; 7.5 mg/46 mg; 11.25 mg/69 mg; 15 mg/92 mg capsules]

Dosing: 3.75 mg/23 mg daily for 14 days; increase to 7.5 mg/46 mg for 12 weeks

Goal: 3% weight loss within 12 weeks. If unsuccessful, increase to 11.25 mg/69 mg for 14 days; increase to 15 mg/92 mg daily for 12 weeks. If 5% baseline weight loss is not achieved, discontinue by slow taper.

Renal/Hepatic Impairment
(CrCl <50 mL/min or Child-Pugh 7-9):
Max dose: 7.5 mg/46 mg daily

Contraindications: Pregnancy; REMS; glaucoma; MAOI use during or within 14 days; hyperthyroidism
Warnings: Increased heart ratemood & sleep disorders; suicidal behavior/ ideation; increased creatinine; metabolic acidosis; cognitive impairment; drug abuse; nephrolithiasis; hypokalemia.

- Taper slowly to discontinue (1 dose every other day for ≥1 week) to prevent seizure. Discontinue if glaucoma or myopia develop.

Naltrexone/Bupropion ER (Contrave®) [8 mg/90 mg tablet]

- **Dosing: Week 1:** 1 AM tablet;
  Week 2: 1 AM tablet, 1 PM tablet;
  Week 3: 2 AM tablets, 1 PM tablet;
  Weeks 4-12: 2 AM tablets, 2 PM tablets
- **Goal:** 5% weight loss within 12 weeks. Discontinue if unsuccessful.

Renal Impairment **(moderate/severe):**
Max dose: 1 tablet twice daily
Not recommended for use in patients with ESRD.
Hepatic Impairment: Max dose: 1 tablet in the morning.

Contraindications: Opioid use; pregnancy; uncontrolled hypertension; seizure disorder; bulimia & anorexia nervosa; abrupt stop of alcohol; acute opioid withdrawal; MAOI's
Warnings: Suicidal thinking/behavior **[Boxed Warning]**; seizures; increased heart rate & blood pressure; neuropsychiatric symptoms; hepatotoxicity; may precipitate withdrawal if receiving opioids; adjust hypoglycemic medications to avoid hypoglycemia

Prescribing Information for Chronic Weight Management Medications[a] (cont.)

Orlistat (Xenical®, Alli®) [120 mg; 60 mg (OTC) capsules]

Dosing:

- Xenical®: 120 mg 3 times daily with a fat containing meal (up to 1 hour after meal); omit dose if meal is occasionally missed or contains no fat
- Alli® OTC labeling: 60 mg 3 times daily with a fat containing meal

Renal/Hepatic Impairment: No adjustments provided by manufacturer

Contraindications: Pregnancy; chronic malabsorption syndrome; cholestasis

Warnings: Hepatotoxicity; cholelithiasis; increased urine oxalate and nephrolithiasis; decreased absorption of fat-soluble vitamins, cyclosporine, thyroid hormone, and anticonvulsants; adjust hypoglycemic drugs to avoid hypoglycemia

Liraglutide (Saxenda®) [6 mg/mL, 3mL injection for subcutaneous use]

Dosing: Initiate 0.6 mg daily for 1 week; increase by 0.6 mg per week to target dose of 3 mg; slow titration may improve tolerability

Goal: 4% weight loss within 16 weeks. Discontinue if unsuccessful.

Renal Impairment: Use with caution

Contraindications: Pregnancy; Personal or family history of medullary thyroid carcinoma or MEN2 **[Boxed Warning]**
Warnings: Thyroid C-cell tumors **[Boxed Warning]**; gallbladder disease; pancreatitis (discontinue); increased heart rate; renal impairment; suicidal behavior/ideation; to reduce the risk for hypoglycemia, decrease concomitant secretagogue (i.e., sulfonylureas) dose (e.g., by 50%) or insulin

[a] In February 2020, the FDA requested the withdrawal of the weight-loss drug lorcaserin (Belviq, Belviq XR) from the U.S. market citing potential risk of cancer outweighs the benefits of use.

https://www.healthquality.va.gov/guidelines/CD/obesity/

OFF label

Do NOT have specific FDA label approval for treatment of obesity

- Topiramate alone (to avoid any phentermine in older patients with heart disease or contraindications to phentermine use)
- Bupropion alone
- If DM type 2 consider: Liraglutide (Victoza 1.8mg daily), Empagliflozin, or Semaglutide injection weekly, acarbose and metformin which can all promote weight loss also

Treatment Course

- Reassess!
- “Effective” is often defined as 5% loss of body weight at 3 months.
- If anticipated weight loss not achieved or if side effects →discontinue (may need to taper back down) consider switch or referral
- Weight loss effects are sustained only while taking these agents.

http://www.nwcr.ws/

Unfortunate bottom line:
Weight loss is associated with reduction in total energy expenditure that is out of proportion to lean body mass. Clinically: individuals must reduce energy intake or increase E expenditure indefinitely to maintain the loss

NWCR Facts

There is variety in how NWCR members keep the weight off. Most report continuing to maintain a low calorie, low fat diet and doing high levels of activity.

- 78% eat breakfast every day.
- 75% weigh themselves at least once a week.
- 62% watch less than 10 hours of TV per week.
- 90% exercise, on average, about 1 hour per day.

Some have lost the weight rapidly; while others have lost weight very slowly--over as many as 14 years.

HBO Documentary Film
(free on Youtube, tell your pts to watch)

Treatment Pearls from an Endocrinologist to consider:

- Am I making weight loss harder for my patient? Review their medication list. Consider getting help from a pharmacist. Ask the patient to review their list with pharmacist and discuss next visit.

- Consider screening for diabetes: BMI >30kg/m2; OR signs of insulin resistance: acanthosis, or metabolic type lipid pattern (low HDL + high TG).

- Ask for permission: “I am concerned about how your weight might be affecting your health. Is this something you feel comfortable discussing today?”

- Assess where your patient is in their desire for change

- Start with lowest hanging fruit: NO LIQUID SUGAR!

Take home messages

1. Obesity is chronic condition requiring lifelong management.

2. Comprehensive lifestyle Intervention is all 3 components (behavior, diet, and exercise) and is foundational to other interventions.

3. Several dietary approaches can be successful. Adherence is most important.

4. Don’t prescribe medications that promote weight gain.

5. Use every tool in the tool box.

6. Obesity is associated with several disease processes – intervention can prevent other diseases.


Merci
de tout
Coeur

Question 1:

- Which agent to treat hypertension will cause the MOST weight gain over time and should be avoided whenever possible?

- A) chlorthalidone
- B) metoprolol (Toprol)
- C) losartan (Cozaar)
- D) amlodipine (Norvasc)

Question 2:

- Which agent can be considered for treatment of diabetic neuropathy that will typically have the LEAST weight gain associated with its use?

- A) gabapentin (Neurontin)
- B) pregabalin (Lyrica)
- C) duloxetine (Cymbalta)
- D) amitriptyline (Elavil)

Question 3:

- What weight loss agents would you want to AVOID in a patient with nephrolithiasis?

- A) topiramate + phentermine (Qsymia)
- B) bupropion + naltrexone (Contrave)
- C) orlistat (Xenical)
- D) liraglutide (Saxenda)

Resources List:

Epidemiology and Pathophysiology:

1. Steinsbekk, S. et al. Front Psychol. 2017; 8: 2038
2. Sun, Q. et al., 2010. Am. J. Epidemiol., 172(12), pp.1442–1454
3. NHANES, National Health and Nutrition Examination Survey https://www.cdc.gov/nchs/nhanes.htm
4. Christakis NA, Fowler JH. N Engl J. Med 2007; 357(4):370-379
5. U.S. Department of HHS CDC National Center for Health Statistics
6. Flegal, K.M. & Graubard, B.I., 2009. *Am. J. Clin. Nutr.*, 89(4), pp.1213–1219
7. McAllister EJ, et al. Crit Rev Food Sci Nutr. 2009; 49(10):868-913
8. Apovian et al. J Clin Endocrinol Metab, February 2015, 100(2):342–362
9. Church TS, et al. PLoS One. 2011;6(5):e19657
10. Speliotes EK et al. Nature Genetics Volume: 42,Pages:937–948 (2010)
11. Bray, George A. Handbook of Obesity: Clinical Applications (Hardcover), 2003

Resources List:

Management:

1. https://www.healthequality.va.gov/guidelines/CD/obesity/
2. Horwitz et al. Surg Obes Relat Dis. 2016
3. Liang et al. Diabetes Res Clin Pract. 2013
4. Messerli et al. Am J of Med (2007) 120, 610-615
5. UK Prospective Diabetes Study Group. BMJ 1998 Sep 12; 317(7160): 713-720
6. Zinman et al. N Engl J Med 2015. 373; 22
7. LEADER Trial New Engl J Med 2016; 375:311-322 July 28, 2016
8. O'Neil et al. Lancet, 2018-08-25, Volume 392, Issue 10148, Pages 637-649
9. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf
10. Cassidy et al. PLOS ONE 2017
11. http://uspreventativeservicestaskforce.org

Resources List:

Management:

1. Voils et al. Trials. 2009 Feb 6;10.10.
2. Johnston et al. JAMA 2014 Sep;312(9):923-33.
3. Yancy et al. CHOICE Ann Intern Med. 2015;162(12):805-814
4. Gardner et al. DIETFITS. JAMA. 2018;319(7):667
5. Horwitz et al. Surg Obes Relat Dis. 2016
6. Liang et al. Diabetes Res Clin Pract. 2013
7. http://win.niddk.nih.gov/publications/gastric.htm
8. http://www.nwcr.ws/

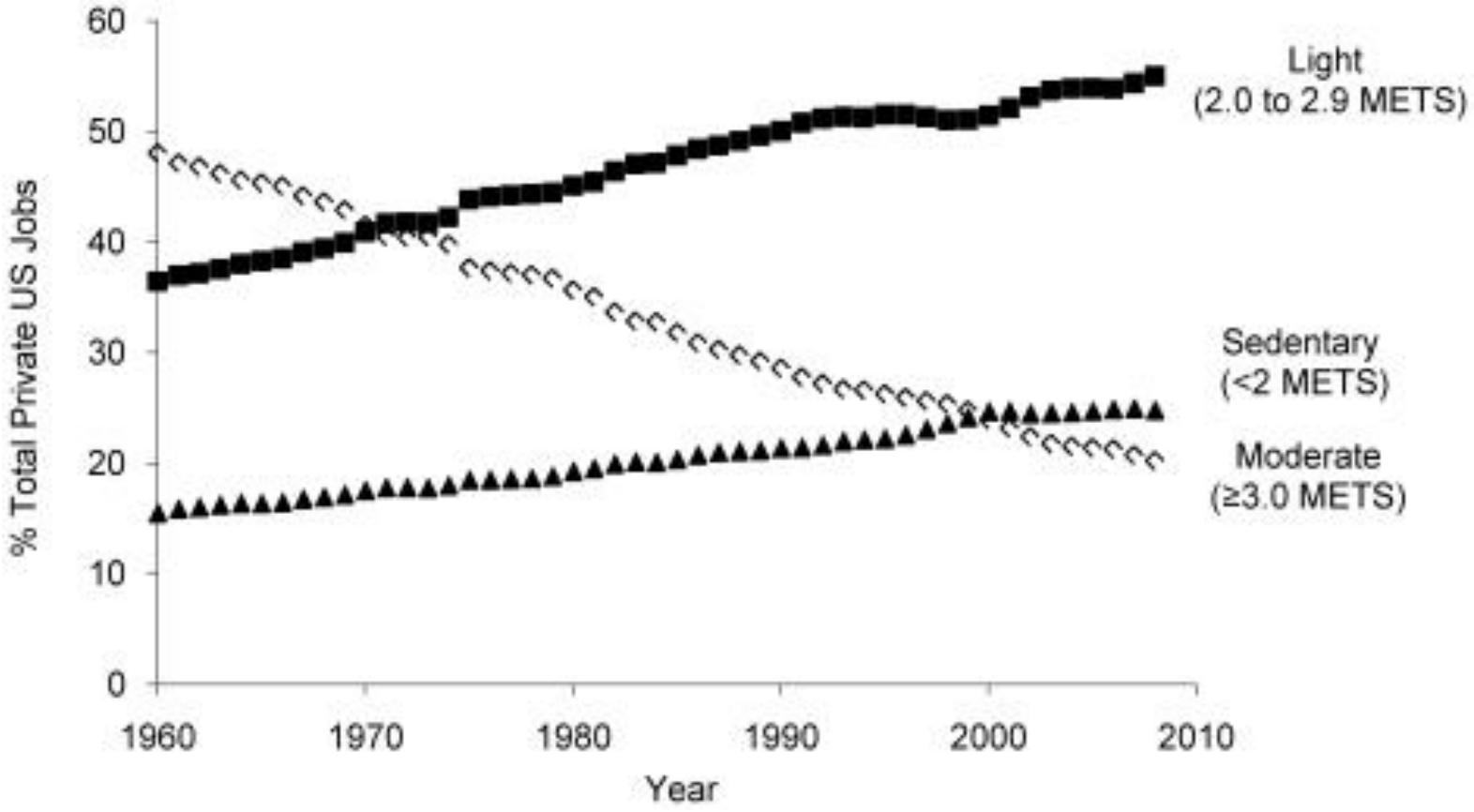
Obesity Medication Choice Considerations

- Awareness and stated importance of weight loss for the patient
- Degree of disease state →BMI and waist circumference
- Contraindications of particular med + patient particulars: Pregnancy plans, seizure disorder, hx of nephrolithiasis, other medications, HTN/Arrhythmia/CVD history
- Comorbidities – migraine headaches? Nephrolithiasis? MTC? Seizure disorder? HTN?
- Patient preference
- Social situation (do they have electricity and access to a fridge?)
- Patient vision and Numeracy limitations
- Cost

1950 (ish) vs. 2019

www.cartoonstock.com

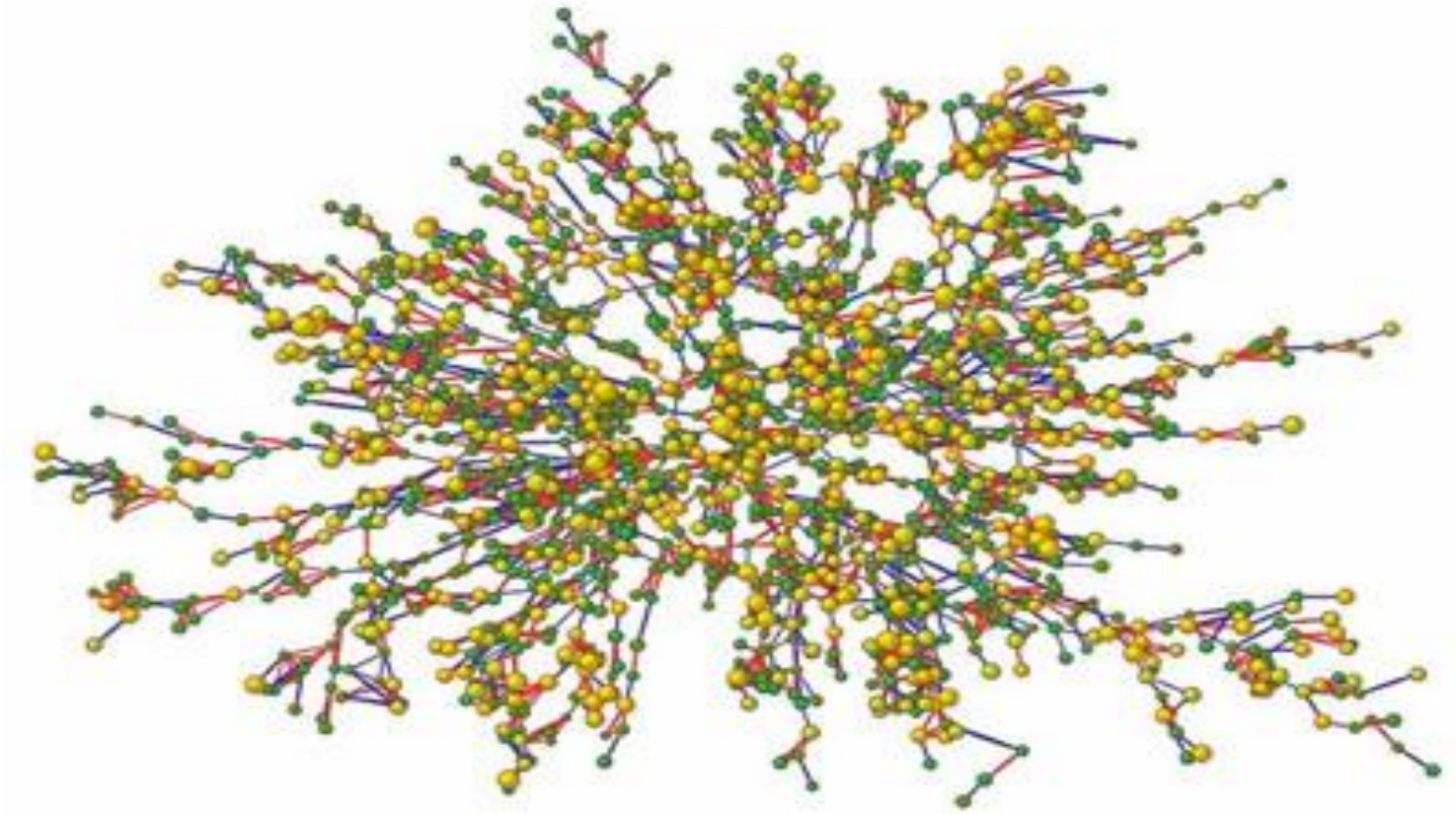
Increase in Sedentary Occupational Activity from 1960 to 2010



Church TS, et al. PLoS One. 2011;6(5):e19657

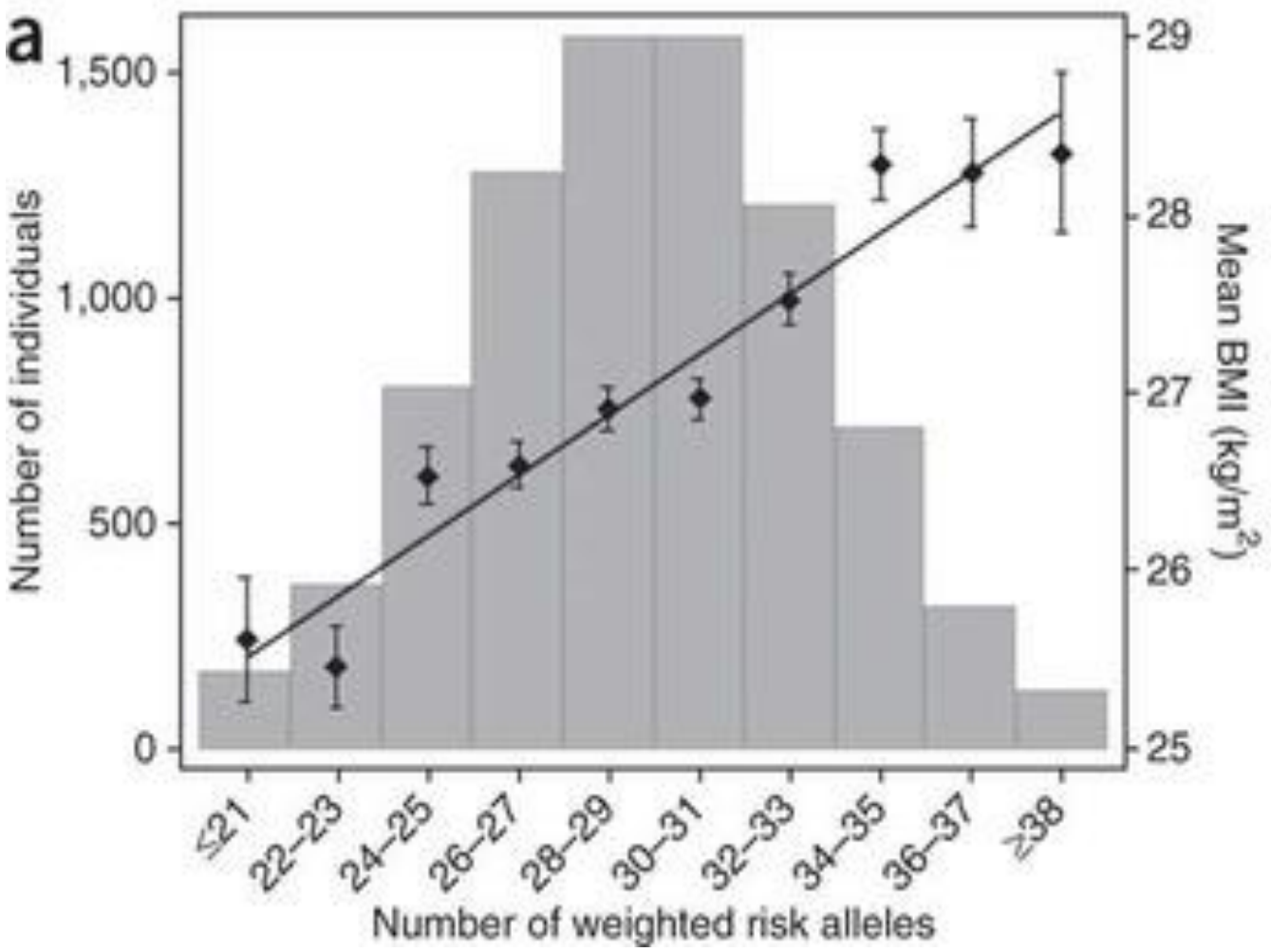
“Feel the Burn”

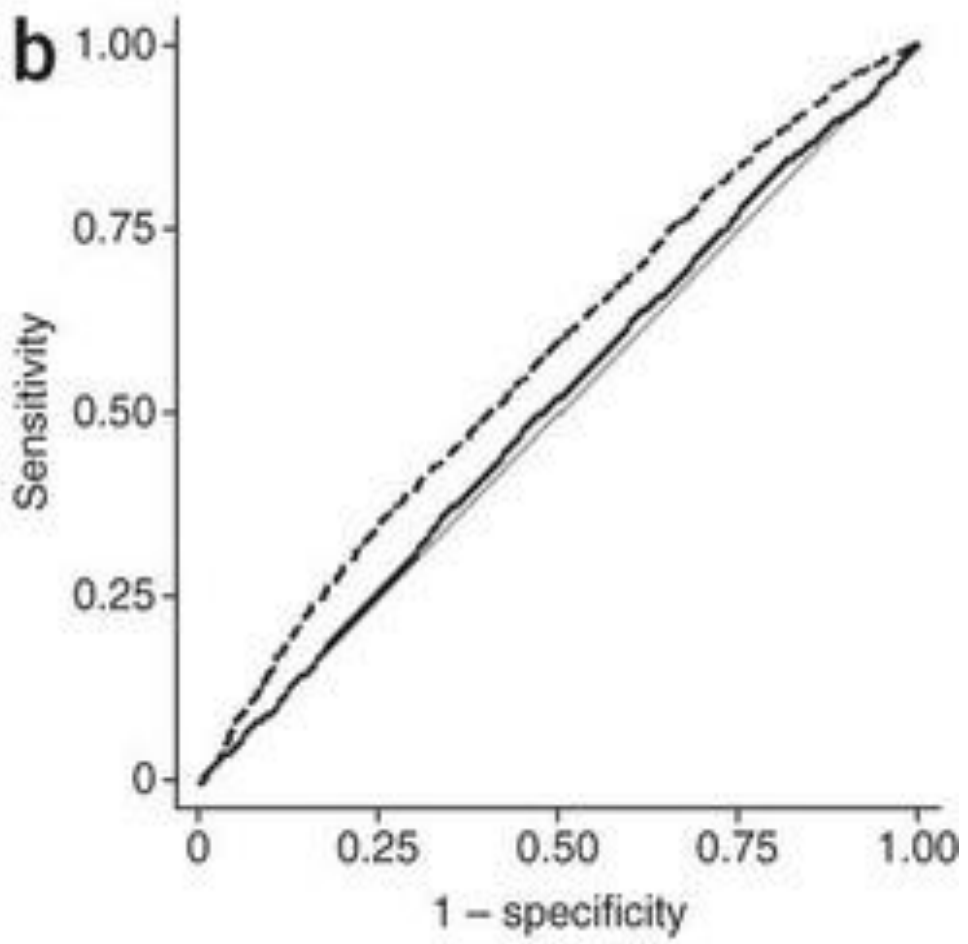
Spread of Obesity in the Framingham Study – Social Networks



Christakis NA, Fowler JH. N Engl J. Med 2007; 357(4):370-379.

BMI Increases with Increasing Number of Risk Alleles





Speliotes EK et al. Nature Genetics Volume: 42,Pages:937–948 (2010)

Myth Busting: Acid Base in Low Carb

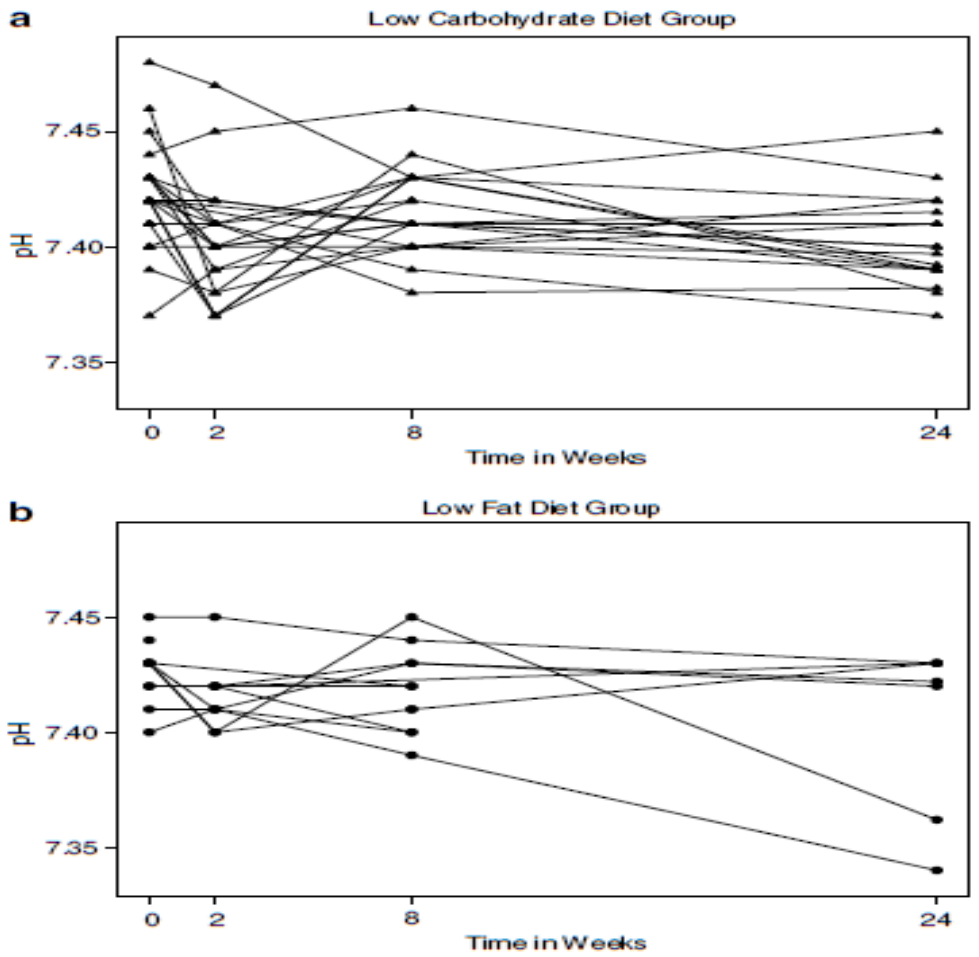
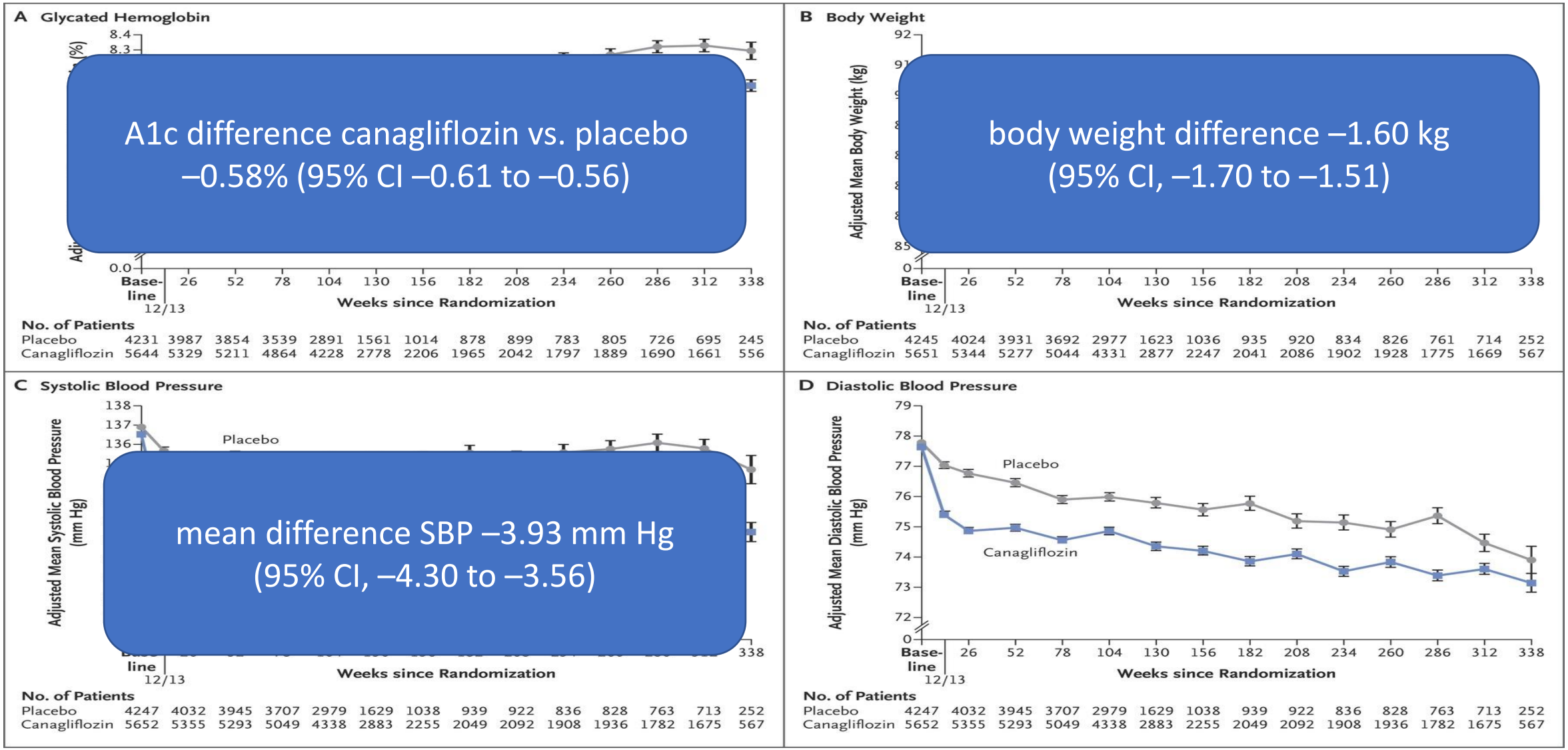


Figure 1 (a–b). Individual arterial blood pH measurements over time by diet group.

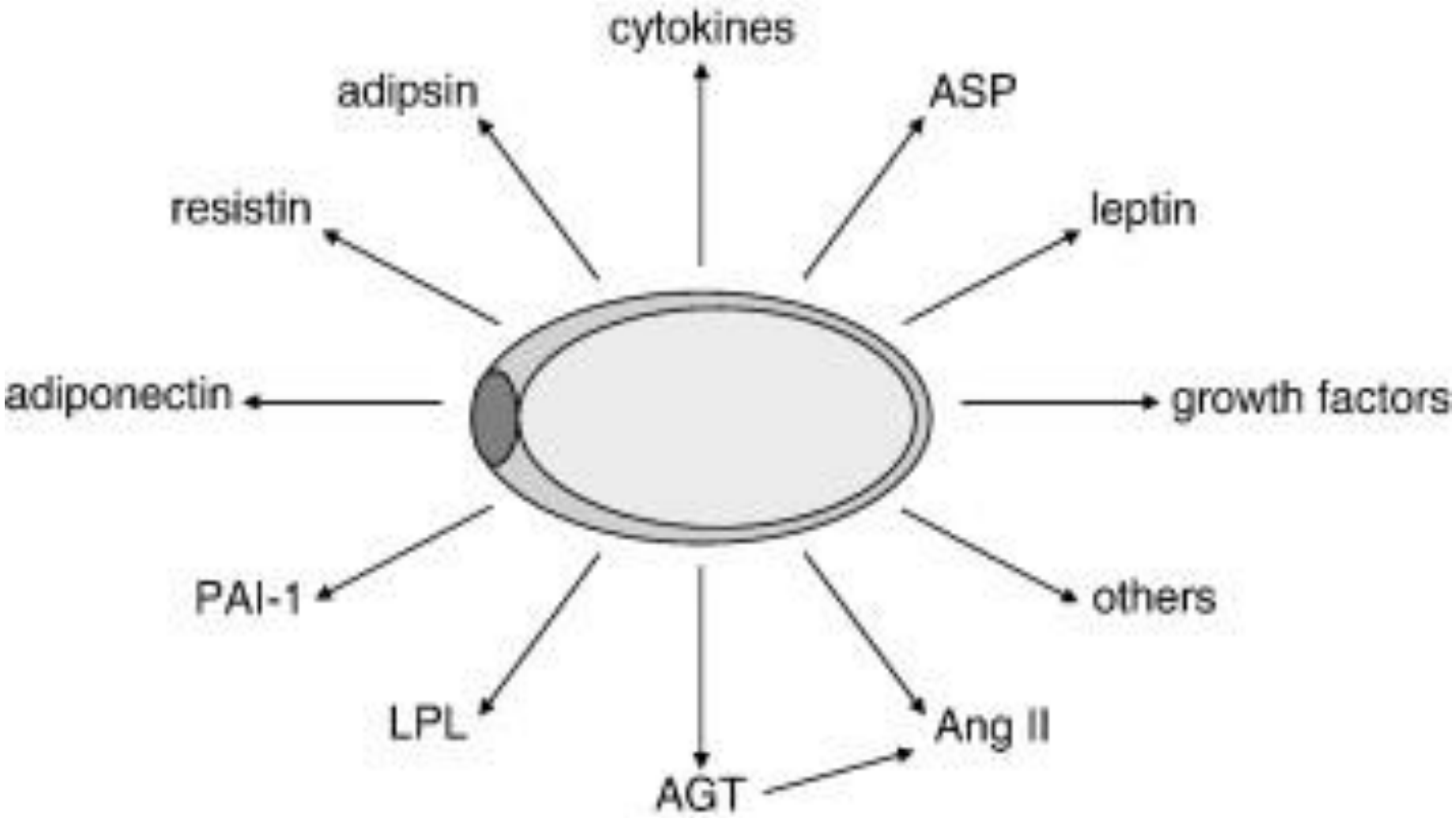
Yancy, WS Jr et al. Acid-base Analysis of Individuals following Two Weight Loss Diets. European Journal of Clinical Nutrition. 2007, 61: 1416-1422

CANVAS: 2 RCTs combined n=10,142



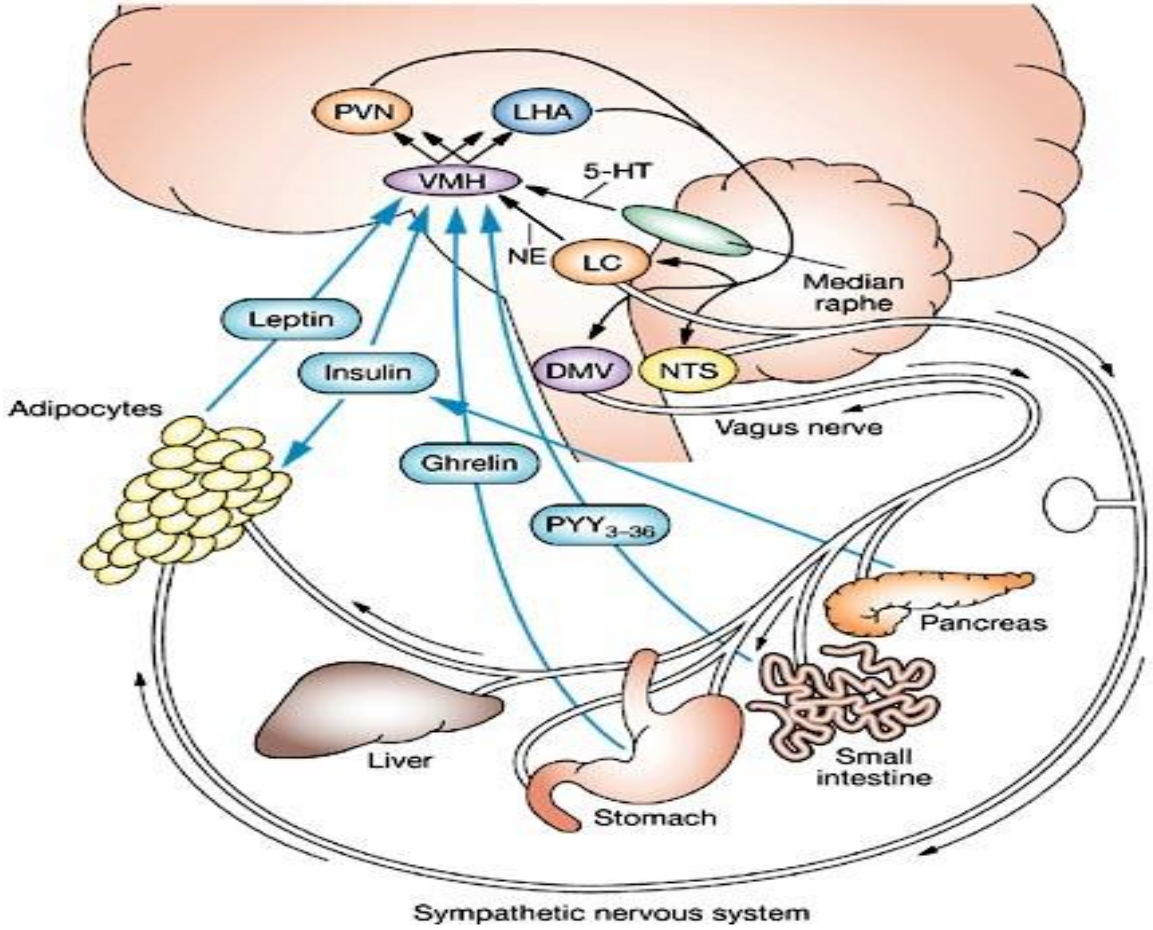
Neal B. et al. “Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.” N Engl J Med. 2017; 377(7):644

Adipocytes are Endocrine Organs



http://dx.doi.org/10.1016/j.physbeh.2007.10.010

Food for Thought



Robert H Lustig. *Nature Clinical Practice Endocrinology & Metabolism* (2006) **2**, 447-458 doi:10.1038/ncpendmet0220

Diabetes Prevention:Treatment of Pre-Diabetes

- DPP trial: intensive lifestyle intervention reduced incidence of DM2 by 58% over 3 years.
- ADA recommends considering metformin therapy in patients with prediabetes, BMI ≥35kg/m2, <age 60, women with GDM (grade A evidence)
- Other agents shown to decrease incident diabetes in patients with pre-DM include alpha glucosidase inhibitors, GLP-1 agonists, thiazolidinediones
- NONE FDA approved for this indication

Knowler W.C. et al. “Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.

Case 1a - Treatment considerations for Obesity in patients with Diabetes

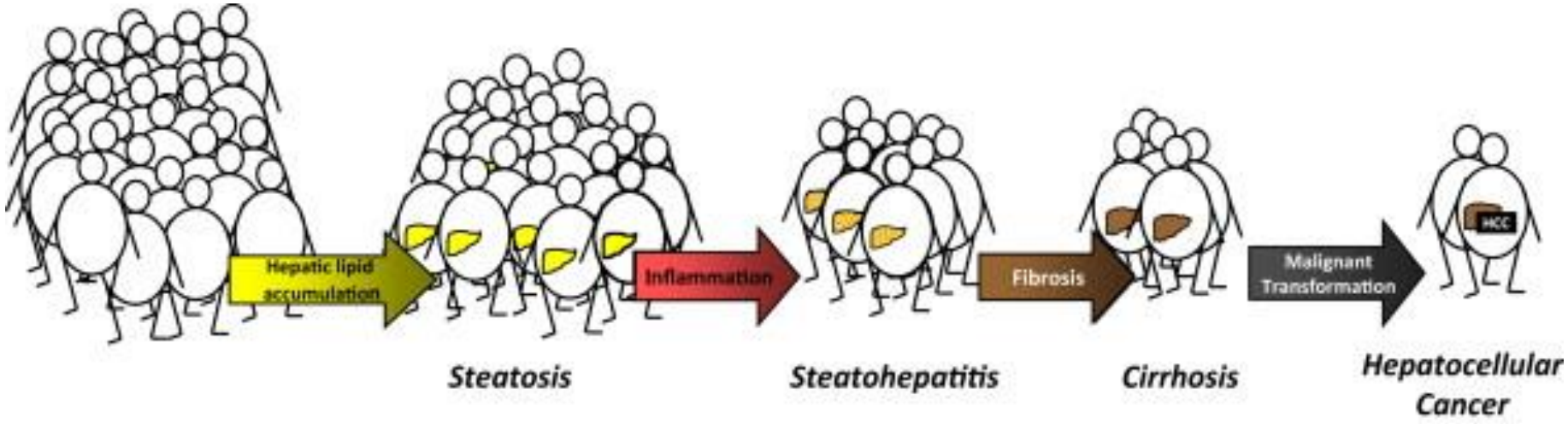
45 y.o. female truck driver with hx of HTN and hyperlipidemia, BMI of 36 kg/m2. A1c of 7.9%, eGFR 70ml/min/1.73m2.

In addition to Lifestyle changes what would you start?

A) Metformin only
B) SGLT2i only
C) GLP-1 injection alone
D) Metformin + second agent (DPP-IV inhibitor or SU)
E) Metformin + second agent (SGLT2i)
F) Metformin + second agent (GLP1 injection)
G) Insulin basal + metformin
H) Insulin basal + insulin bolus

NAFLD: Hepatic Manifestation of Metabolic Syndrome

- NAFLD: most common cause of chronic liver disease in the world
- >30% of adults in developed countries, increasing incidence
- Progression from NAFLD →NASH



Peter Dietrich and Claus Hellerbrand. "Non-alcoholic fatty liver disease, obesity and the metabolic syndrome." Best Practices and Research Clinical Gastroenterology, Vol, 28 (4); August 2014, p 637-653

N=44 treated with 500-1000kCal Deficit Diet in Iran

(30% fat, 15% protein, 55% carbohydrate)

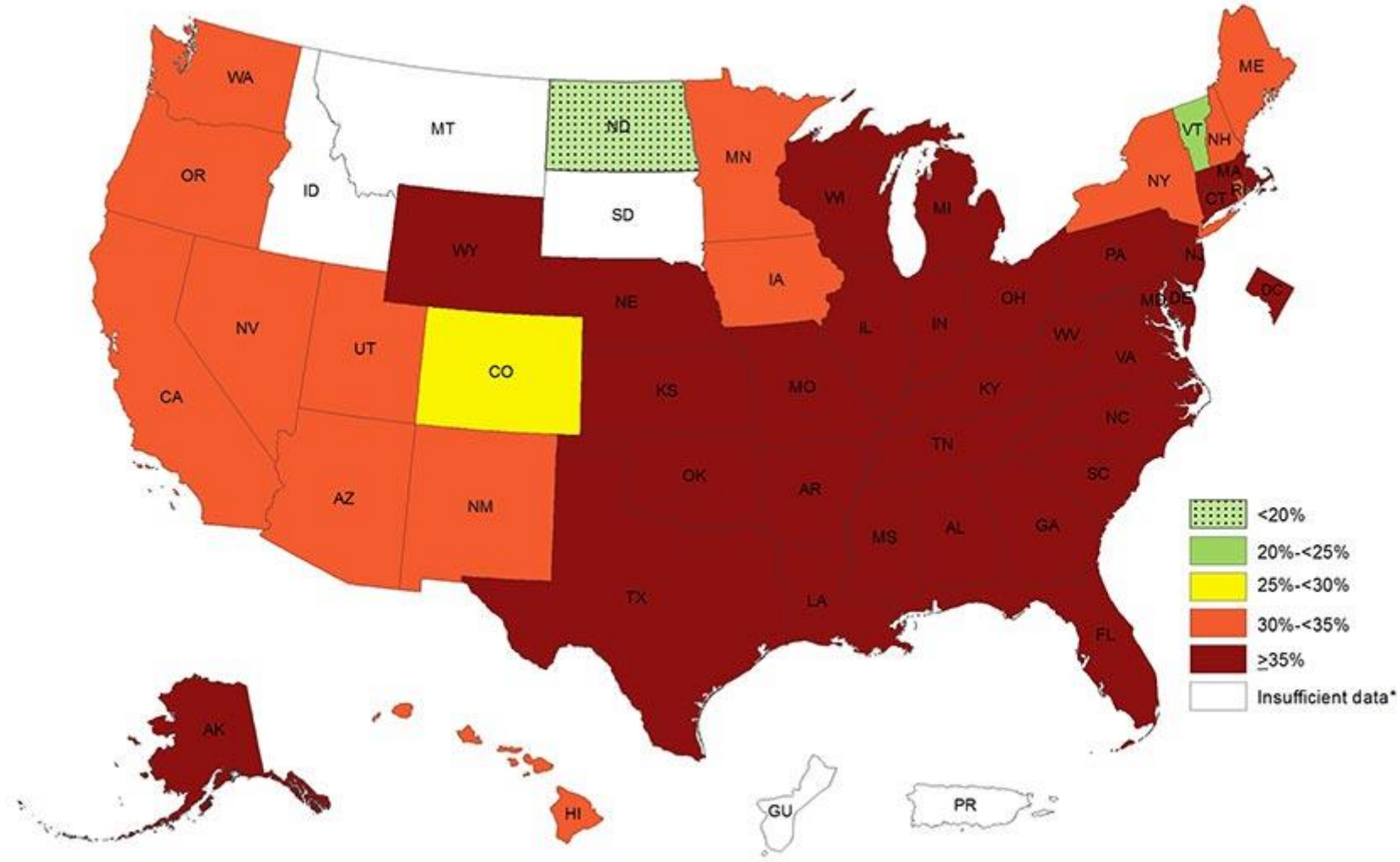
Table 2. Anthropometric, Clinical Parameters and Liver Enzyme Level for Adherent and Nonadherent Patients at Baseline and After 3 and 6 Months of Nutritional Intervention[a]

Characteristic	Adherent (n = 25)			Non adherent (n = 19)		
	Baseline	3 months	6 months	baseline	3 months	6 months
Weight, kg	93.7 ± 15.8	86.6 ± 13.5[c]	84.2 ± 13.4[c,d]	94 ± 16.6	92.1 ± 16.5[c]	92.2 ± 16.2[e]
BMI , kg/m²[b]	32.7 ± 3.9	30.4 ± 3.3[c]	29.5 ± 3.2[c,d]	31.8 ± 5.4	31.2 ± 5.4[c]	31.1 ± 5.3[c]
Waist circumference, cm	105.1 ± 12.6	99.5 ± 10.4[c]	97.4 ± 9.8[c,d]	106.8 ± 14.2	104.3 ± 14[c]	103.7 ± 14[c]
WHR[b]	0.92 ± 0.08	0.90 ± 0.06[e]	0.90 ± 0.06	0.96 ± 0.08	0.95 ± 0.08	0.94 ± 0.08[e]
SBP , mmHg[b]	120.4 ± 8.9	120.6 ± 5.4	118.1 ± 6.3	118.9 ± 5.7	117.9 ± 6.3	117.8 ± 7.1
DBP , mmHg[b]	80.2 ± 5.1	81.2 ± 2.6	76.9 ± 5[c,d]	79.7 ± 4.2	78.4 ± 3.7	77.5 ± 4.5
ALT , IU/L[b]	87.1 ± 40.8	45.9 ± 23.6[c]	45.6 ± 19.8[c]	69.1 ± 32.4	48.9 ± 21.7[c]	57.8 ± 33.1
AST , IU/L[b]	51.9 ± 25.2	31.5 ± 11.9[c]	31.3 ± 11.4[c]	42.7 ± 12	34.3 ± 12.2[e]	39.5 ± 19.4
GGT , IU/L[b]	56.1 ± 36.8	43.4 ± 33.9[c]	43.2 ± 31[c]	32.9 ± 12.9	31.8 ± 11.9	35.7 ± 11.9

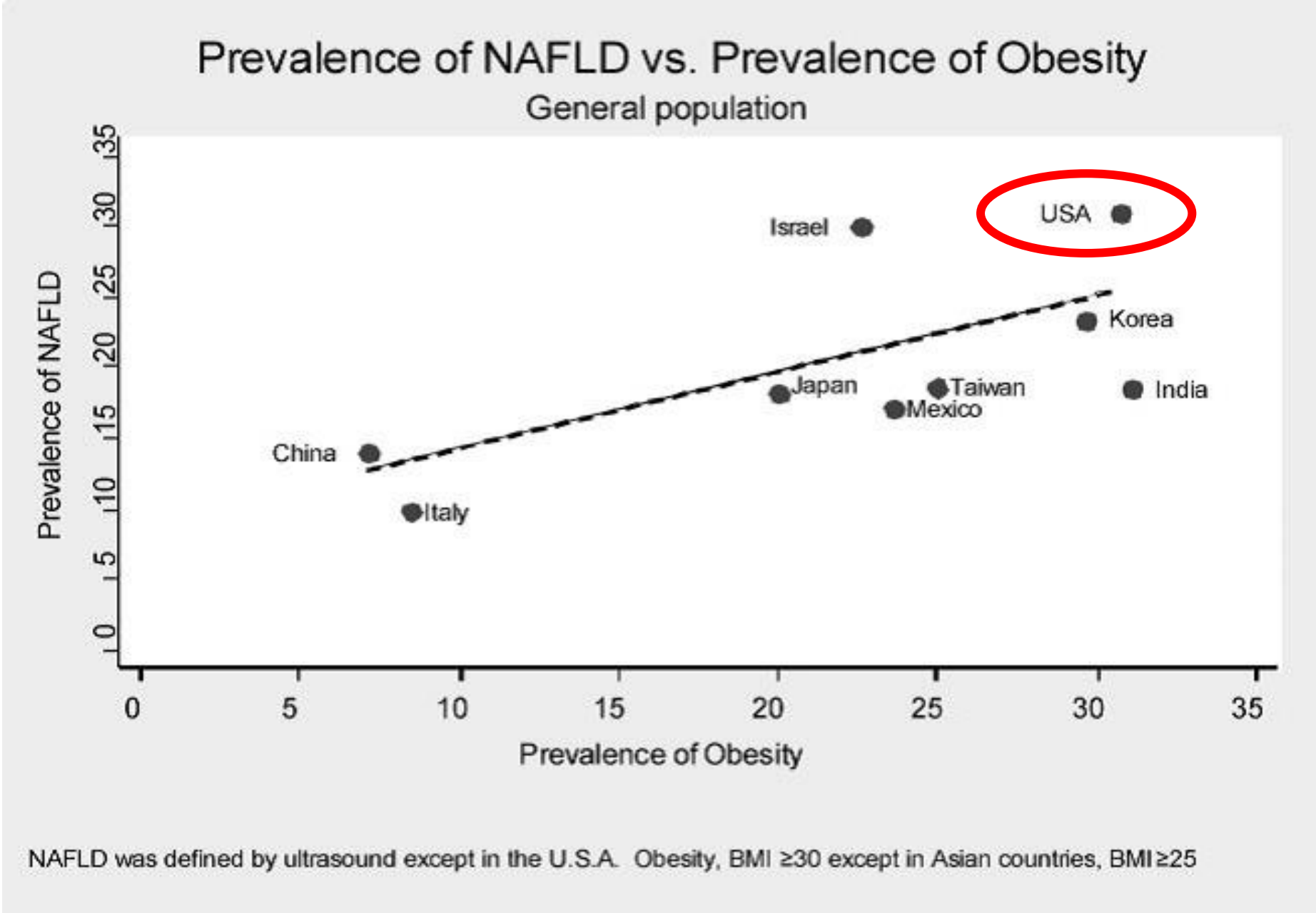
[a] Values are expressed as mean ± SD.
[b] Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; DBP, Diastolic blood pressure; GGT, γ-glutamyltransferase; SBP, Systolic blood pressure; WHR, Waist to hip ratio.
[c] P< 0.001 Comparison with baseline within group.
[d] P< 0.001 Comparison with month 3 within group.
[e] P< 0.05 Comparison with baseline within group.

Ghaemi et al. “How much Weight loss is Effective on Nonalcoholic Fatty Liver Disease?” Hepat Mon. 2013 December; 13(12)

Self-Reported Obesity in US Non-Hispanic Black Adults 2014-2016

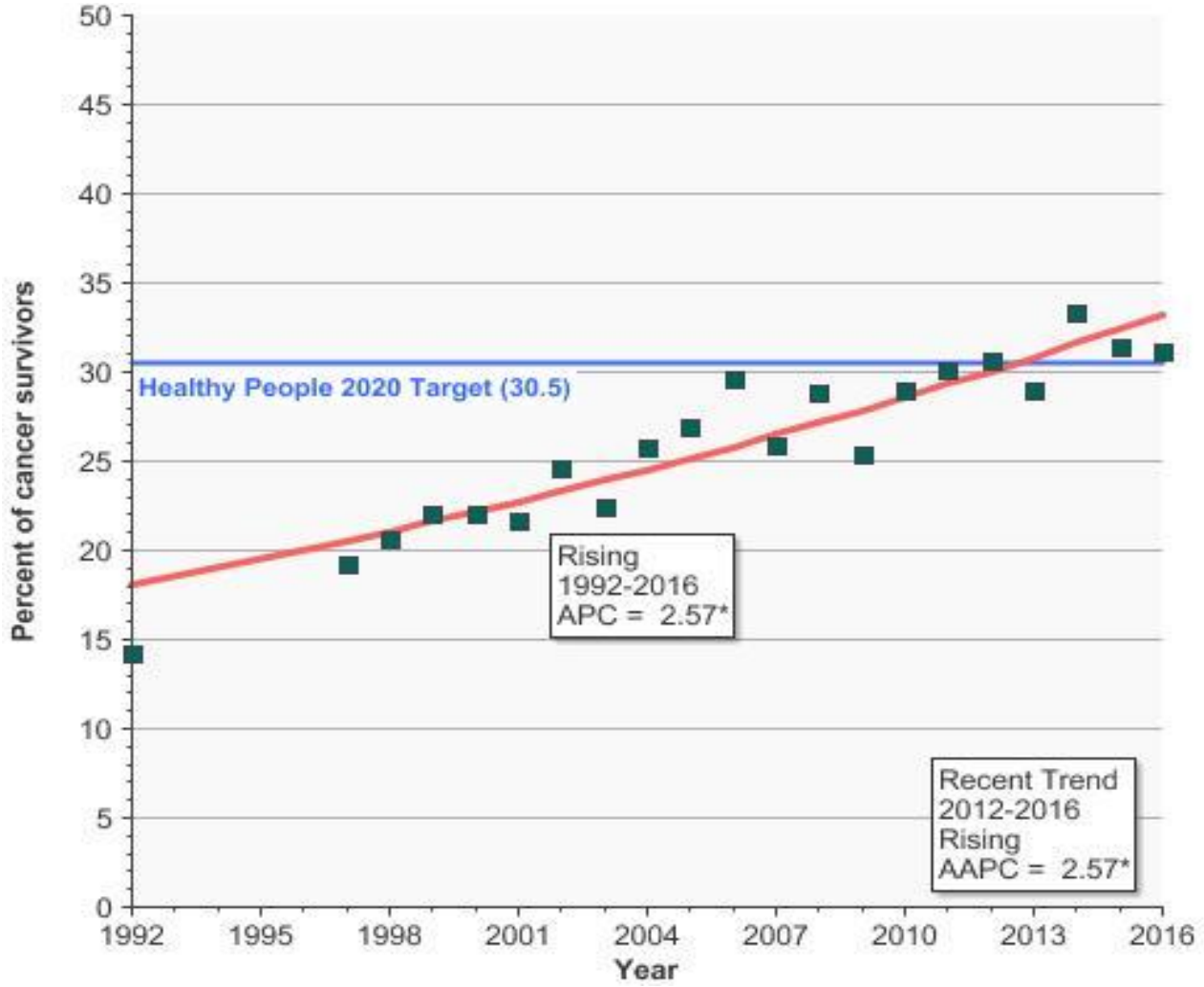


Source: Behavioral Risk Factor Surveillance System – (telephone survey with self-reported height and weight)



Lazo et al. “The Epidemiology of Nonalcoholic Fatty Liver Disease: A Global Perspective.” Semin Liver Dis. 2008; 28(4): 339-350.

Percentage of cancer survivors ≥20 years with BMI ≥ 30kg/m2, both sexes, 1992-2016



* The Annual Percent Change (APC)/Average Annual Percent Change (AAPC) is statistically significant.

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Interview Survey.

Carb advice from ‘on high’

“Number 11: Thou Shalt Not Eat Carbs. I think I’m gonna have trouble selling that one!”

Alternative Perspective

"What's wrong with eating donuts to cure obesity? Don't you believe in alternative medicine?"

Weight loss agent	MOA	Pros	Cons
1. Orlistat	inhibits pancreatic lipase, limiting fat absorption	Pill form Inhibits fat absorption	Greasy stools, fecal urgency (Pregancy X - contraindicated)
2. Saxenda (Liraglutide); Victoza dosing can achieve results not FDA approved for weight loss	binds to GLP-1 receptors (β cells and CNS) inc glucose-dep insulin sec., dec glucagon sec, inc ß cell growth, slows gastric emptying, receptors dorsal vagal complex centrally promote satiety	Treats diabetes, prediabetes	Nausea, vomiting Daily Injection Contraindicated if pancreatitis, medullary thyroid ca, suicidality (Pregnancy, not studied, contraindicated)
3. Topiramate (OFF-label when used alone)	antiepileptic (GABA receptor modulation?)	Pill form Treats neuropathic pain, migraines, seizure disorders inexpensive	Confusion Contraindicated if kidney stones, glaucoma (Pregnancy D – adverse findings in animals)
4. Qsymia (Topiramate/phentermine)	antiepileptic (GABA receptor modulation?) + Anorexiant; CNS Stimulant; Sympathomimetic amine =amphetamine	Pill form Treats neuropathic pain, migraines, seizure disorders	Confusion, Contraindicated if kidney stones, glaucoma+ Increases blood pressure, pulse. CI: advanced arteriosclerosis, severe hypertension; pulmonary hypertension; hyperthyroidism; glaucoma; agitated states, history of drug abuse; during or within 14 days MAOi (Pregnancy class X - contraindicated)
6. Contrave (Bupropion-naltrexone)	Bupropion: dopamine and norepinephrine reuptake inhibitor that stimulates POMC neurons + Naltrexone opioid antagonist potentiates the feedback inhibition of POMC neurons (promoting satiety)	Pill form Treats depression, smoking cessation	Contraindicated if another SSRI, opiates, uncontrolled BP, seizure disorder (Pregnancy X - contraindicated)
7. [illegible]ntermine	Anorexiant; CNS Stimulant; Sympathomimetic amine =amphetamine	Pill form	Increases blood pressure, pulse 12 week course (unless lower doses with topiramate) (Pregnancy class X - contraindicated)
8. [illegible]yipropi[illegible]R 3xD [illegible]R 1xD)	Anorexiant; CNS Stimulant; Sympathomimetic amine =amphetamine	Pill form	Only approved for “short term” use (weeks) CI with: advanced arteriosclerosis, severe hypertension; pulmonary hypertension; hyperthyroidism; glaucoma; agitated states, history of drug abuse; during or within 14 days MAOi