Management of Cardiovascular Toxicity

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1. Understand some of the impacts on cardiovascular health related to obesity
2. Understand how different eating plans influence different CV comorbid conditions
3. Understand new exercise guidelines

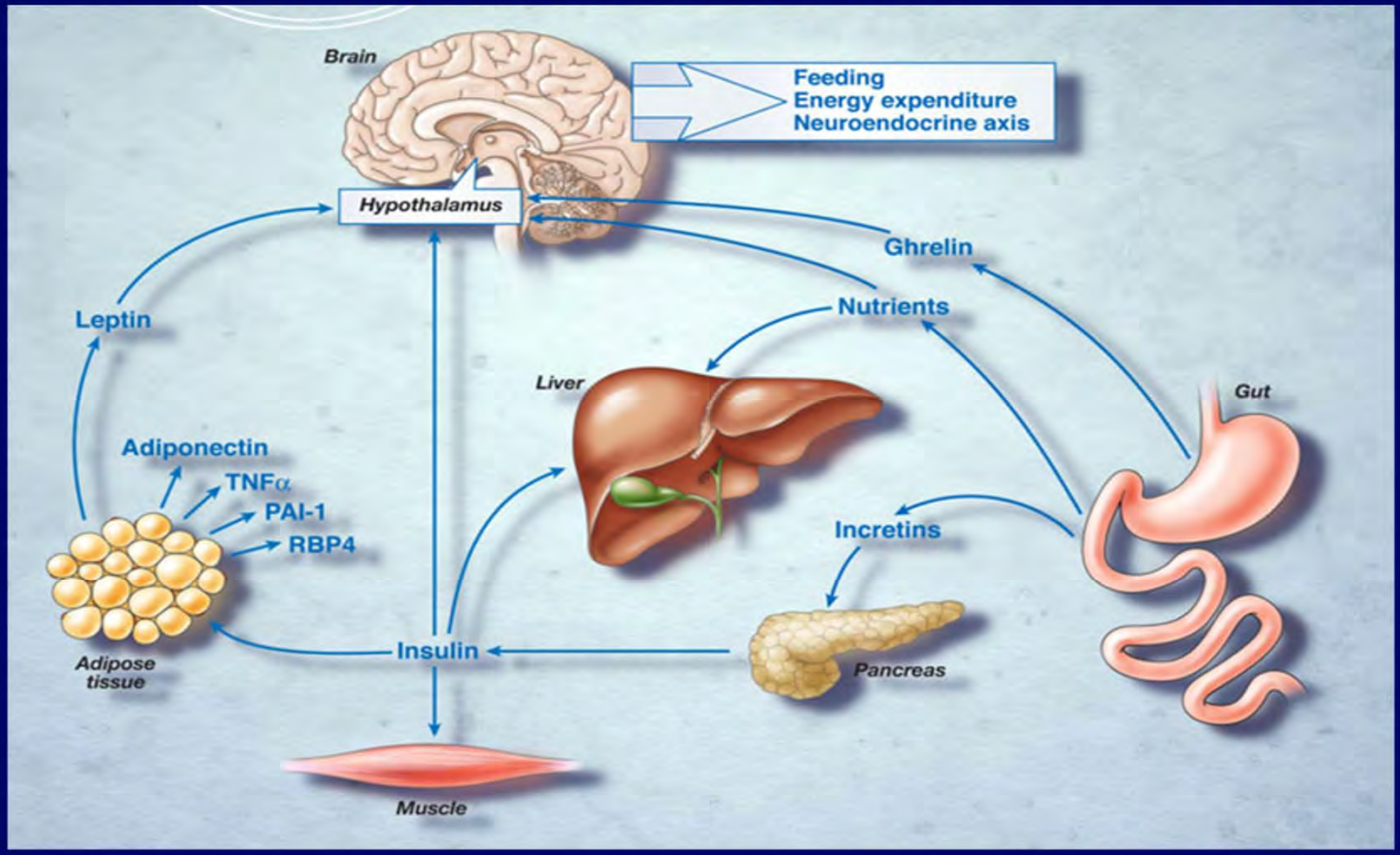
Disclosures

- Speaker's Bureau
  - Sanofi
  - Regeneron
  - Amgen
- Consultant
  - Akcea

Adipose tissue is an active organ that can become dysfunctional

Body Weight is Under Biological Control

Complex interconnected feedback mechanisms



Ahima, Gastroenterology 2007

CV Consequences of Obesity

- Atherosclerosis
- Heart failure
  - Systolic and diastolic
- LVH
- Prolonged QTc
- Afib
- Not to mention indirect actors like
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - OSA
  - Pulmonary htn

Hindawi, Journal of Diabetes Research, Volume 2018, Article ID 3407306,

Proposed Mechanism for Atherosclerosis

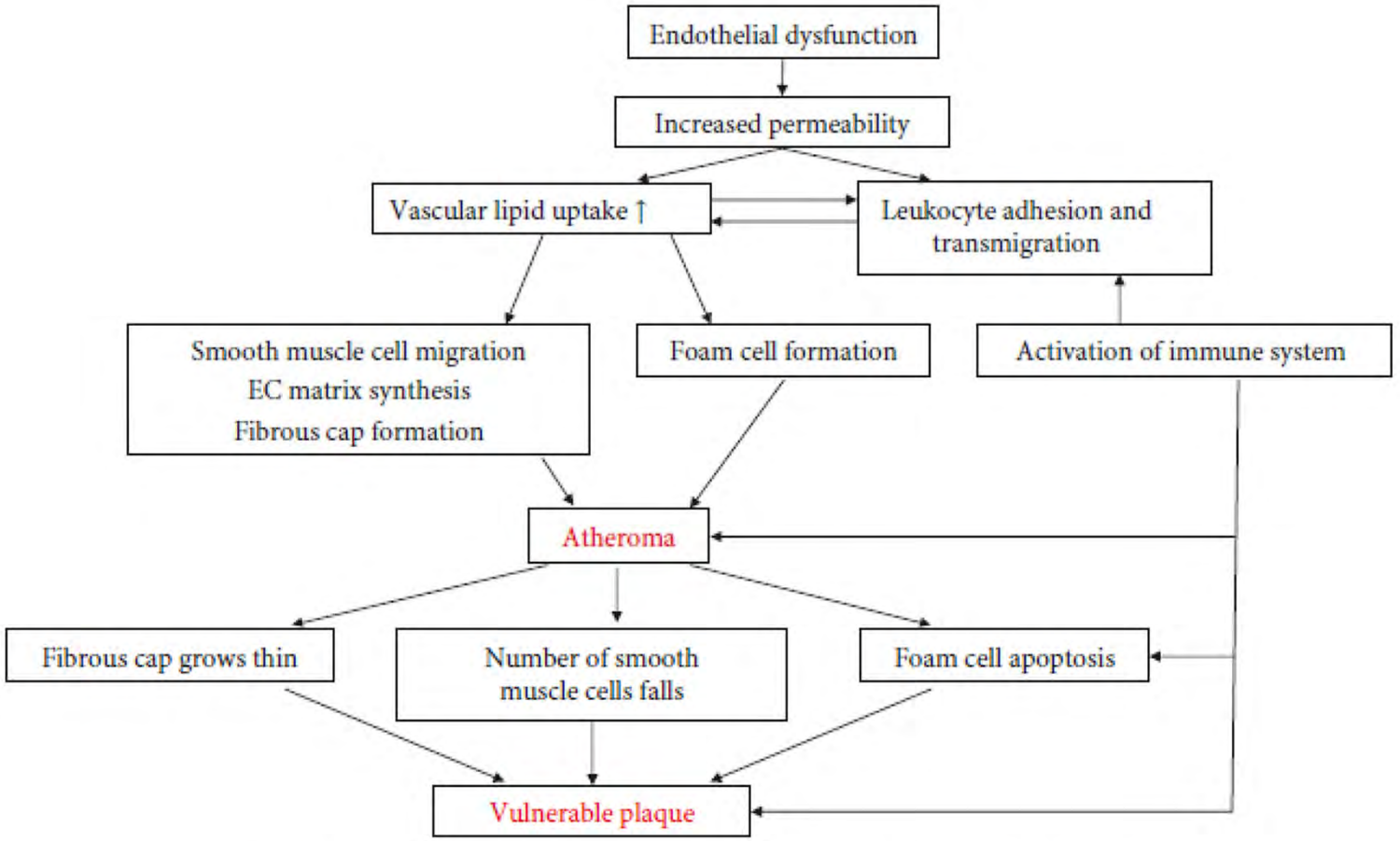


FIGURE 1: The pathomechanism of coronary artery disease in obesity.

Hindawi, Journal of Diabetes Research, Volume 2018, Article ID 3407306,

Proposed Mechanism for Heart Failure

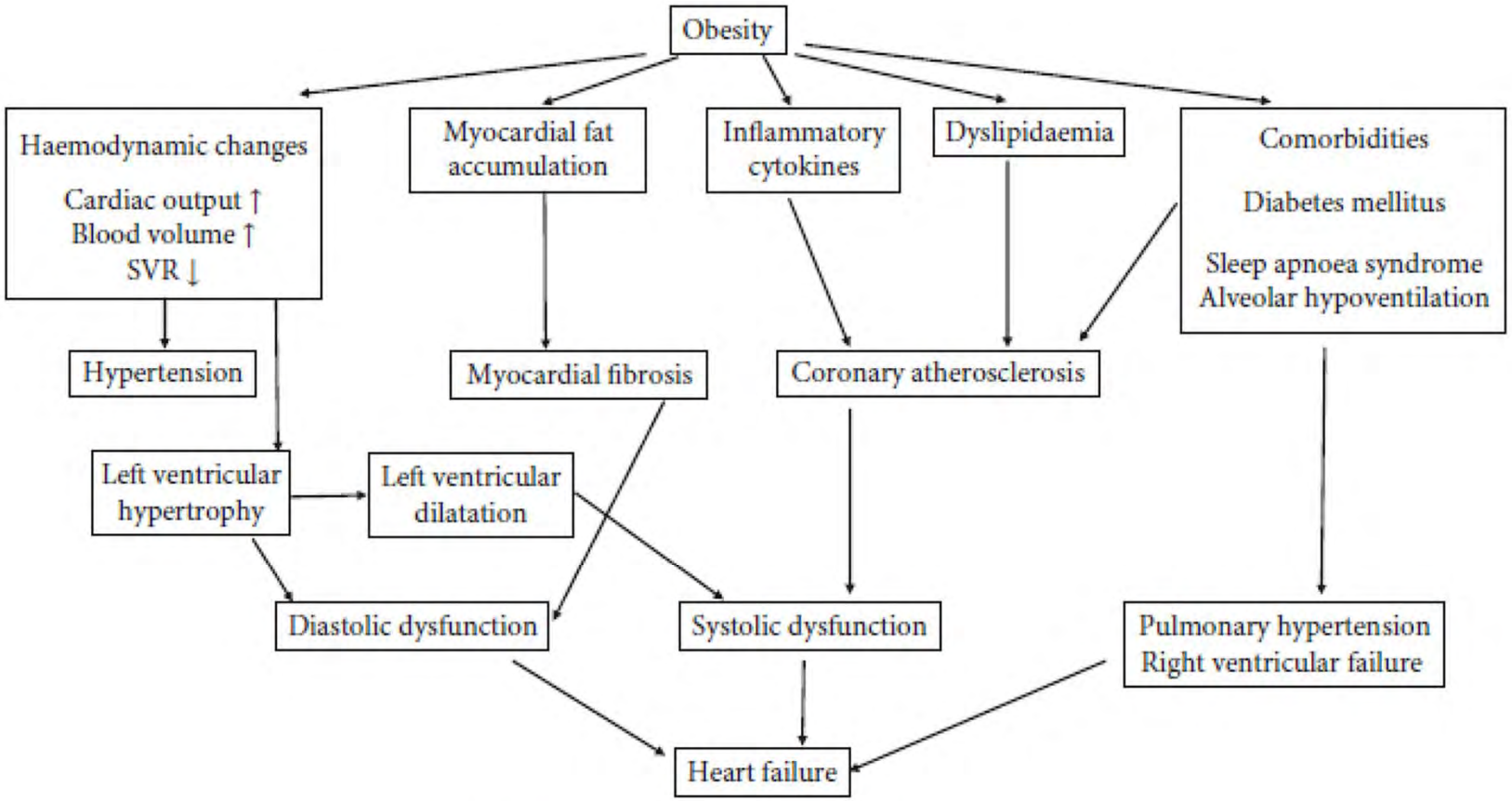


FIGURE 2: The pathomechanism of heart failure in obesity.

Hindawi, Journal of Diabetes Research, Volume 2018, Article ID 3407306,

Proposed Mechanism for A fib

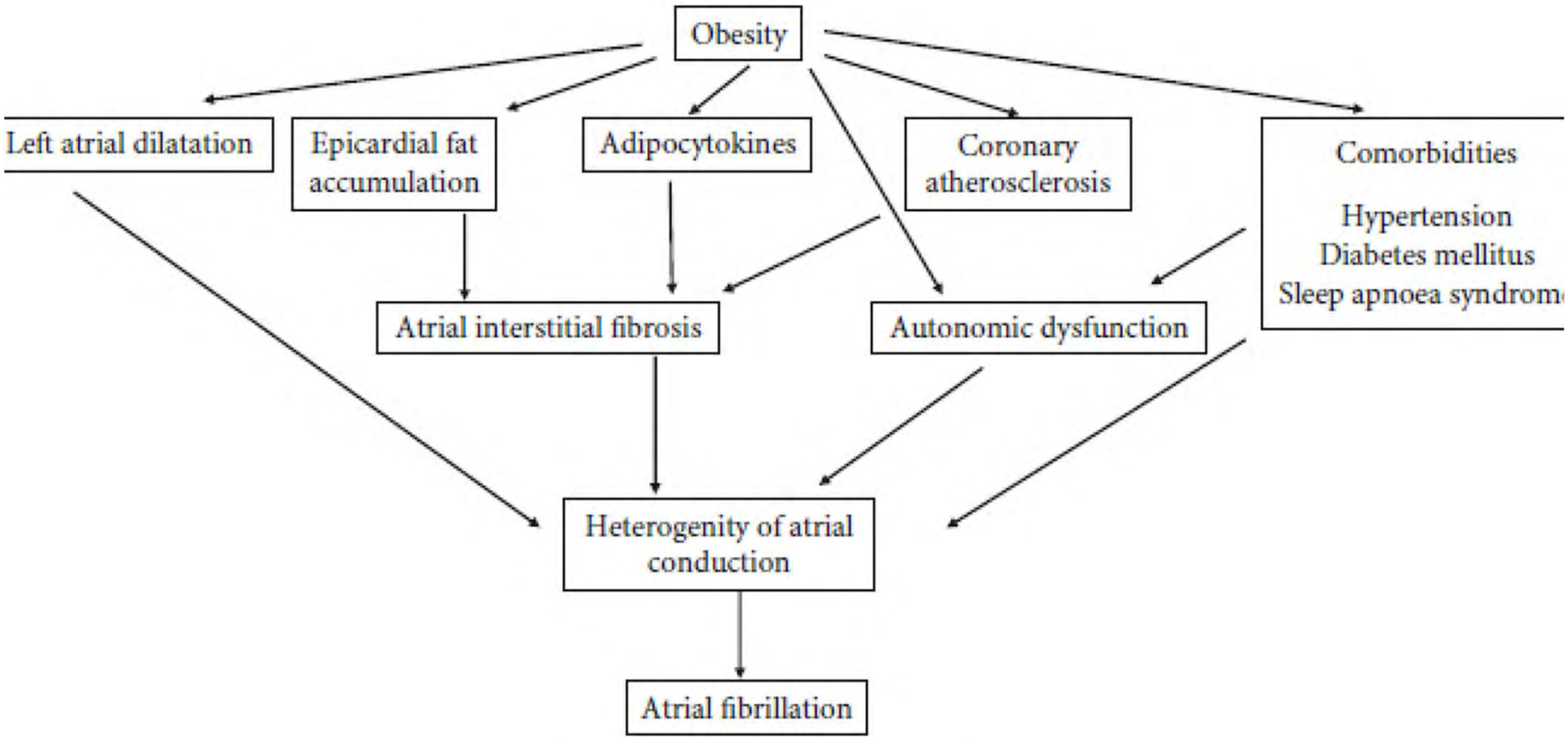


FIGURE 3: The pathomechanism of atrial fibrillation in obesity.

Hindawi, Journal of Diabetes Research, Volume 2018, Article ID 3407306,

Metabolic Syndrome and Link to CVD

Table 1. Definitions of metabolic syndrome

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia‡ (plasma insulin >75th percentile)	Central obesity (waist circumference§): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m^2	Waist circumference: ≥94 cm (M), ≥80cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria†		

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
†Urinary albumin excretion of ≥20 μg/min or albumin-to-creatinine ratio of ≥30 mg/g.
‡Reliable only in patients without T2D.
§Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

Huang PL. Dis Model Mech. 2009; 2(5-6): 231-237

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Metabolic Syndrome's Effects on the Heart

- 1.58X Increase in All-Cause Mortality
- 2.35X increase in CVD
- 2.4X increase in CV death
- 1.99X increase in MI
- 2.27X increase in stroke

Salvatore M, et al, JACC vol56 no14, 2010

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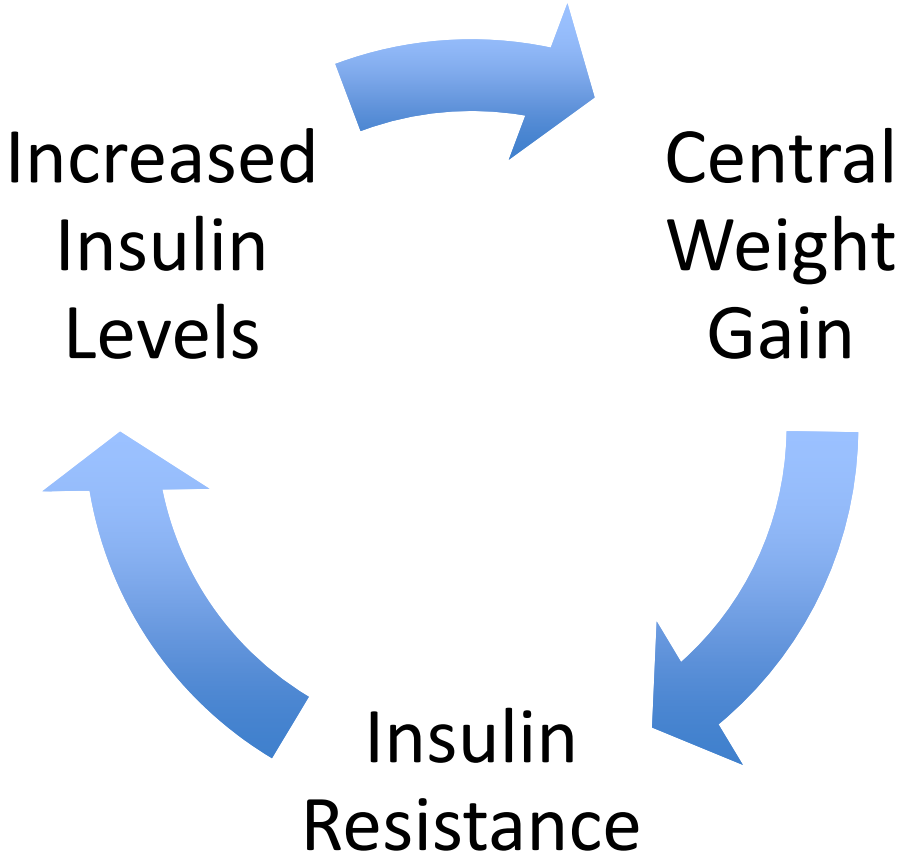
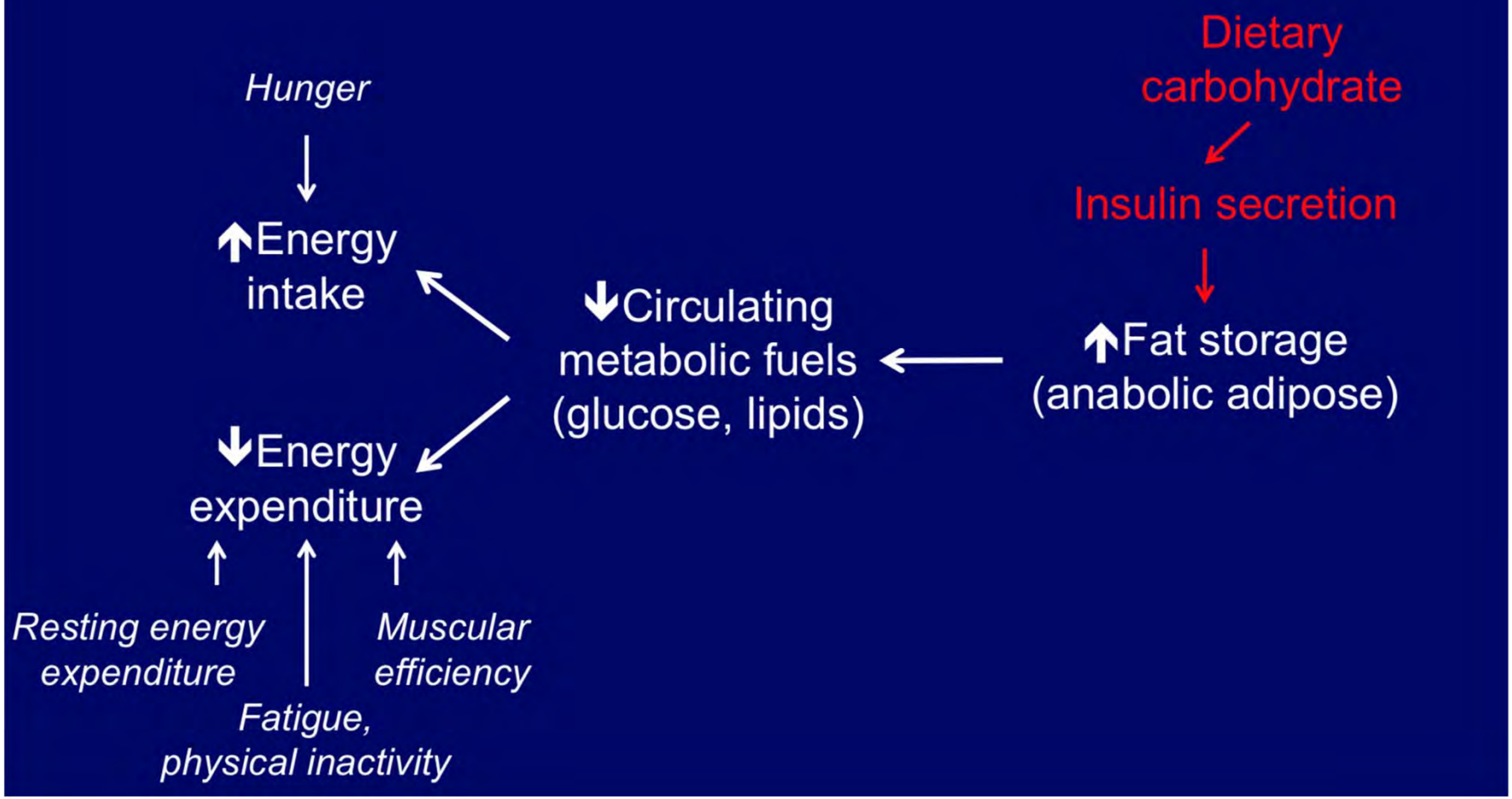
Vicious Cycle of Insulin Resistance



Carbohydrate-Insulin Model

Excessive anabolic drive in adipose tissue



Ludwig D, JAMA int med 2018; 178(8):1098-1103

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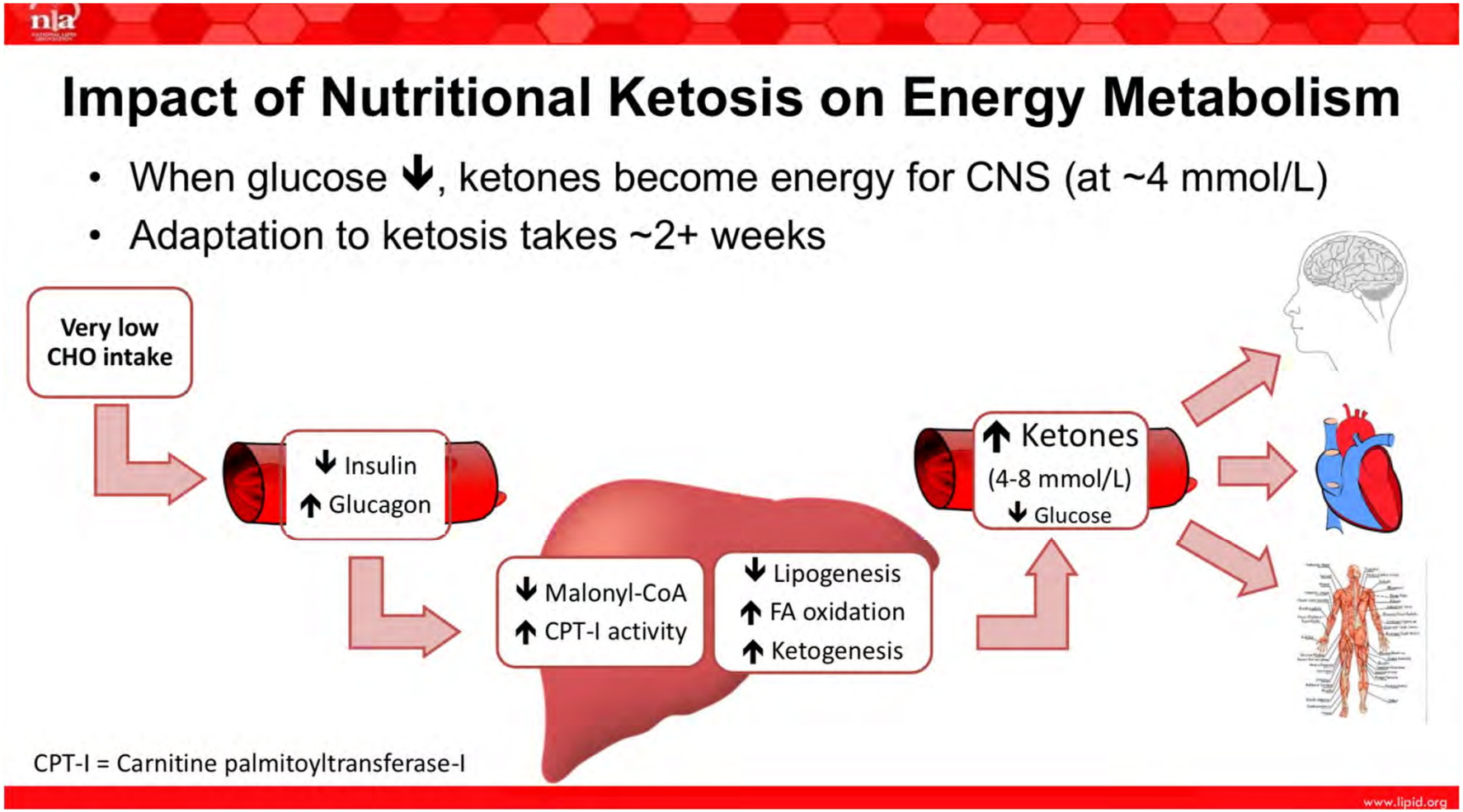
NLA Scientific Statement on low carb diets



Kirkpatrick CF et al JCL 2019 (in press)

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NLA Scientific Statement on low carb diets

Effects of CHO-restricted Diets on Energy Balance and Body Weight

- RCTs – substitution of **fat for CHO results in ↑ energy expenditure**
  - – ? mechanisms
  - – ? changes in catecholamines and thyroid hormone levels
- RCTs – **↓ appetite and hunger** reported
  - – ? mechanisms
  - – ? protein content, changes in gut hormones
- Other
  - – Diuretic effects (ketosis and ↓ insulin)
  - – ↑ adipose tissue lipolysis
  - – ↑ fat oxidation
  - – ↑ metabolic costs (gluconeogenesis)
  - – Thermic effect of protein

www.lipid.org

Kirkpatrick CF et al JCL 2019 (in press)

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NLA Scientific Statement on low carb diets

A low-CHO diet (50-130 g CHO/day) or very-low-CHO/KD (~20-49 g CHO/day) **is a reasonable option for some patients for a limited period of time (2-6 months) to induce weight loss.**	IIa	B-R
Because low-CHO diets or very-low-CHO/KDs are **difficult to maintain long-term**, a more **moderate CHO intake (>130-225 g/day) is reasonable for longer-term (>6 months) weight loss and maintenance.**	IIa	B-R

Kirkpatrick CF et al JCL 2019 (in press)

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NLA Scientific Statement on low carb diets

Key Recommendations for Cardiometabolic Risk Factors*	COR	LOE
To achieve an **improvement in a patient's cardiometabolic risk factor profile**, a weight reduction diet that achieves a **clinically significant weight loss (5-10% of body weight)** is recommended.	I	A
As part of low-CHO and very-low-CHO diets, it is reasonable for a patient to **choose unsaturated fatty acids over SFAs**.	IIa	B-R
In patients with overweight or obesity with or without T2D and with elevated TG levels, **a low-CHO diet is reasonable for lowering TG levels (and VLDL-C)** compared to a HCLF diet.	IIa	B-R
Because **substantial variation in lipid responses** has been observed in patients choosing to follow low-CHO and very-low-CHO diets, **baseline and follow-up lipid profiles are reasonable**.	IIa	B-R

Kirkpatrick CF et al JCL 2019 (in press)

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NLA Scientific Statement on low carb diets

- Challenges
  - Difficult long term adherence
    - Weight loss and metabolic effects tend to regress to other diets after 6 months
  - Could lead to LBW reduction if insufficient protein intake
    - Gout
    - Kidney stones
  - Could lead to high Saturated fat intake
    - Increased LDL

Kirkpatrick CF et al JCL 2019 (in press)

DASH DIET

The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to help lower blood pressure and prevent heart disease, stroke, diabetes and even some forms of cancer. It focuses on eating more fresh fruits and vegetables.

This is a guide to how much of each food group you should eat every day, based on eating 2,000 calories per day.

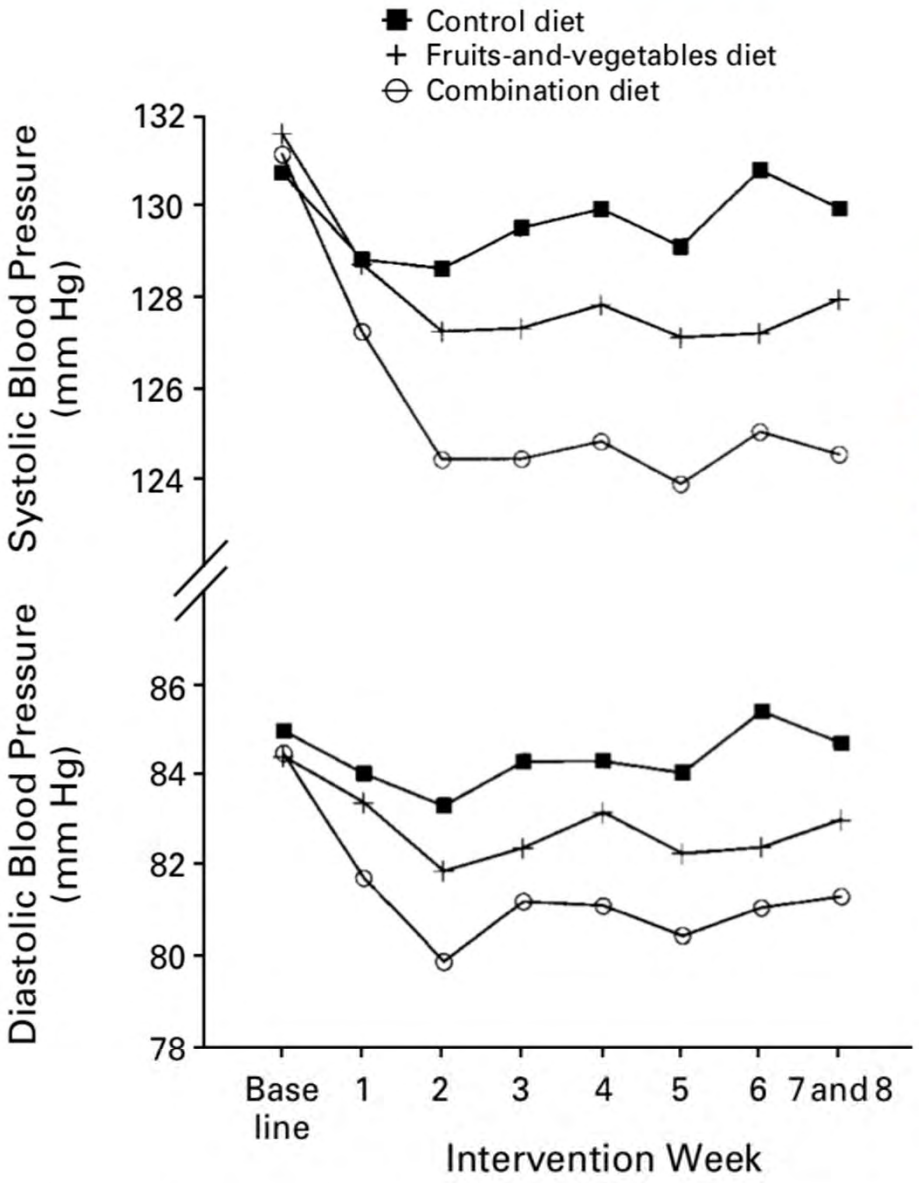

Figure 1. Mean Systolic and Diastolic Blood Pressures at Base Line and during Each Intervention Week, According to Diet, for 379 Subjects with Complete Sets of Weekly Blood-Pressure Measurements.

Appel L et al, NEJM 1997 DASH

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Many Trials have shown the downstream benefits of DASH diet beyond HTN

- Dixon LB, Subar AF, Peters U, Weissfeld JL, Bresalier RS, Risch A, Schatzkin A, Hayes RB. Adherence to the USDA Food Guide, DASH Eating Plan, and Mediterranean dietary pattern reduces risk of colorectal adenoma. J Nutr. 2007 Nov;137,11, p.2443-50
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- Obarzanek E, Vollmer WM, Lin PH, Cooper LS, Young DR, Ard JD, Stevens VJ, Simons-Morton DG, Svetkey LP, Harsha DW, Elmer PJ, Appel LJ. Effects of individual components of multiple behavior changes: the PREMIER trial. American Journal of Health Behavior. 2007 Sep-Oct; 31, 5, p 545-60
- Levitan EB, Wolk A, Mittleman MA. Relation of consistency with the dietary approaches to stop hypertension diet and incidence of heart failure in men aged 45 to 79 years. American Journal of Cardiology. 2009 Nov 15;104(10):1416-20.
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High Triglycerides

- GISSI-Prevenzione
  - Lancet 1999
- Jelis
  - Lancet 2007
- REDUCE-IT
  - NEJM 2019

- CV benefits of supplementation with marine based omega 3s

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REDUCE-IT results

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

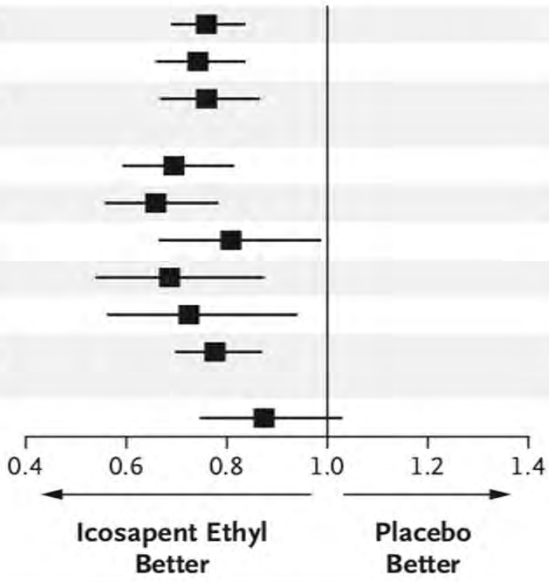

Figure 4. Hierarchical Testing of End Points.

Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.

Bhatt D NEJM 2019

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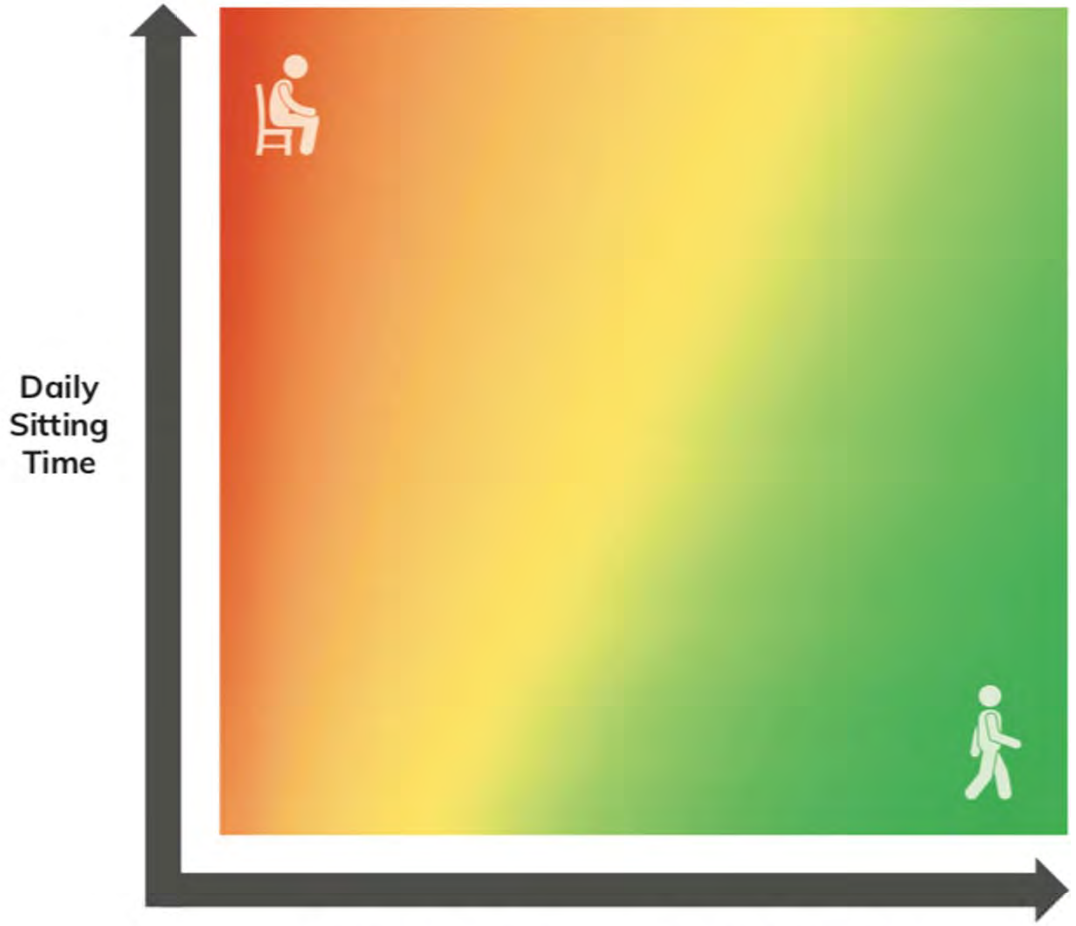
Guidelines (HHS/AHA)

- Move more + Sit Less
- 150 to 300 minutes of moderate intensity exercise/week or 75 to 150 minutes of vigorous intensity exercise/week
- Mix of Aerobic and muscle strengthening exercises that should be spread out throughout the week

Figure 1-3. Relationship Among Moderate-to-Vigorous Physical Activity, Sitting Time, and Risk of All-Cause Mortality in Adults

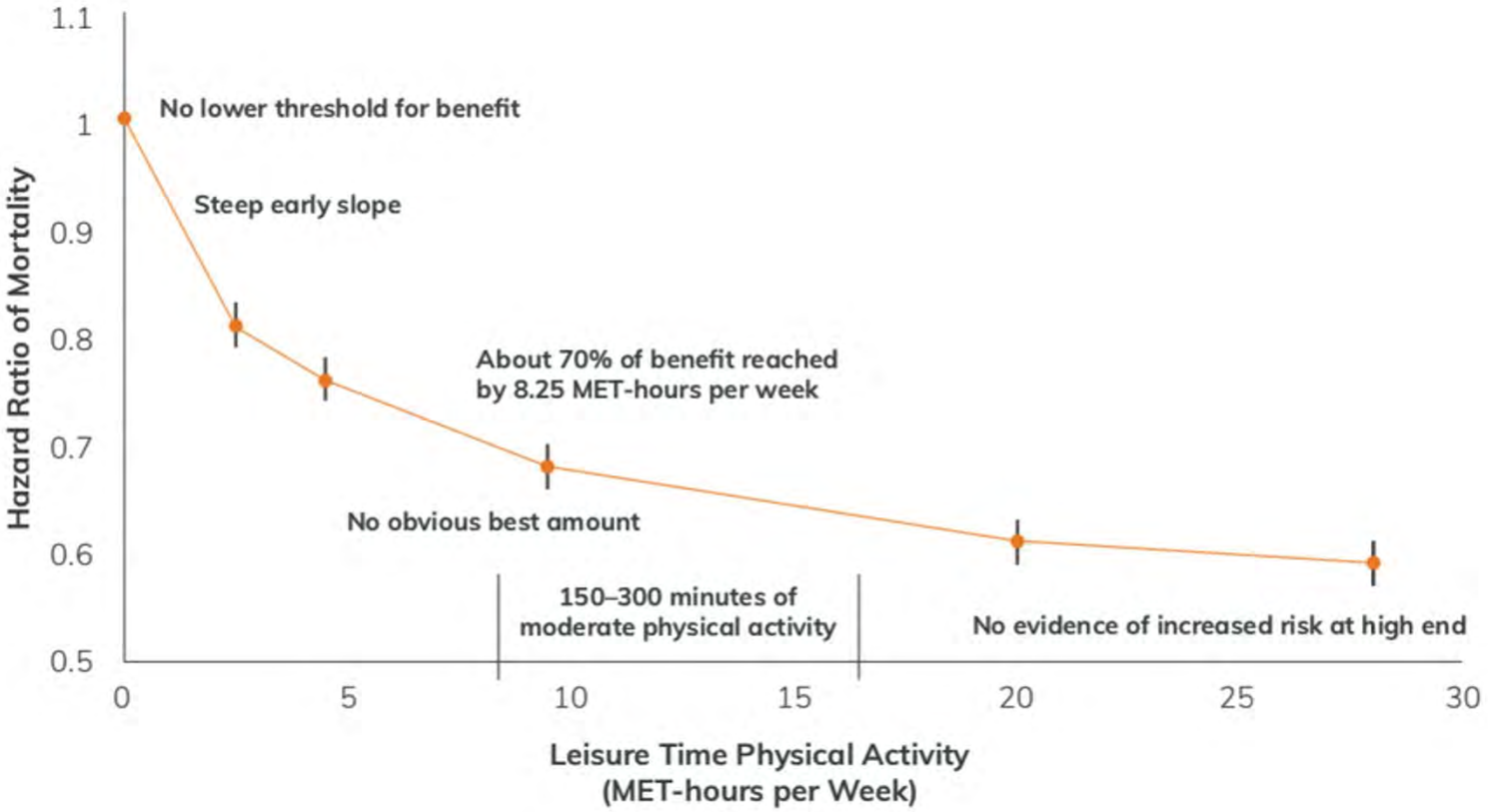


Risk of all-cause mortality decreases as one moves from red to green.

Source: This heat map is adapted from data found in Ekelund U, Steene-Johannessen J, Brown WJ. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonized meta-analysis of data from more than 1 million men and women. Lancet. 2016;388:1302-1310. doi:10.1016/S0140-6736(16)30370-1.

All Cause Mortality

Figure 2-1. Relationship of Moderate-to-Vigorous Physical Activity to All-Cause Mortality



Source: Adapted from data found in Moore SC, Patel AV, Matthews CE. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. PLoS Med. 2012;9(11):e1001335. doi:10.1371/journal.pmed.1001335.

Table 4-1. Examples of Different Aerobic Physical Activities and Intensities, Based on Absolute Intensity

Moderate-Intensity Activities
▪ Walking briskly (2.5 miles per hour or faster) ▪ Recreational swimming ▪ Bicycling slower than 10 miles per hour on level terrain ▪ Tennis (doubles) ▪ Active forms of yoga (for example, Vinyasa or power yoga) ▪ Ballroom or line dancing ▪ General yard work and home repair work ▪ Exercise classes like water aerobics
Vigorous-Intensity Activities
▪ Jogging or running ▪ Swimming laps ▪ Tennis (singles) ▪ Vigorous dancing ▪ Bicycling faster than 10 miles per hour ▪ Jumping rope ▪ Heavy yard work (digging or shoveling, with heart rate increases) ▪ Hiking uphill or with a heavy backpack ▪ High-intensity interval training (HIIT) ▪ Exercise classes like vigorous step aerobics or kickboxing

Adults and Older Adults

- Lower risk of all-cause mortality
- Lower risk of cardiovascular disease mortality
- Lower risk of cardiovascular disease (including heart disease and stroke)
- Lower risk of hypertension
- Lower risk of type 2 diabetes
- Lower risk of adverse blood lipid profile
- Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach
- Improved cognition*
- Reduced risk of dementia (including Alzheimer's disease)
- Improved quality of life
- Reduced anxiety
- Reduced risk of depression
- Improved sleep
- Slowed or reduced weight gain
- Weight loss, particularly when combined with reduced calorie intake
- Prevention of weight regain following initial weight loss
- Improved bone health
- Improved physical function
- Lower risk of falls (older adults)
- Lower risk of fall-related injuries (older adults)

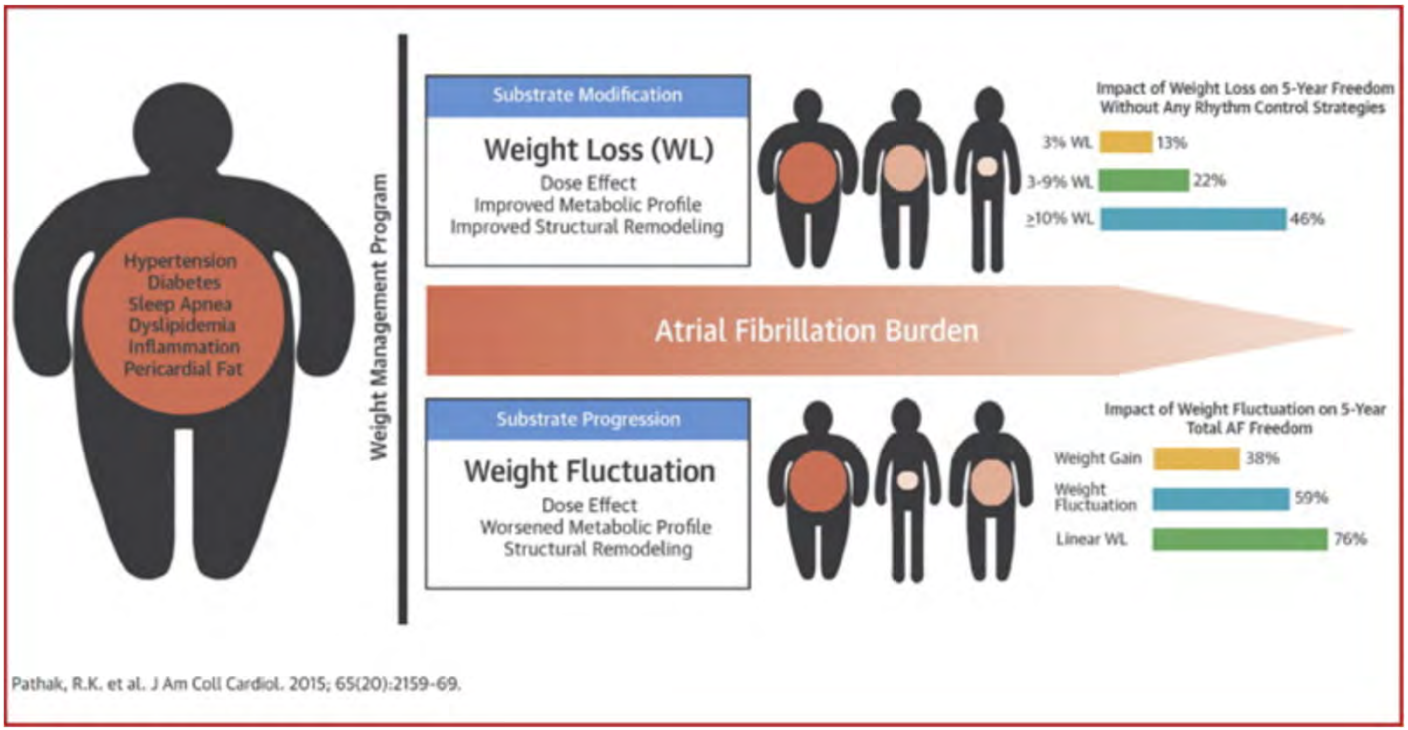
Note: The Advisory Committee rated the evidence of health benefits of physical activity as strong, moderate, limited, or grade not assignable. Only outcomes with strong or moderate evidence of effect are included in this table.

*See Table 2-3 for additional components of cognition and brain health.

Being Active Doesn't Take Much

Exercise per week

Effect of Weight Reduction on AFib

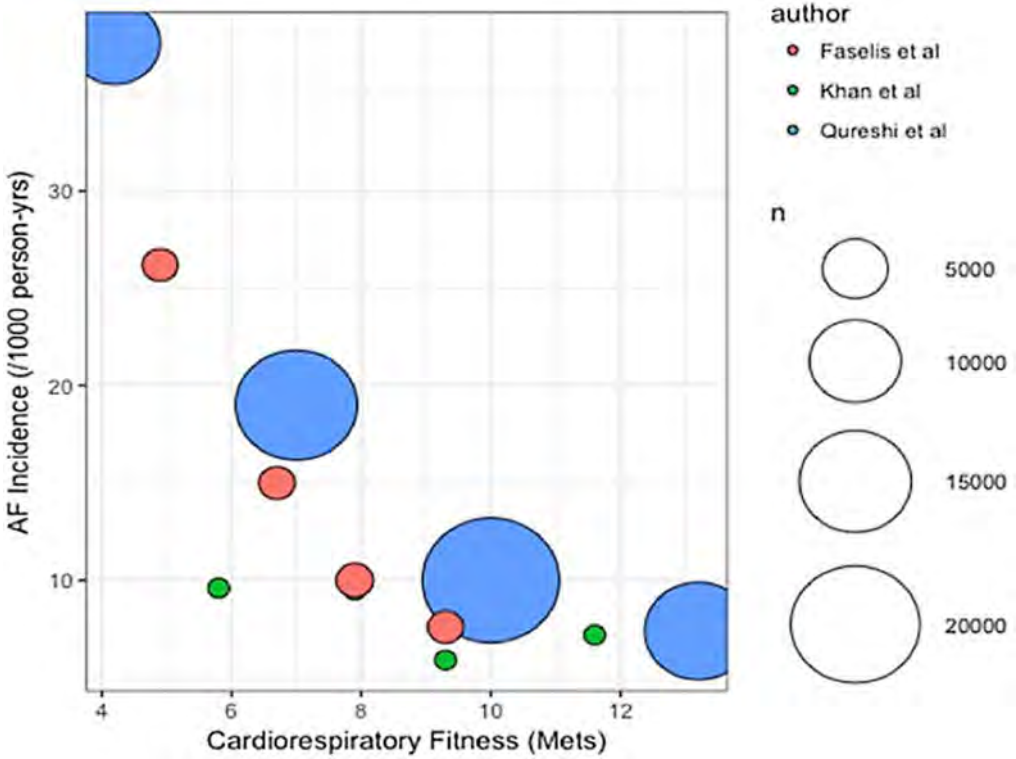


Pathak, R.K. et al. J Am Coll Cardiol. 2015; 65(20):2159-69.

- 1415 patients
- Weight loss of >10% resulted in a 6-fold greater probability of remaining arrhythmia free

Exercise and AFib: Yes, it is good for you

- Better cardio-pulmonary fitness leads to less AFib
- Endurance sports athletes trend towards more AFib

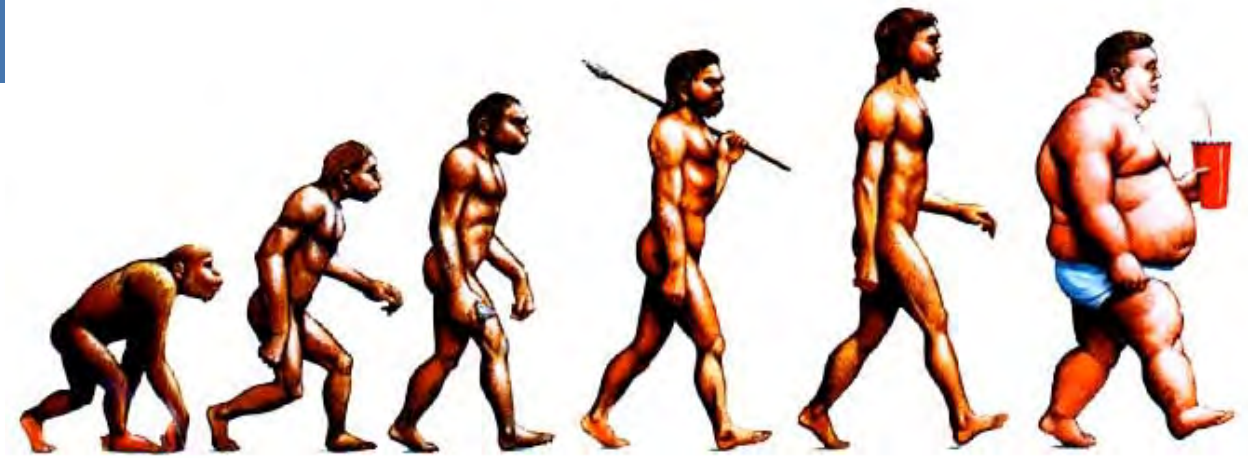


Elliott et al. Heart Rhythm 2017; 14, 1713-1720
Myrstad et al. Am J Cardiol. 2014;114(8):1229-33.

Summary

- Obesity has many direct and indirect effects on cardiovascular health
- A comprehensive approach to weight reduction leads to the sustained lifestyle changes needed to maintain weight and CV benefits
- Focus the interventions in a more personalized fashion based on the clinical manifestations effecting the patient

Where we are headed



Where we can go