Non-Alcoholic Fatty Liver Disease (NAFLD)

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Disclosures

Jennifer C. Lai, MD, MBA

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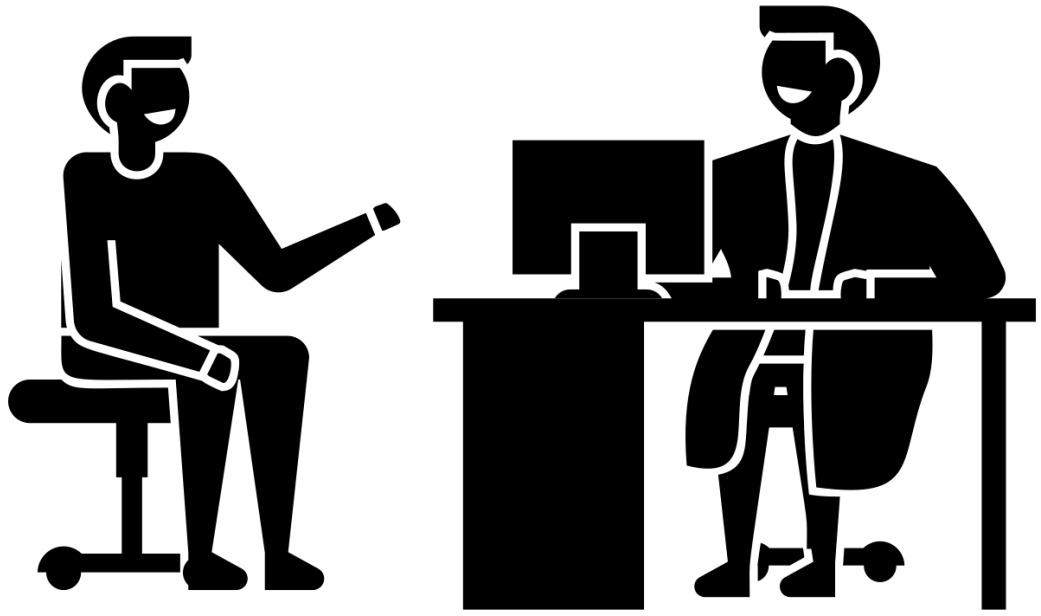
I disclose the following financial relationship(s) with a commercial interest:

- Novo Nordisk (Advisory Board)
- GenFit (consultant)
- Nestle Nutrition Institute (independent educational grant, no personal fees)
- Axcella Health, Inc (independent research funding)
- Lipocene (clinical trial site PI)

40 year old obese woman with hepatic steatosis on ultrasound

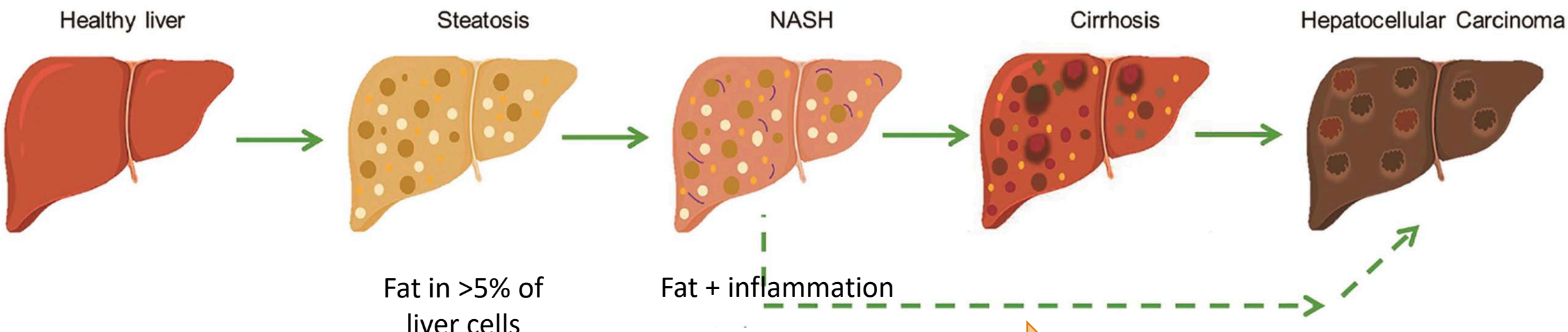
“It looks like you have fat in your liver on u/s.”



“What does that mean? Is this something I need to worry about?”

Non-alcoholic fatty liver disease

The Basics

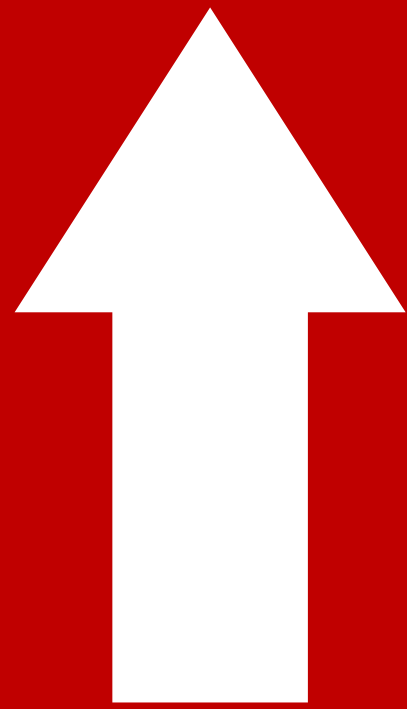


50+ years

25-30 years

Rojas A, *et al*. J Clin Transl Hep 2022. Singh, CGH 2015. Ekstadt, Hepatol 2015.

1 in 2



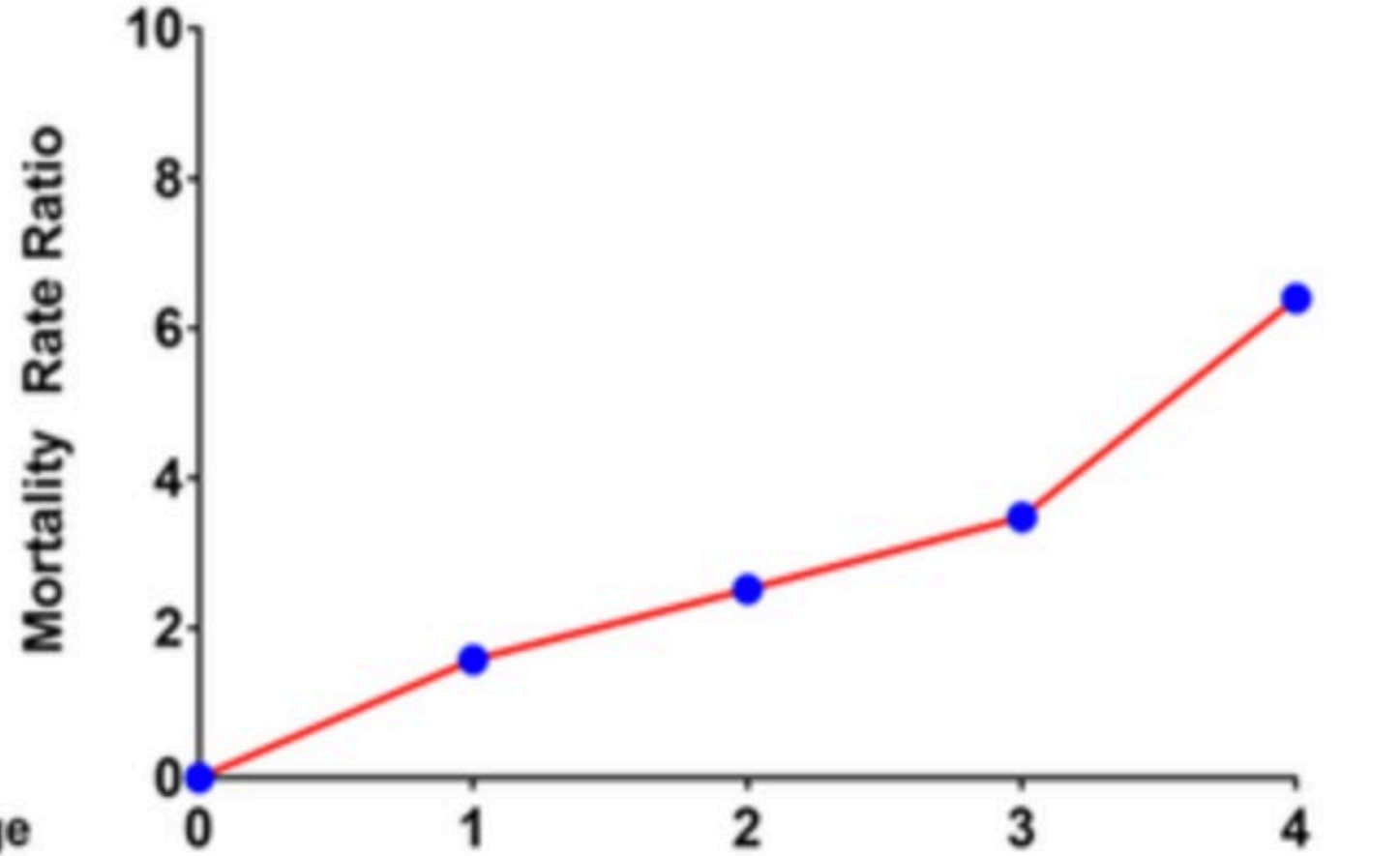
1 in 4 people
in the U.S. have NAFLD.

30% increased risk of death

(vs. general population)

Fibrosis is a potent predictor of death

Dulai, Hepatol 2017



Prevalence of advanced fibrosis in general population (0.9-2%)

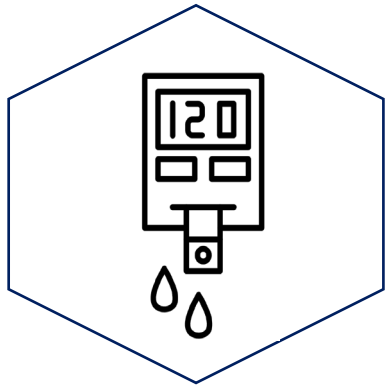
Harrison, J Hepatol 2021
Wong, Gut 2012
Harris,Lancet Gastroenterol Hepatol 2017
Kang, Aliment Pharmacol Ther 2020

AASLD and AGA recommend screening in populations at high risk for advanced fibrosis

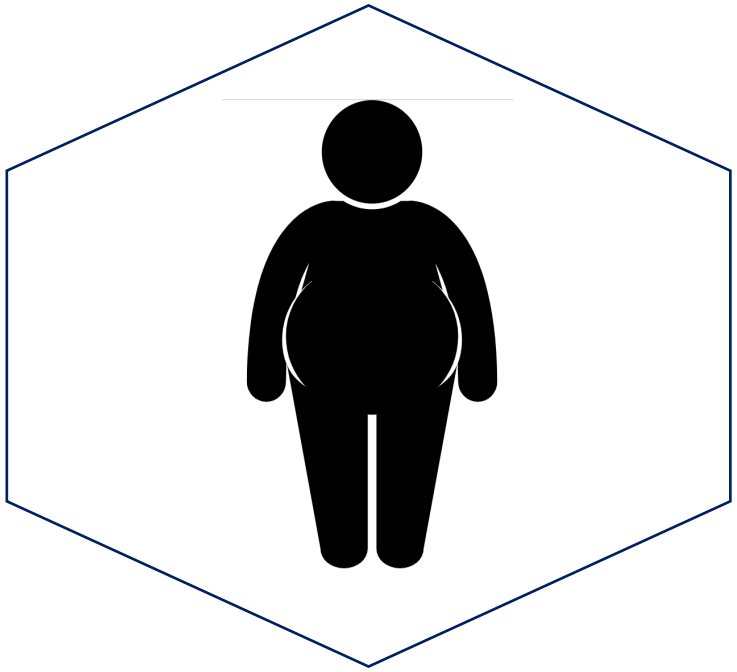
Rinella, *et al*
Hepatology 2023.

Kanwal, *et* al
Gastroenterology 2021.

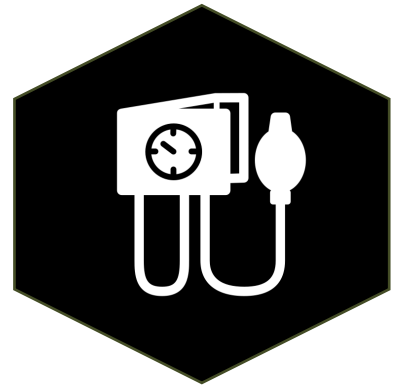
RISK FACTORS



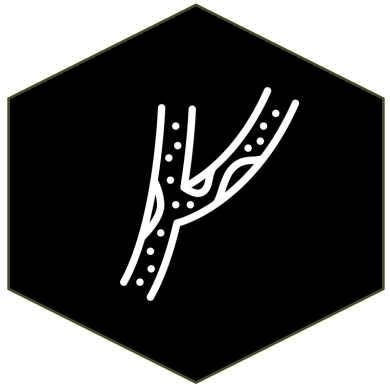
DIABETES



OBESITY



HYPERTENSION



DYSLIPIDEMIA

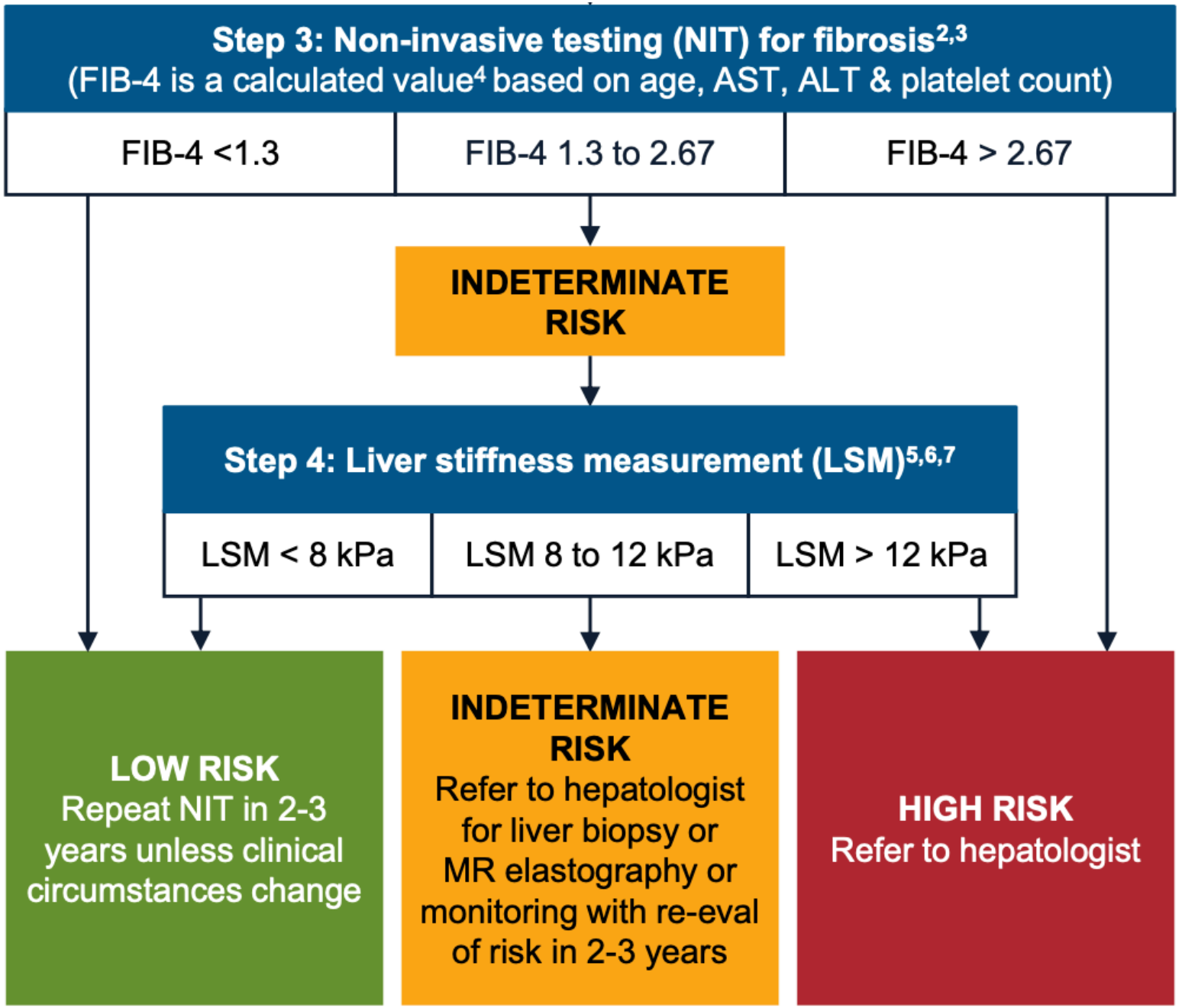
INSULIN RESISTANCE

Primary screening for fibrosis : use a non-invasive testing method

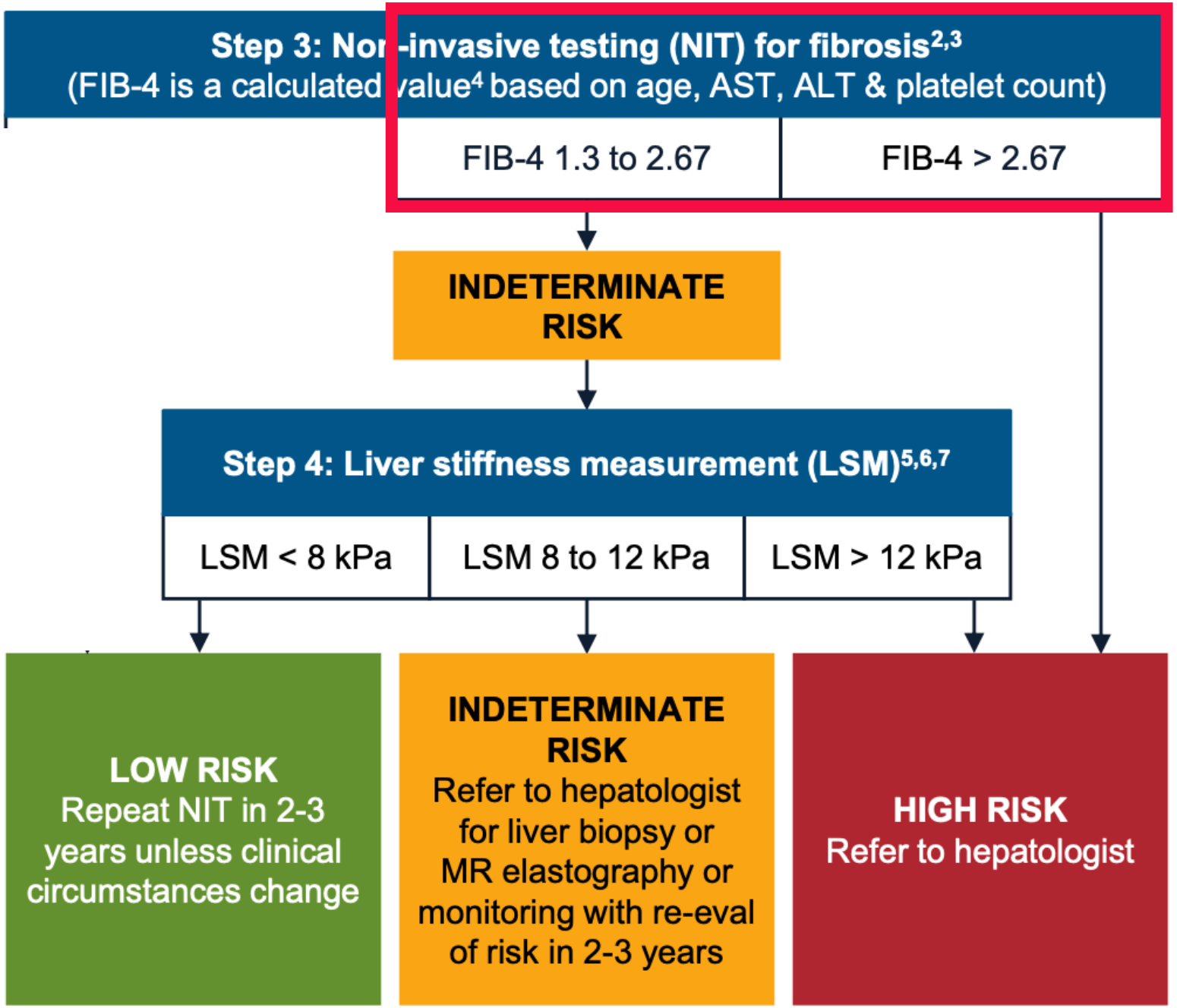
Step 3: Non-invasive testing (NIT) for fibrosis[2,3] (FIB-4 is a calculated value[4] based on age, AST, ALT & platelet count)		
FIB-4 <1.3	FIB-4 1.3 to 2.67	FIB-4 > 2.67

2. For patients 65+, use FIB-4 ≤2.0 as the lower cutoff.
3. Other NITs derived from routine labs can be used instead of FIB-4.
4. Many online FIB-4 calculators are available.

Kanwal, *et* al Gastroenterology 2021.



Kanwal, *et* al Gastroenterology 2021.



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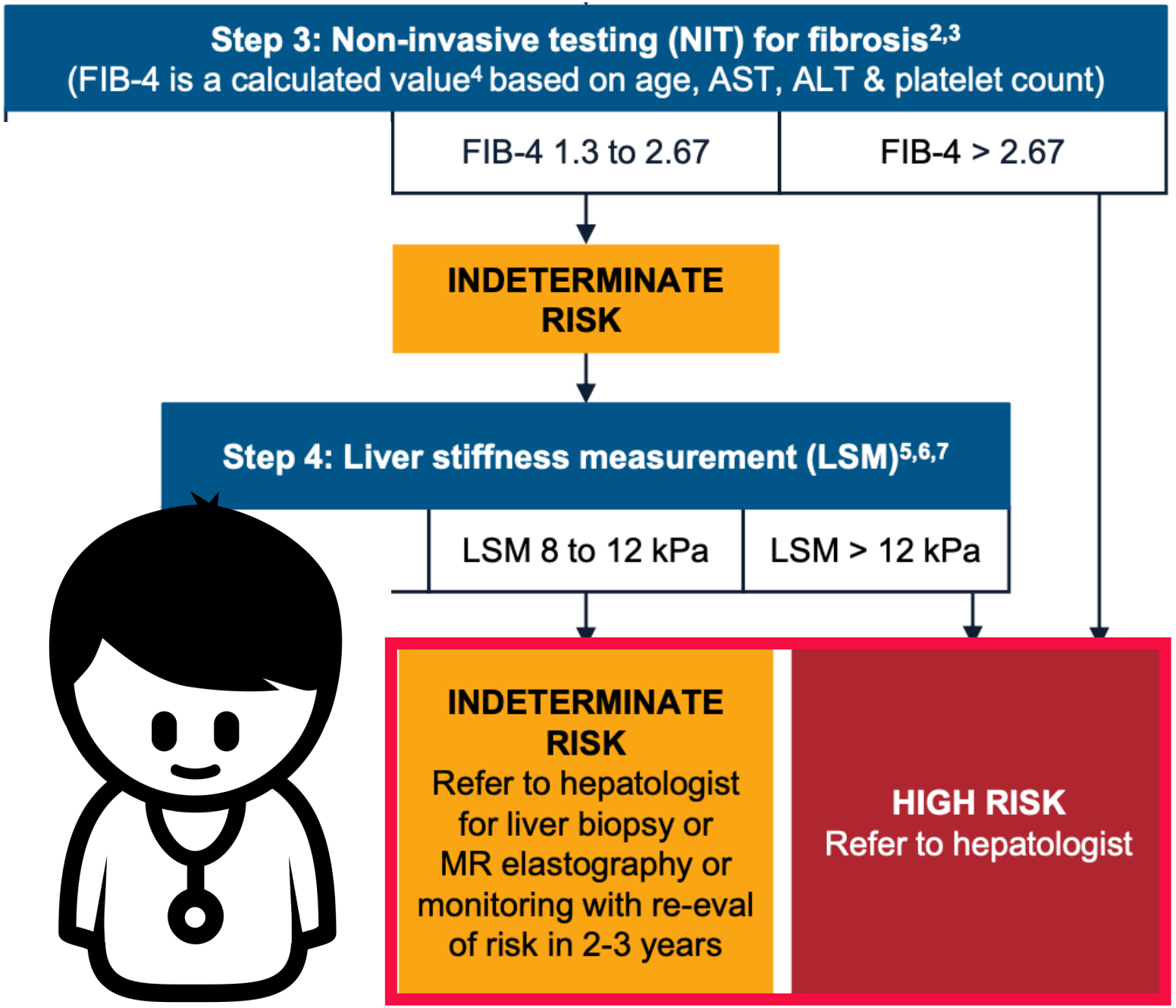


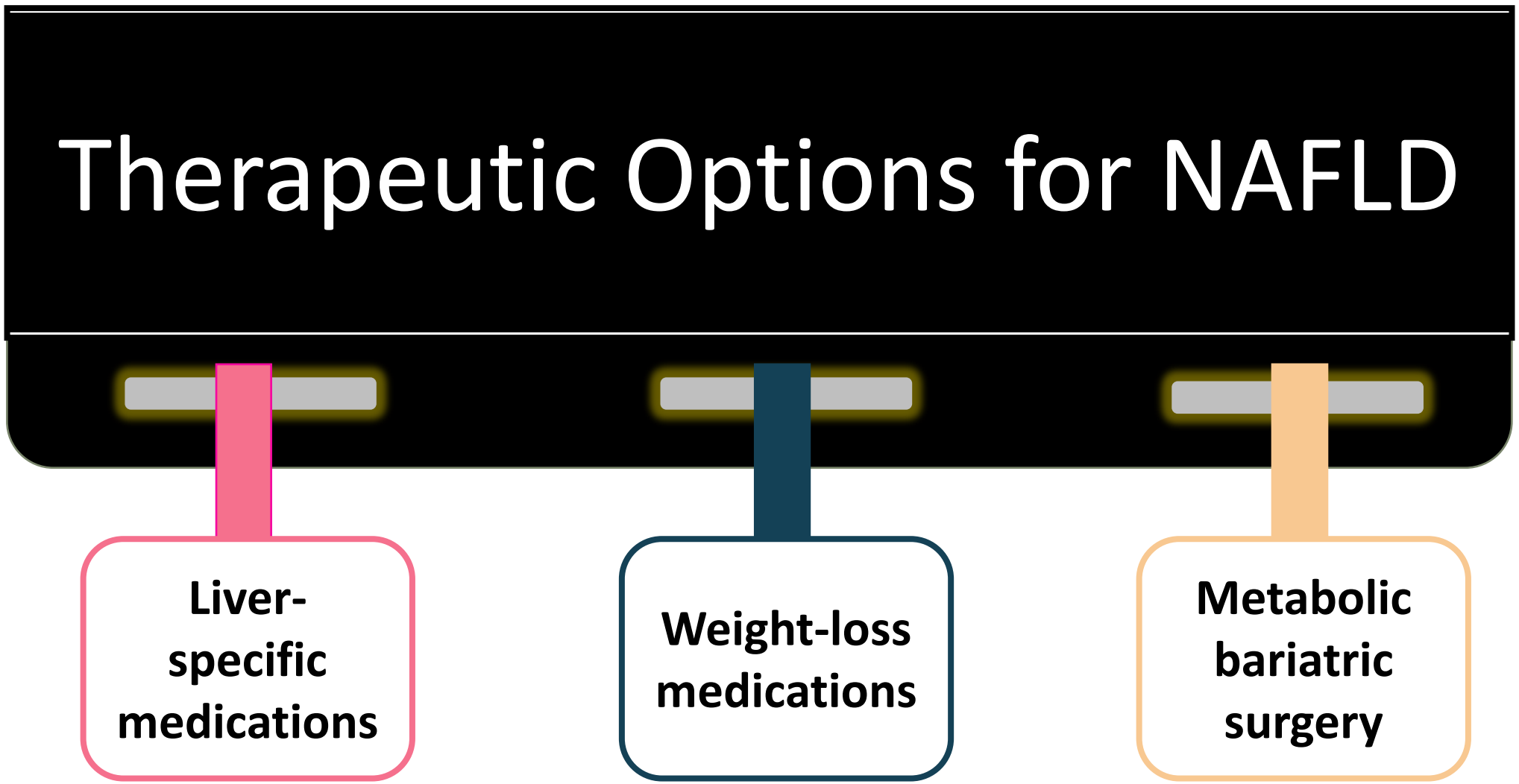
Kanwal, *et* al Gastroenterology 2021.

Management of NAFLD/NASH based on patient's risk

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal, *et* al Gastroenterology 2021.

Therapeutic Options for NAFLD

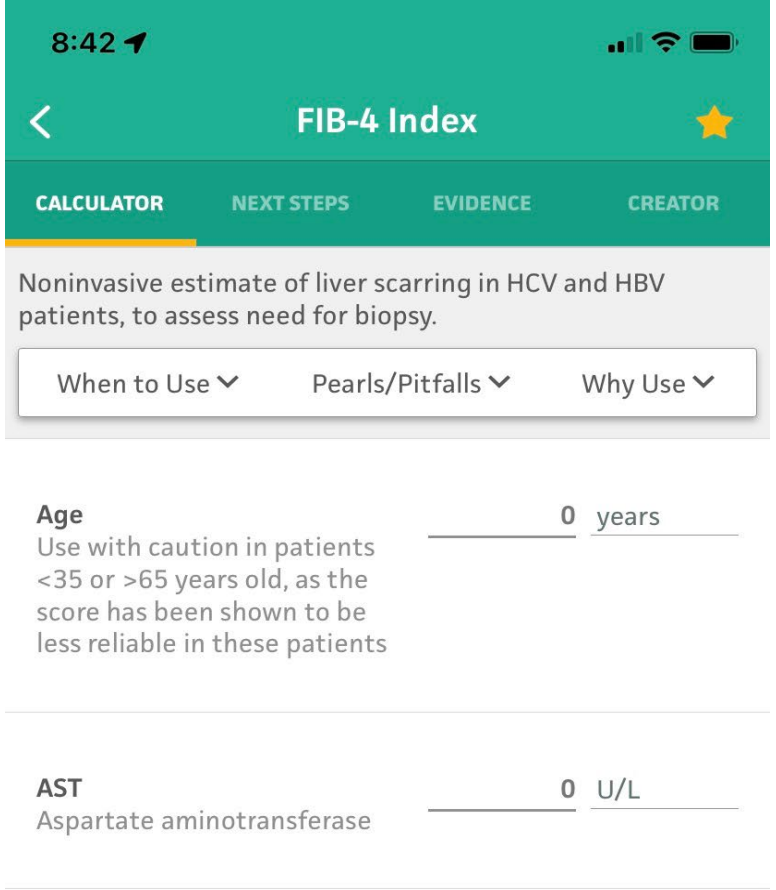


Medication	FDA Indication	Population	Clinical Benefits	Potential Side Effects	Cardiac Benefit
Vitamin E (rrr-alpha) 800 IU daily[379, 488]	N/A	NASH without T2DM or cirrhosis	Improves steatosis NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke ? risk of prostate cancer	No
Pioglitazone 30-45mg po daily (387, 390, 489)	**T2DM**	**NASH with and without T2DM**	**Improves steatosis, activity and NASH resolution** **Fibrosis improvement?** **Improves insulin sensitivity** **Prevention of diabetes** **CV risk reduction and stroke prevention**	**Weight gain** **Risk of heart failure exacerbation** **Bone loss post-menopausal women**	**Yes**
Liraglutide* 1.8mg SC daily (T2DM) 0.6-3mg SQ daily (obesity) (404)	**T2DM** **Obesity**	**NASH without cirrhosis**	**Improves steatosis** **No proven impact on fibrosis**	**Gastrointestinal** **Gallstones (related to wt**	**Yes**
Semaglutide ¥ 0.4mg SC daily 0.25-2.4mg SQ w (405)			**Improvement in insulin sensitivity** **Weight loss** **Improves CV and renal outcomes** **Stroke prevention**	**Pancreatitis**	**Yes**
Tirzepatide (406, 407)	T2DM Obesity	T2DM or Obesity with NAFLD	Reduces steatosis on imaging Improvement in insulin sensitivity Significant weight loss	Gastrointestinal Gallstones related to wt loss Pancreatitis	Unknown
SGLT2i (409, 413, 414)	**T2DM**	**T2DM and NAFLD**	**Reduction in steatosis by imaging** **May improve insulin sensitivity** **Improves CV and renal outcomes** **Modest weight loss**	**Risk of genitourinary yeast infection, volume depletion** **Bone loss**	**Yes**

None are FDA-approved for the indication of NASH at this moment

Slide courtesy of Dr. Rohit Loomba.

Back to our patient

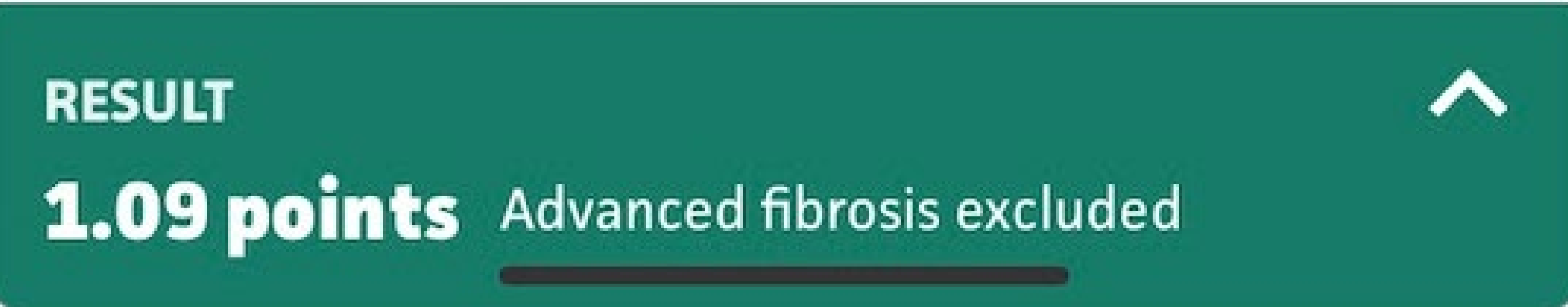


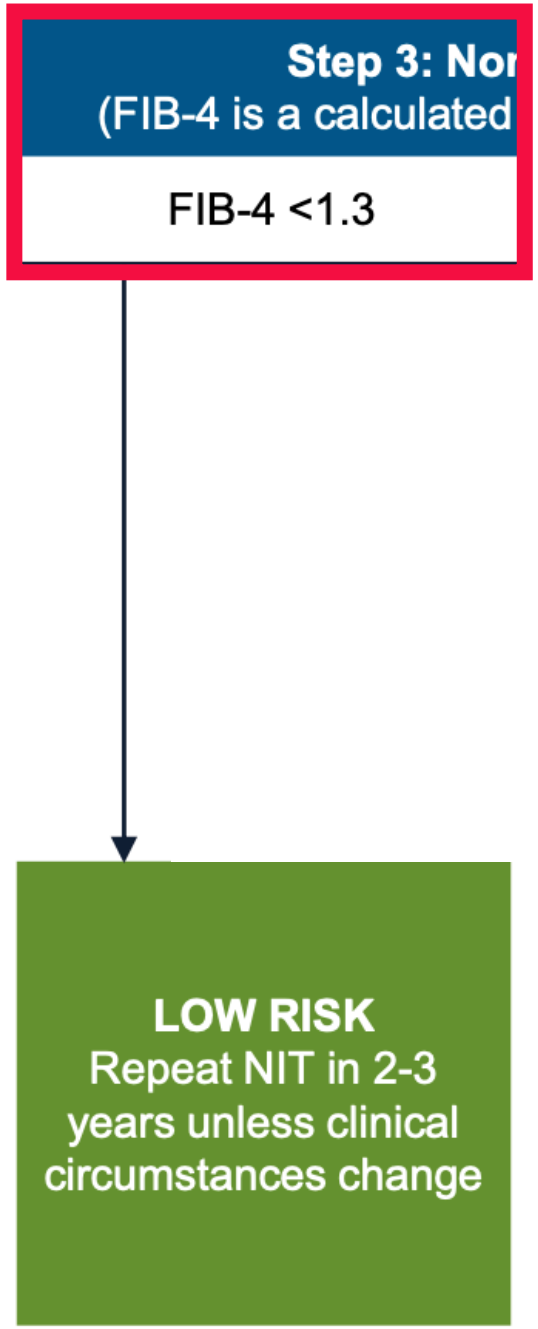
Age: 40 years

AST: 35

ALT: 30

Plt: 234





Kanwal, *et* al Gastroenterology 2021.

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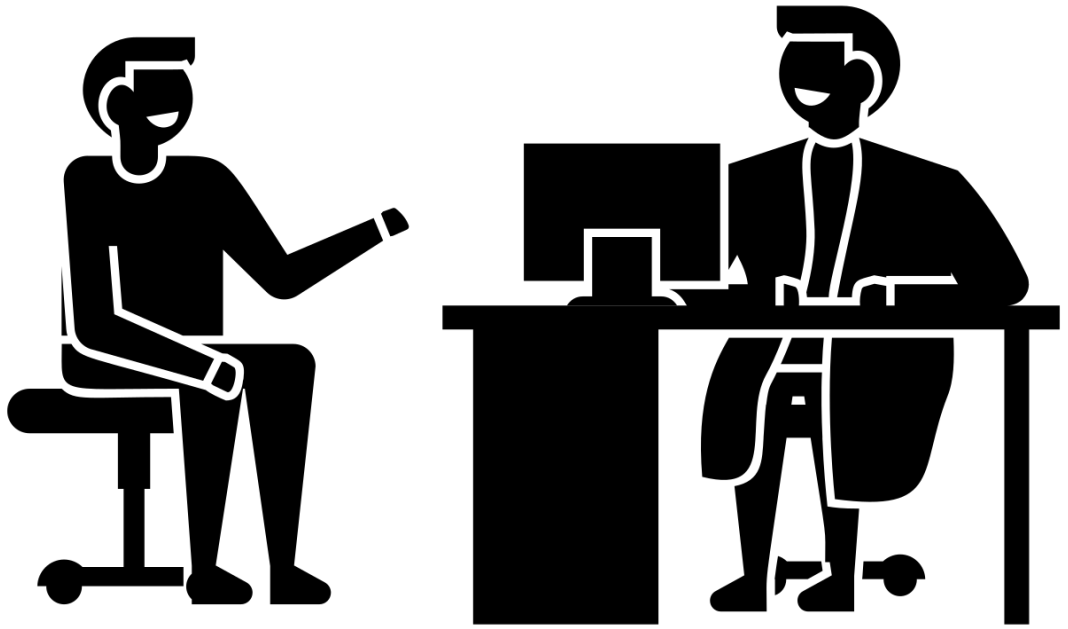
Kanwal, *et* al Gastroenterology 2021.

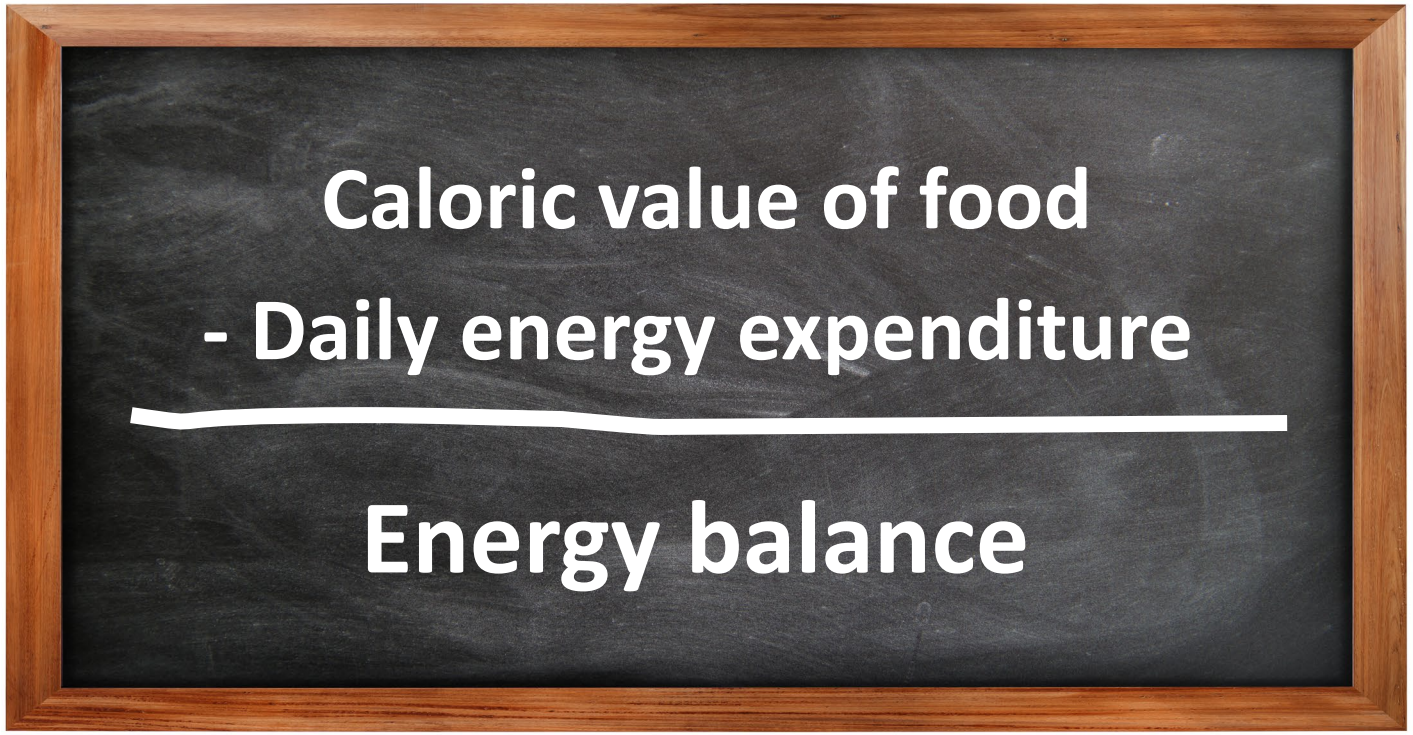


“Good news. You are at low risk for having significant scarring of your liver. The main treatment for fatty liver disease is weight loss. Just eat less and exercise more.”

“What does that mean? Is this something I need to worry about?”

Behavioral management strategy

Calories in, Calories out

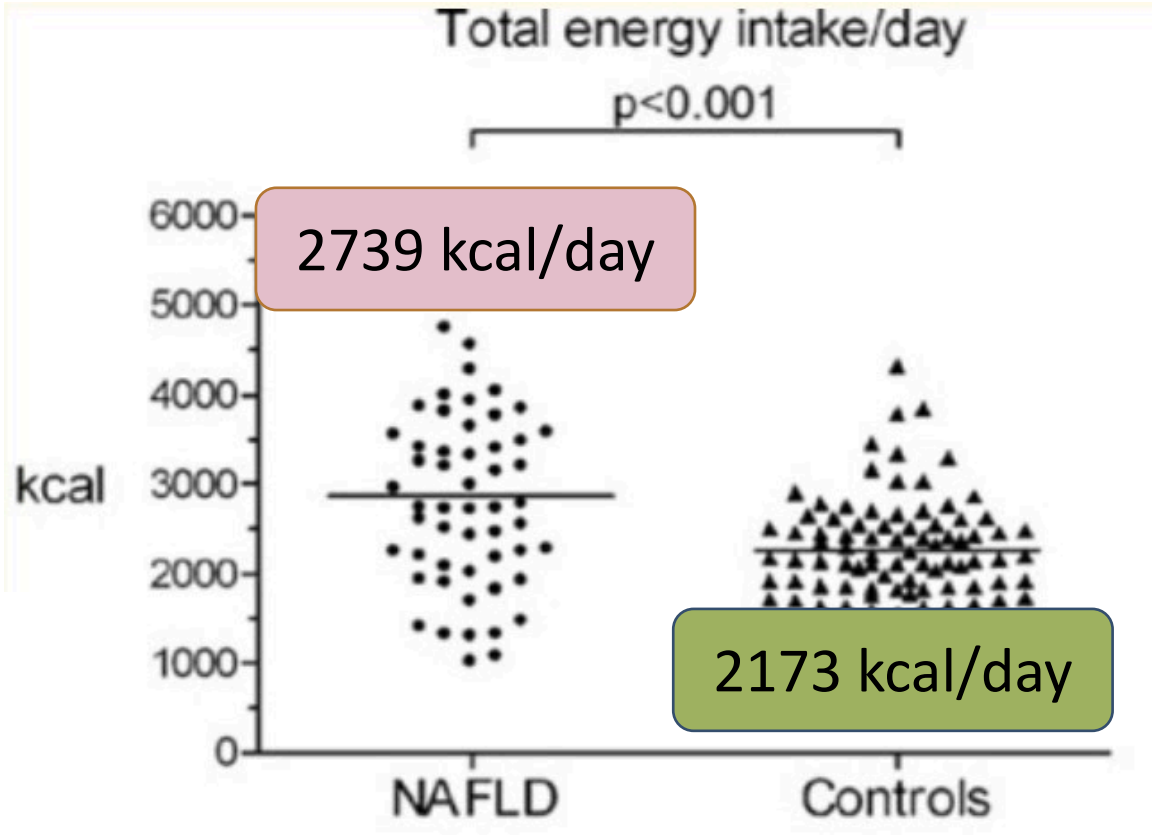


Weight loss

Weight maintenance

Weight gain

Patients with NAFLD report eating 500+ additional calories per day

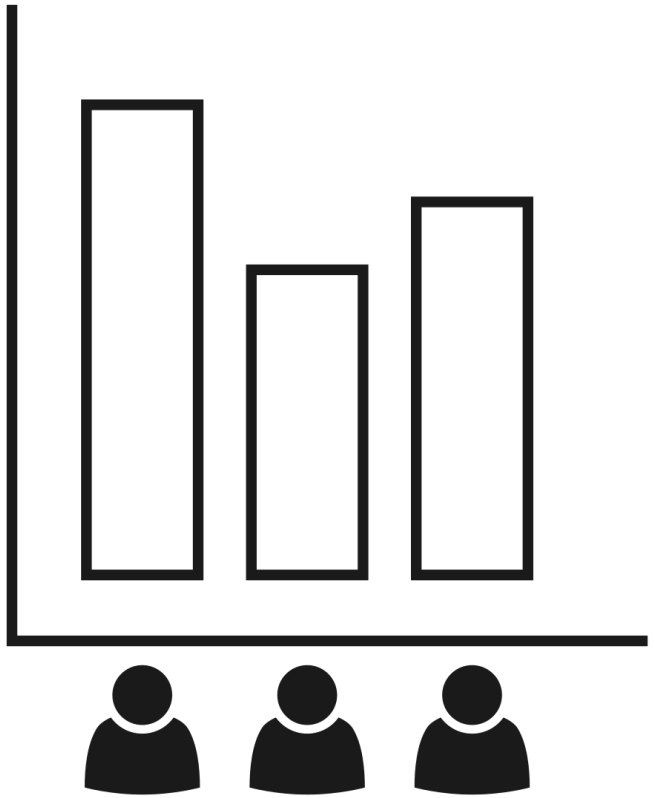


Diet composition per 1000 kcal

	NAFLD	Controls
Carb (g)	104	103
Protein (g)	36	35
Fat (g)	43	45
Sat fat (g)	18	18
Fructose (g)	10.5	10.3

Wehmeyer M, *et al*. Medicine 2016.

Effective?



- Most patients
- ~Half of patients
- < Half of patients
- Very few patients
- Almost none

Meta-analysis

Effectiveness of behavioural interventions for weight loss

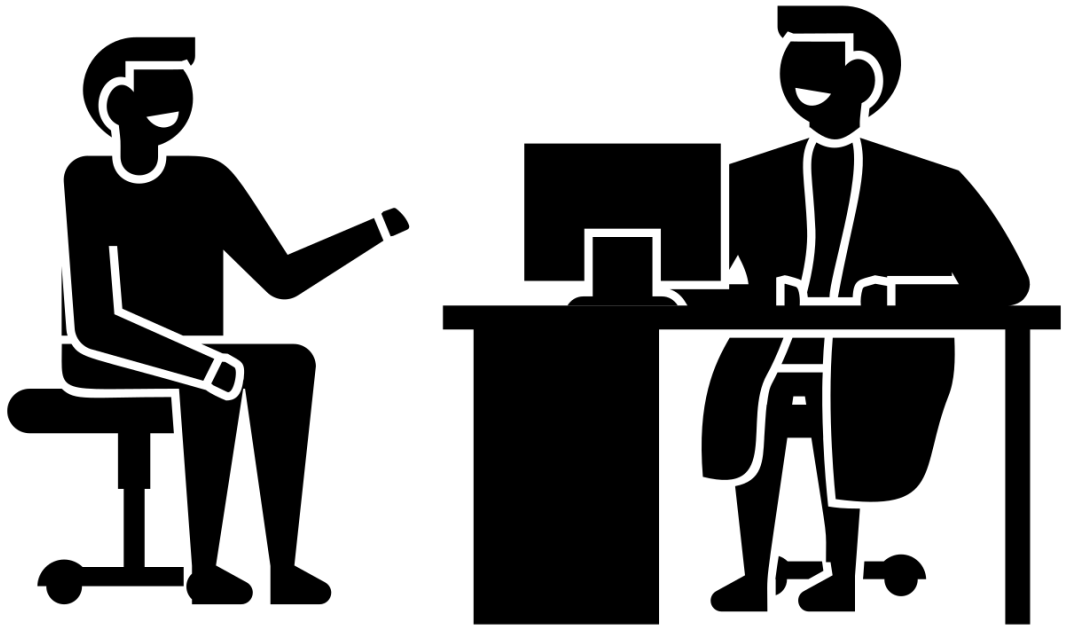
15 RCTs
4539 participants
≥12 mo f/u

-3.0 lb
(12 months)

-2.7 lb
(24 months)

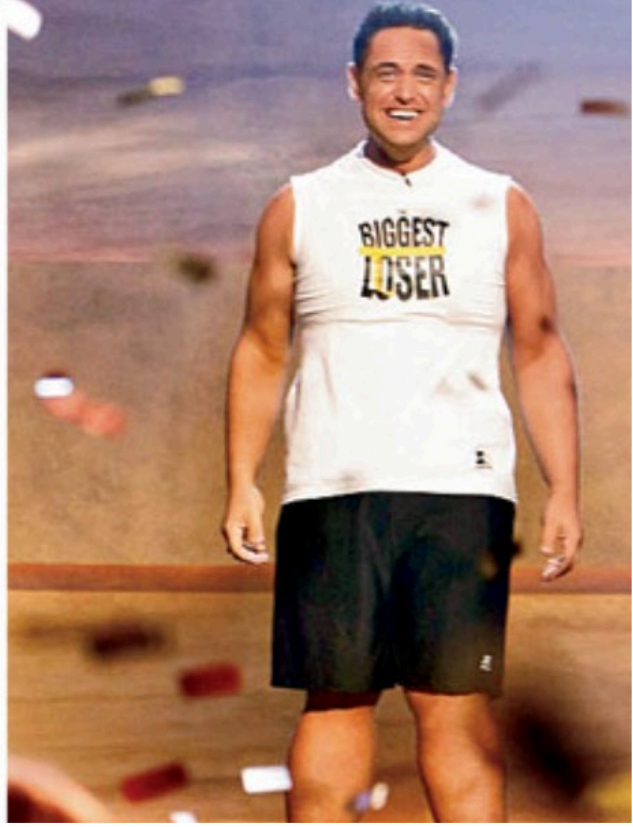
Booth H, *et al*. Family Practice 2014.

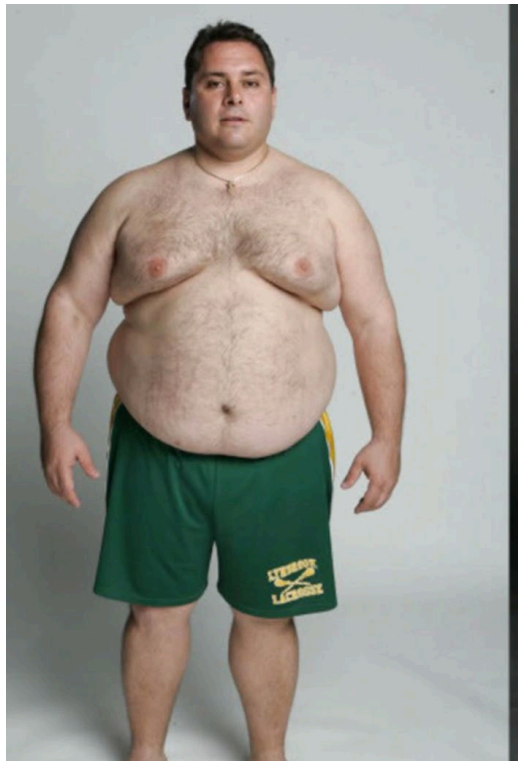
“Our scale shows that you have gained 5 pounds since your last visit.”



“I don’t understand what I am doing wrong. I’ve been doing everything you told me to. I barely eat, and I’ve been walking very day!”

THE BIGGEST LOSER





Changes in The Biggest Loser participants

	Baseline	End of competition (30 weeks)
Weight (lb)	328 (+/- 89)	199 (+/- 54)

Fothergill, *et al*. Obesity 2016.

Metabolic adaptation

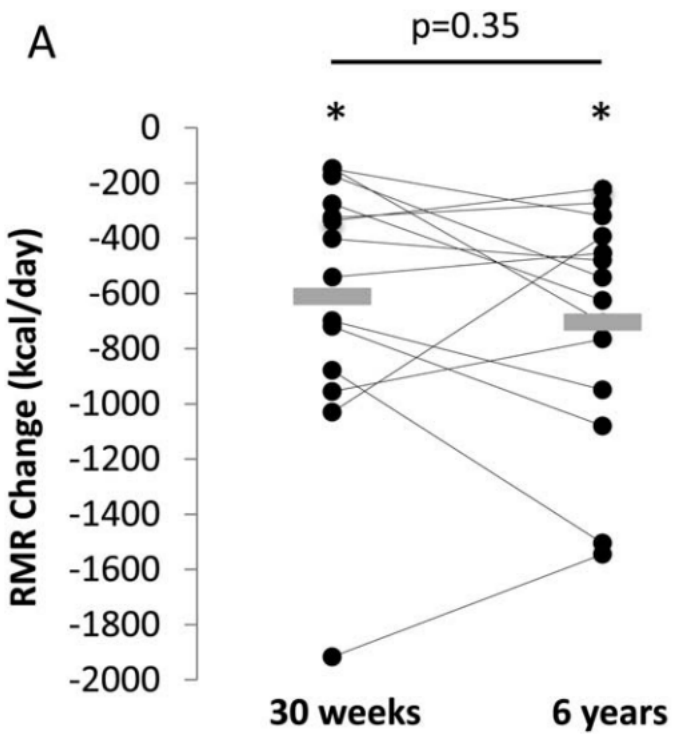
The slowing of resting metabolic rate that accompanies weight loss and is often greater than would be expected based on measured changes in body composition

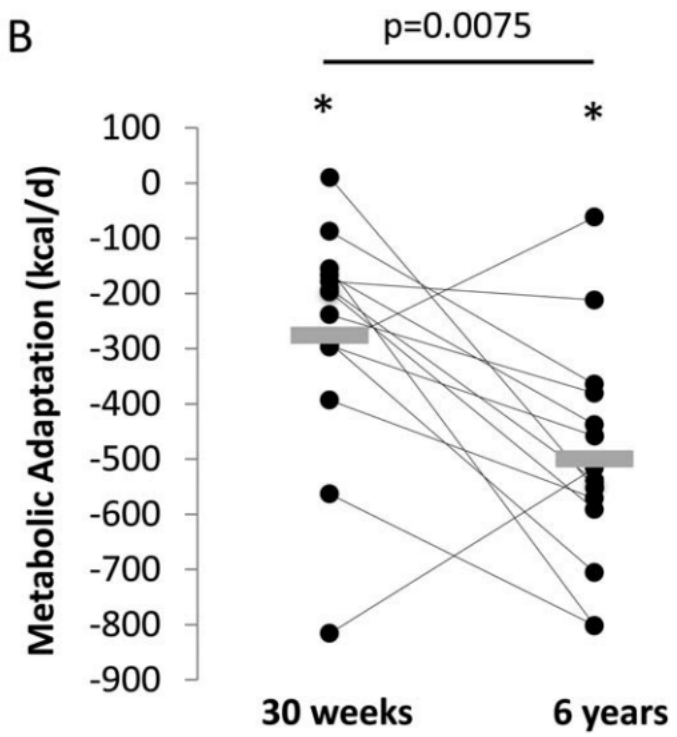
Johanssen DL, *et al.* J Clin Endocrinol Metab 2012.

Metabolic adaptation in The Biggest Loser

	Baseline	End of competition (30 weeks)	Follow up at 6 years
RMR kcal/d	2,607	1,996	1,903

RMR





Metabolic adaptation

Fothergill, *et al*. Obesity 2016.

Calories in, calories out

Caloric value of food

- Daily energy expenditure

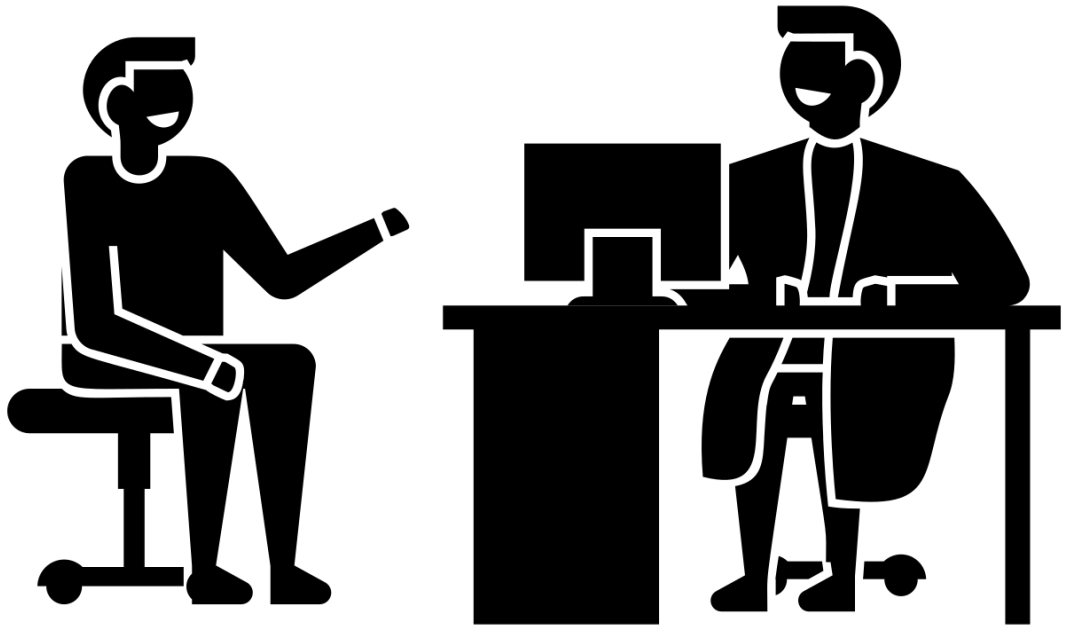
Energy balance

Weight loss

Weight maintenance

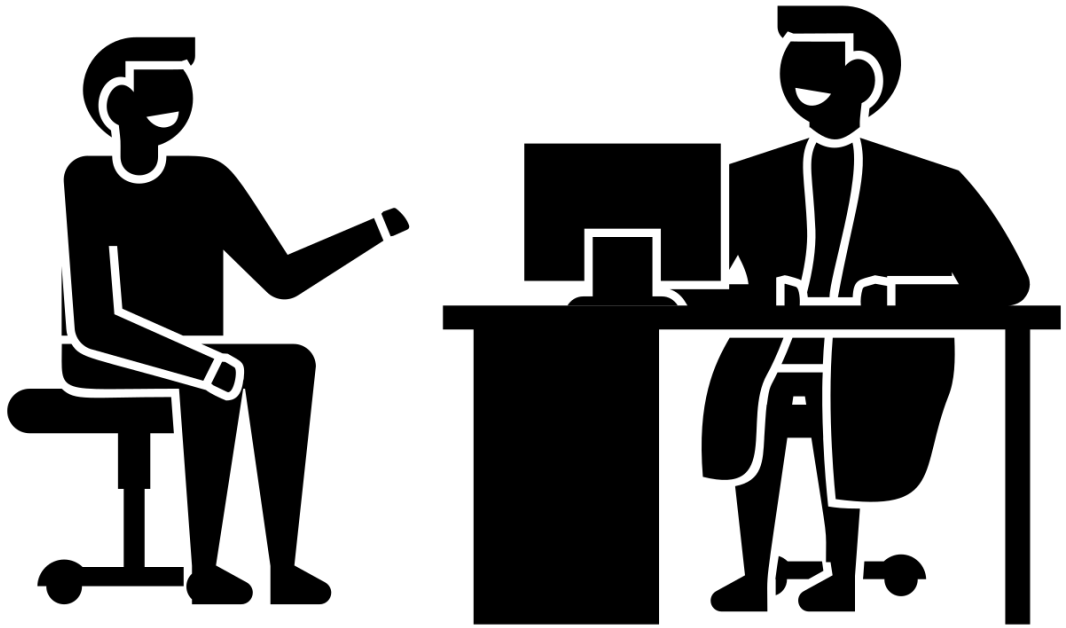
Weight gain

“Lose weight by eating less and exercising more.”



“I don’t understand what I am doing wrong.”

“The first goal is to stop ongoing weight gain.”



Calories In

Food	Kcal
Bagel + cream cheese	380
Grande vanilla latte	250
Chicken breast	250
Banana	100
Orange juice (1c)	100
Pepperoni pizza	300
Red wine	125

Calories Out

Activity (per 30 min)	Kcal
Walk	100
Exercise bike	100
Playing with children	100
Doubles tennis	150
Gardening	100
Zumba	150-450

Alternative eating strategies for patients with NAFLD

Diet Quality

"…a diversified, balanced and healthy diet, which provides energy and all essential nutrients for growth and a healthy and active life. "

www.iaea.org

Ultra-processed food

"Industrial formulations typically with 5 or more and usually many ingredients. …include food substances not commonly used in culinary preparations whose purpose is to imitate sensorial qualities of unprocessed or minimally processed foods"

"food substance"
e.g., hydrolyzed protein, modified starches, and hydrogenated oils, and additives

"to imitate sensorial qualities"
e.g., colorants, flavorings, nonsugar sweeteners

Monteiro CA, *et al*. Rome, FAO. 2019

Identifying ultra-processed foods

1) Wrapped in plastic

+

2) Contains at least one ingredient that would not be found in a domestic kitchen

NOVA Food Classification System

Endorsed by the Food and Agriculture Organization of the United Nations

#4 ULTRA-PROCESSED

Many ingredients + food additives

Cold cuts
Soft drinks
Ice cream
Cereal
Hot dogs

#3 PROCESSED

Industrial products made using preservation methods such as canning, bottling, fermentation.

Bread
Cheese
Jam
Tofu

#2 PROCESSED CULINARY FOODS

Obtained directly from foods in group #1 and created by industrial processes (e.g., pressing, extracting, refining)

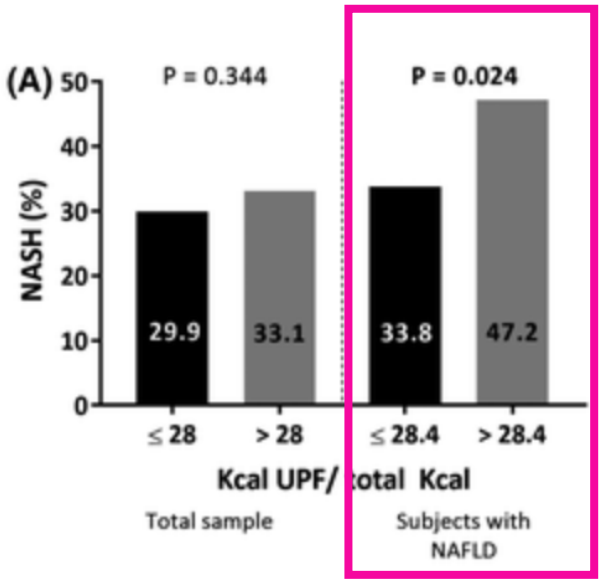
Oil, salt, sugar, butter

#1 UNPROCESSED / MINIMALLY PROCESSED

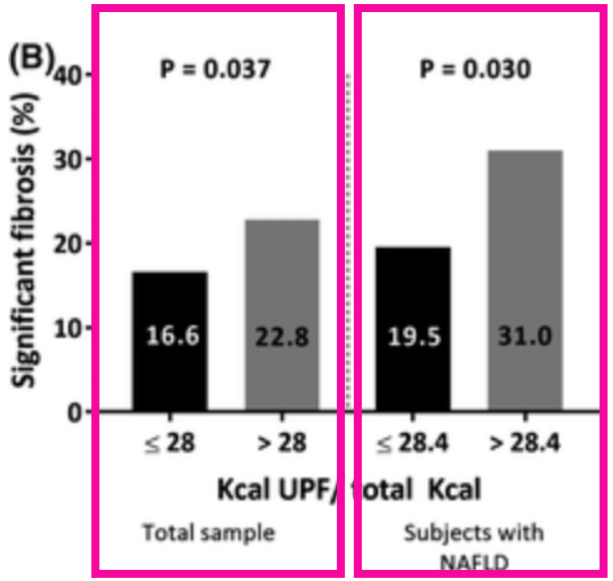
Vegetables
Fruits
Nuts
Meat
Milk
Eggs

Evidence : Ultra-processed food consumption and fatty liver

Rates of NASH

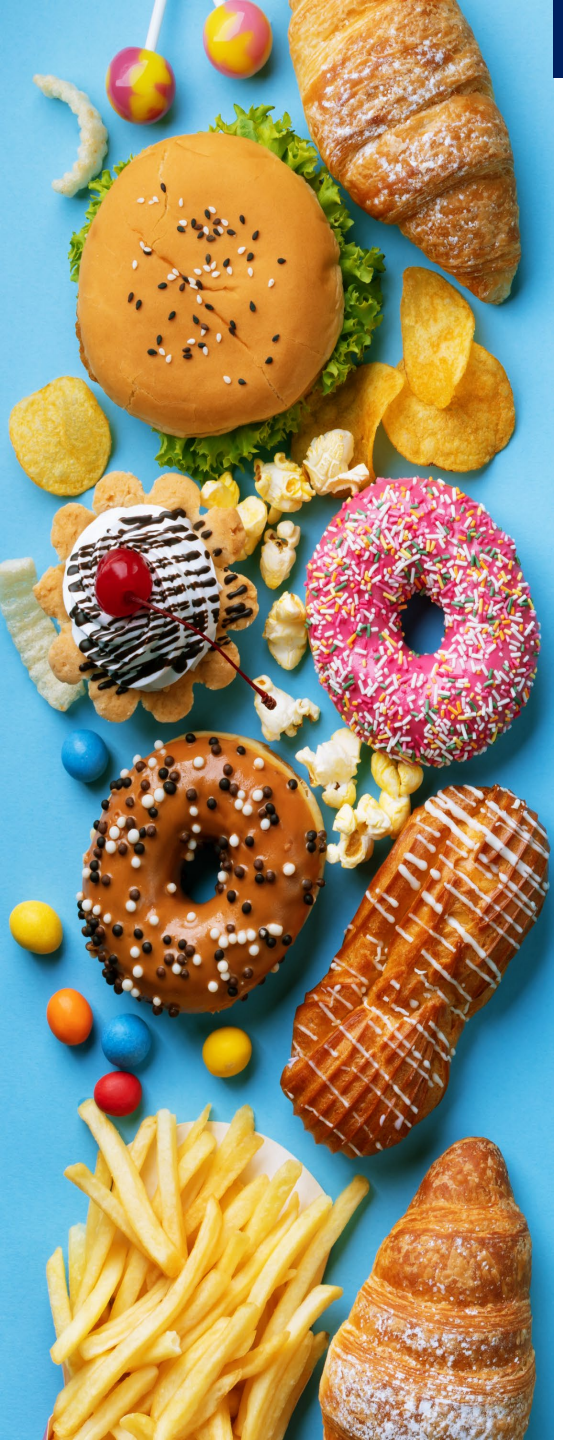


Higher fibrosis



- 800 patients
- Food frequency questionnaire
- Non-invasive test for fatty liver and fibrosis

Ivancovsky-Wajcman D, *et al.* Liver Int 2021.

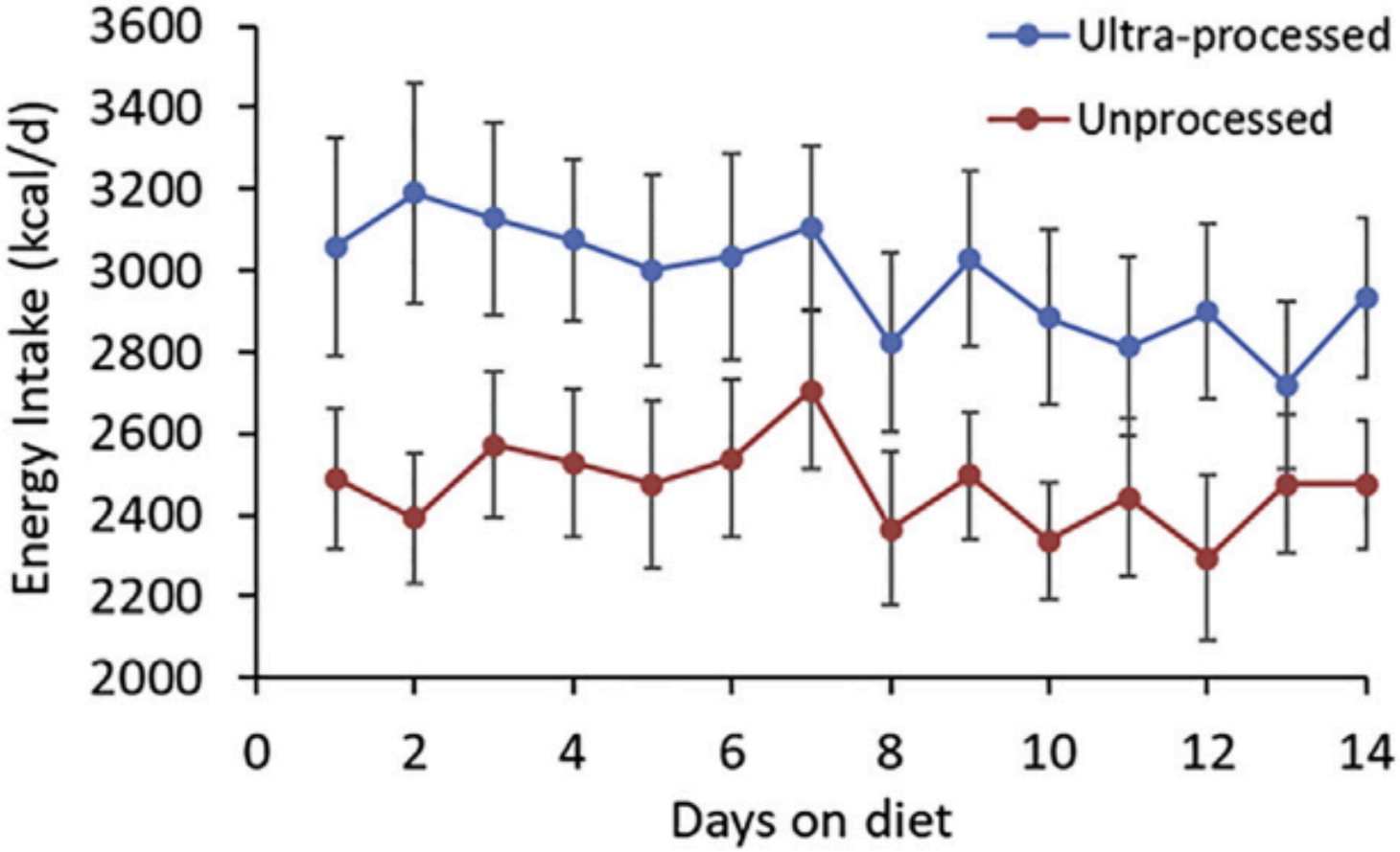


Ad-libitum diet study

- 20 healthy men and women
  - Mean age 31 years
  - Mean BMI 27 kg/m^2
- NIH Metabolic Clinical Research Unit
  - 2 weeks
- Randomized to *ad libitum* diets
  - Ultra-processed
  - Not ultra-processed

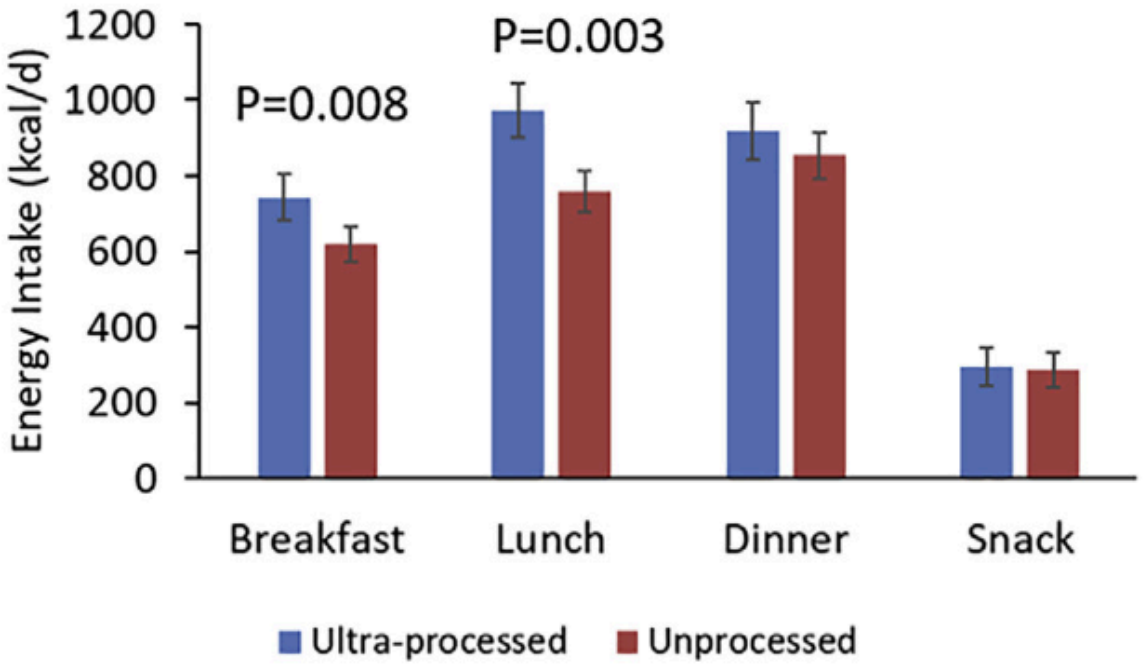
Hall, Cell Metabolism 2019.

Ultra-processed dieters ate more calories…



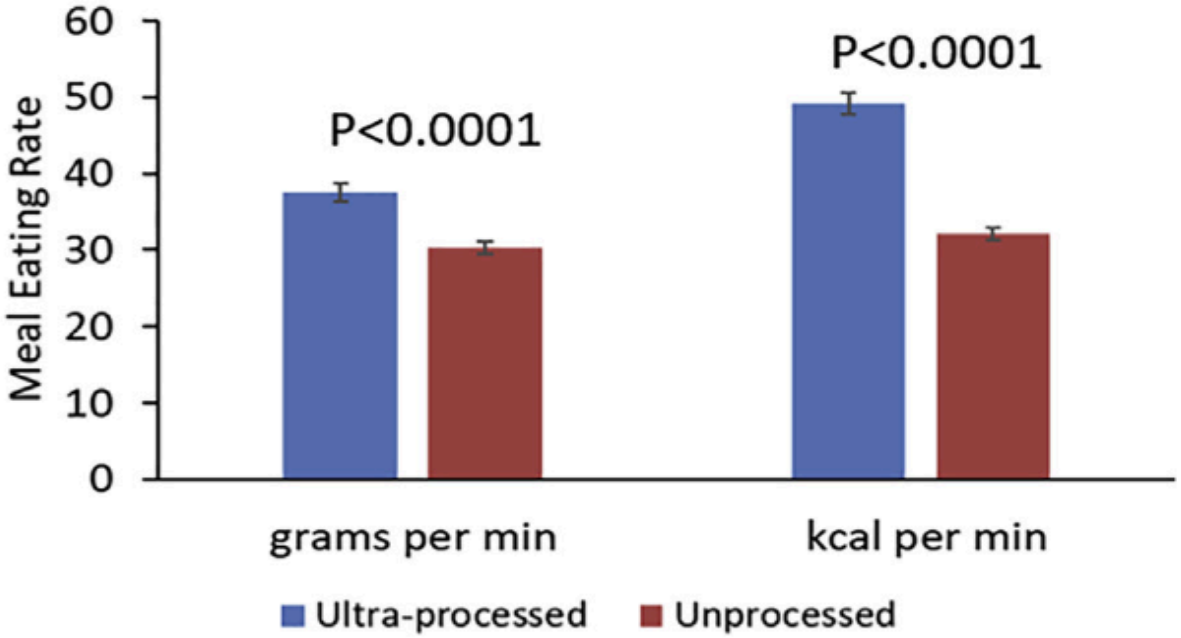
Hall, Cell Metabolism 2019.

Evidence



...at breakfast/lunch

...and more efficiently



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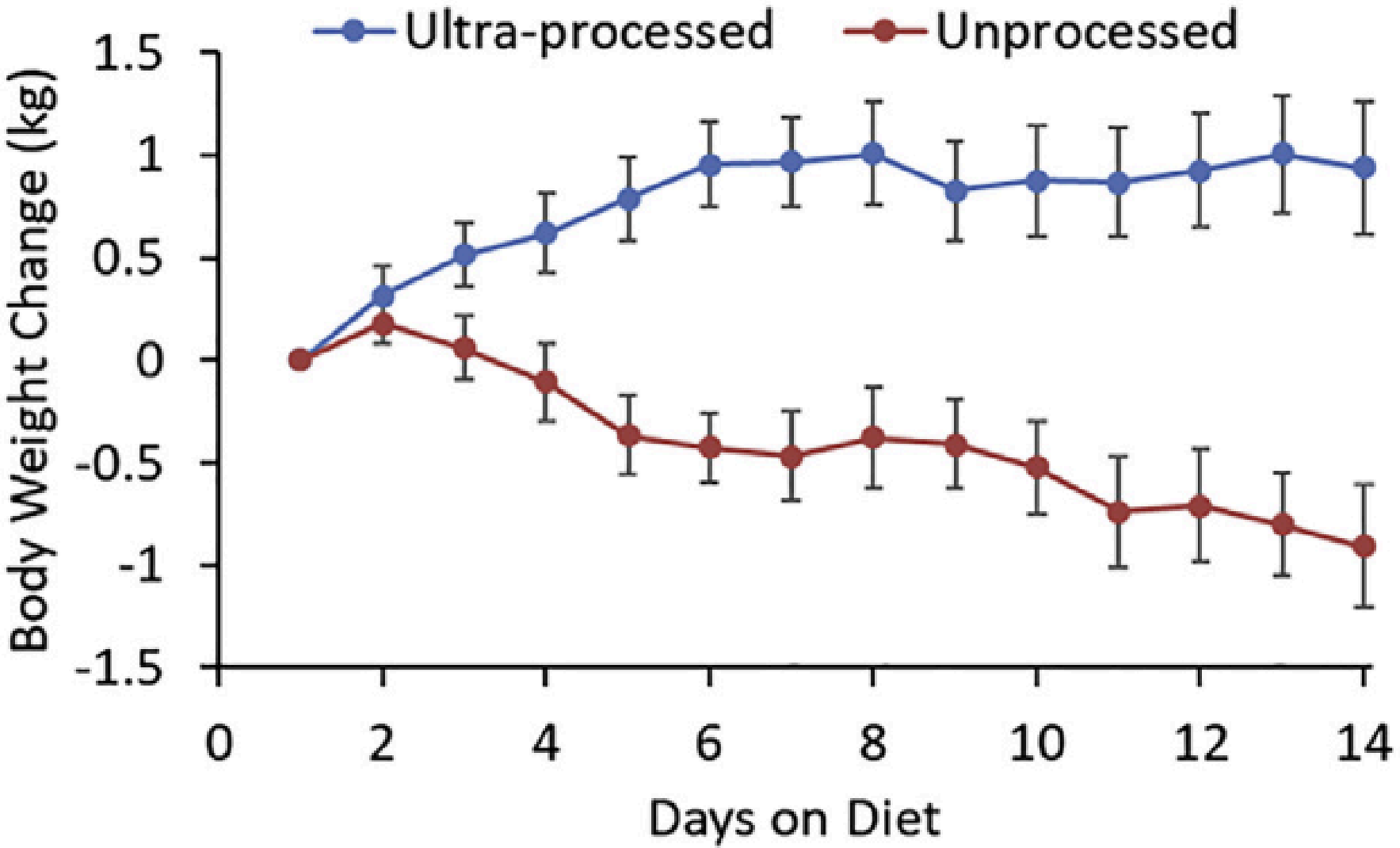
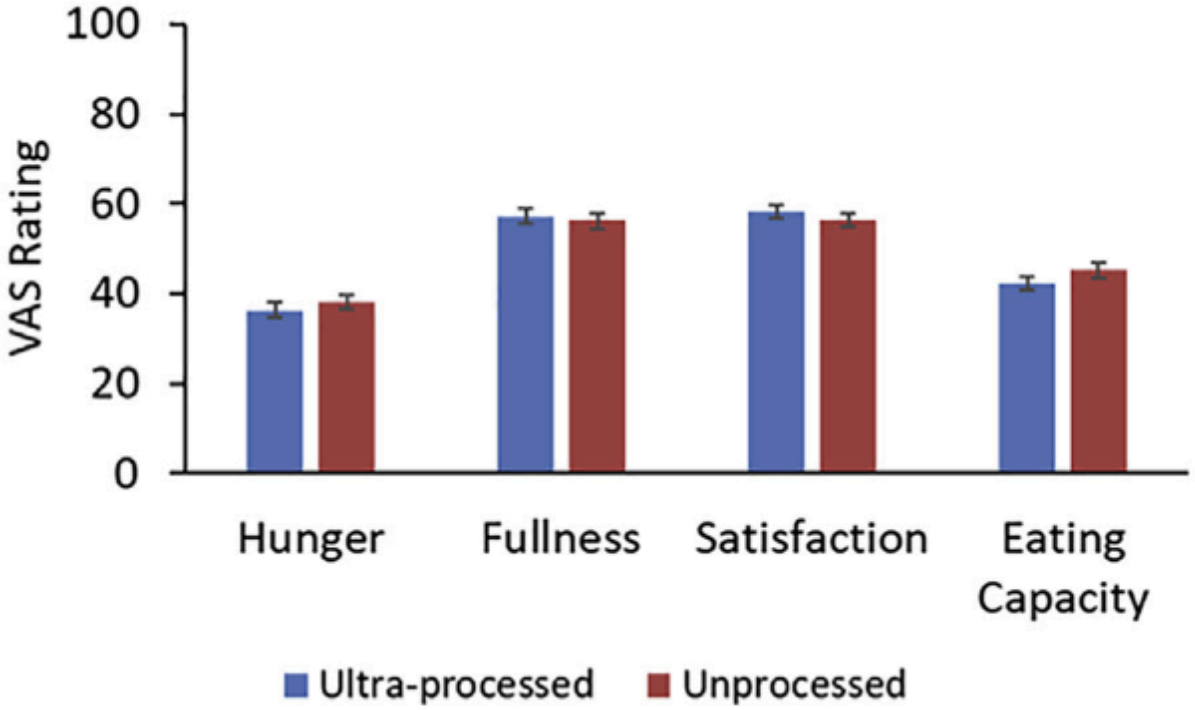
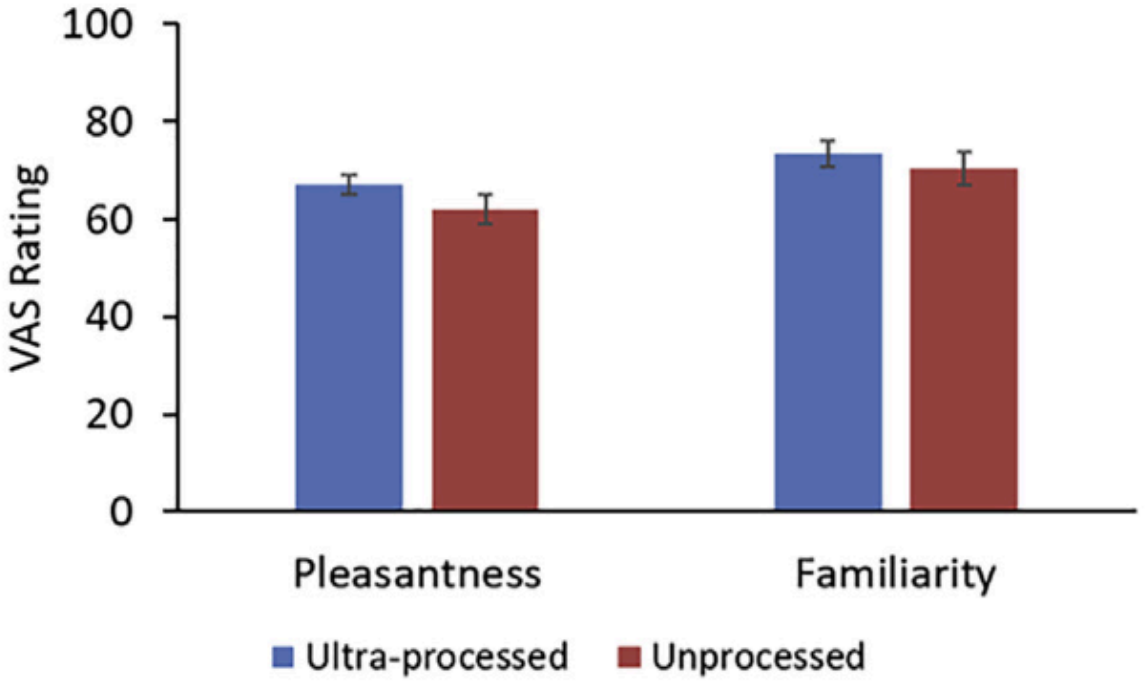


Hall, Cell Metabolism 2019.

Patient-reported measures were similar

Appetitive measures, pleasantness, and familiarity





Hall, Cell Metabolism 2019.

Fast-food diet study

- 18 healthy men and women
- Asked to eat 2 fast food meals per day for 2 weeks
- Alcohol consumption maintained at baseline

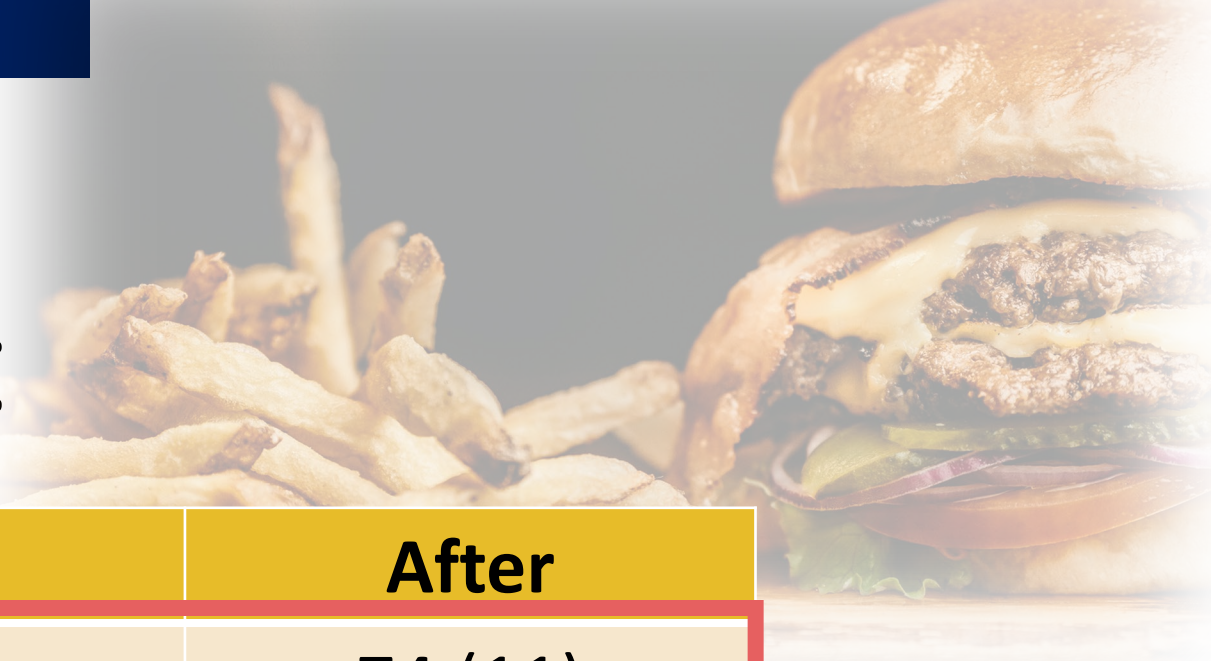
Kechagias, Gut 2008.

Food composition

	Before	Fast food diet
Total kcal	2273	5753
Energy from fat	36%	43%
Energy from carbohydrate	48%	45%
Energy from protein	16%	12%
Saturated fat, g/day	33 g	111 g
Sugar	95 g	285 g
Fiber	26 g	37 g

Kechagias, Gut 2008.

Changes before and after the fast food diet



	Before	After
Weight, kg	68 (9)	74 (11)
BMI, kg/m^2	22 (2)	24 (2)
ALT	22 (2)	69 (76)
Hepatic triglyceride content by MRS	1.1% (1.9)	2.8% (4.8)
Body fat	20% (10)	24% (9)

Kechagias, Gut 2008.

Strategy to reduce consumption of ultra-processed foods

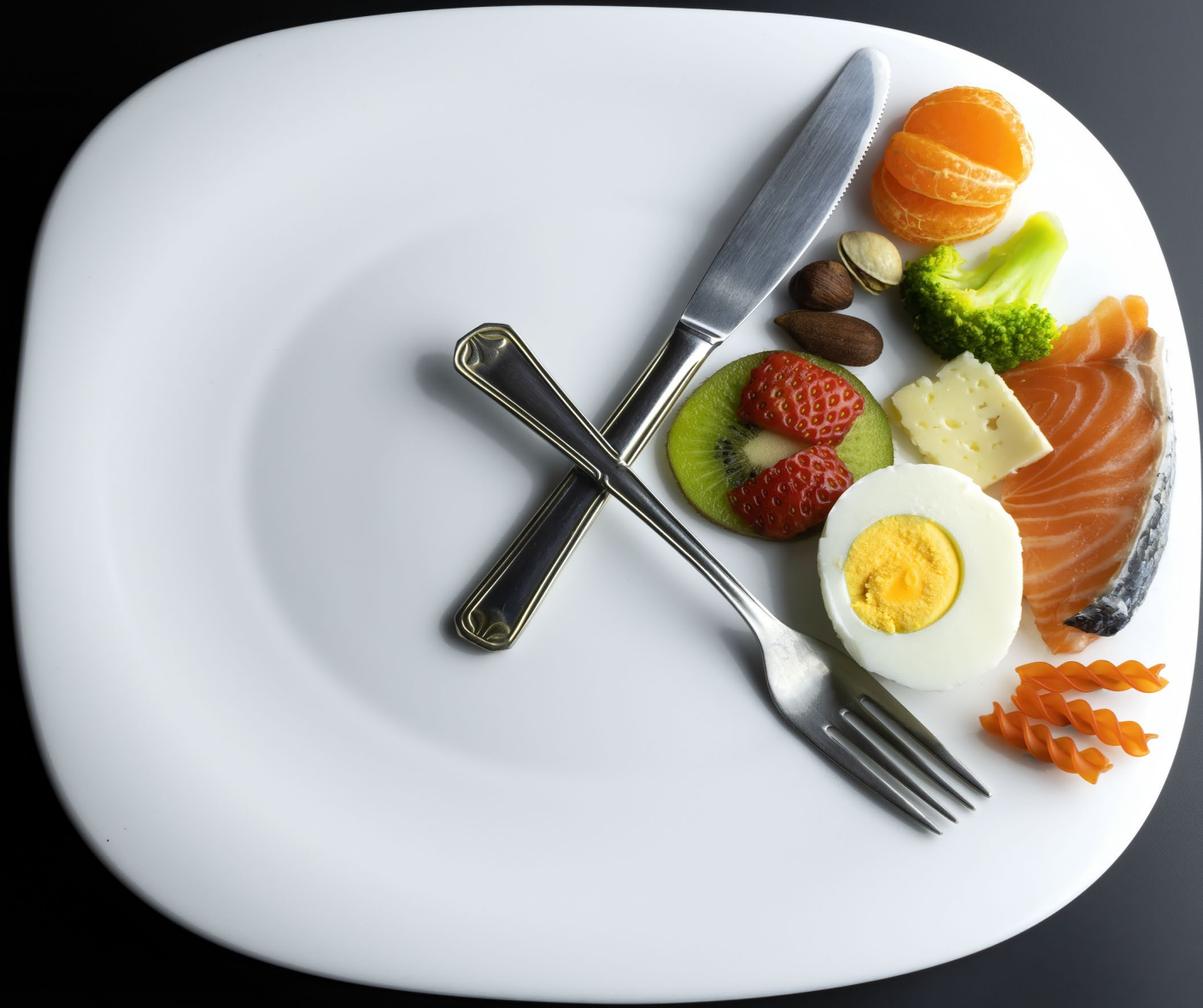
Eat from a bowl, not a bag

Can I recognize where this food came from?

Would my great-grandmother recognize this food?

Shop the perimeter

Timing



Intermittent Fasting

A pattern of meal timing schedules that cycle between voluntary fasting and non-fasting over a given period of time.

Intermittent Fasting

COMMON METHODS

ALTERNATE DAY FASTING

Severe restriction of calories every other day

E.g., Eating 500 calories every other day

5:2 METHOD

Eat only 500 calories 2 days a week, then normal diet the other 5 days a week

E.g., eat a 300 calorie meal + 200 calorie meal

TIME-RESTRICTED EATING

Voluntary fasting for at least 10 hours during set windows every day

E.g., 16/8, eating between 12-8pm

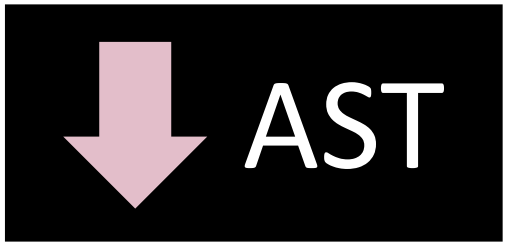
Meta-analysis

Intermittent Fasting vs. “non-fasting” in patients with NAFLD

6 studies
417 patients

- Modest reduction in body weight
  Mean difference -2.45 kg (-3.98 to -0.91)
- BMI -0.50 kg/m2 (-0.93 to -0.07)

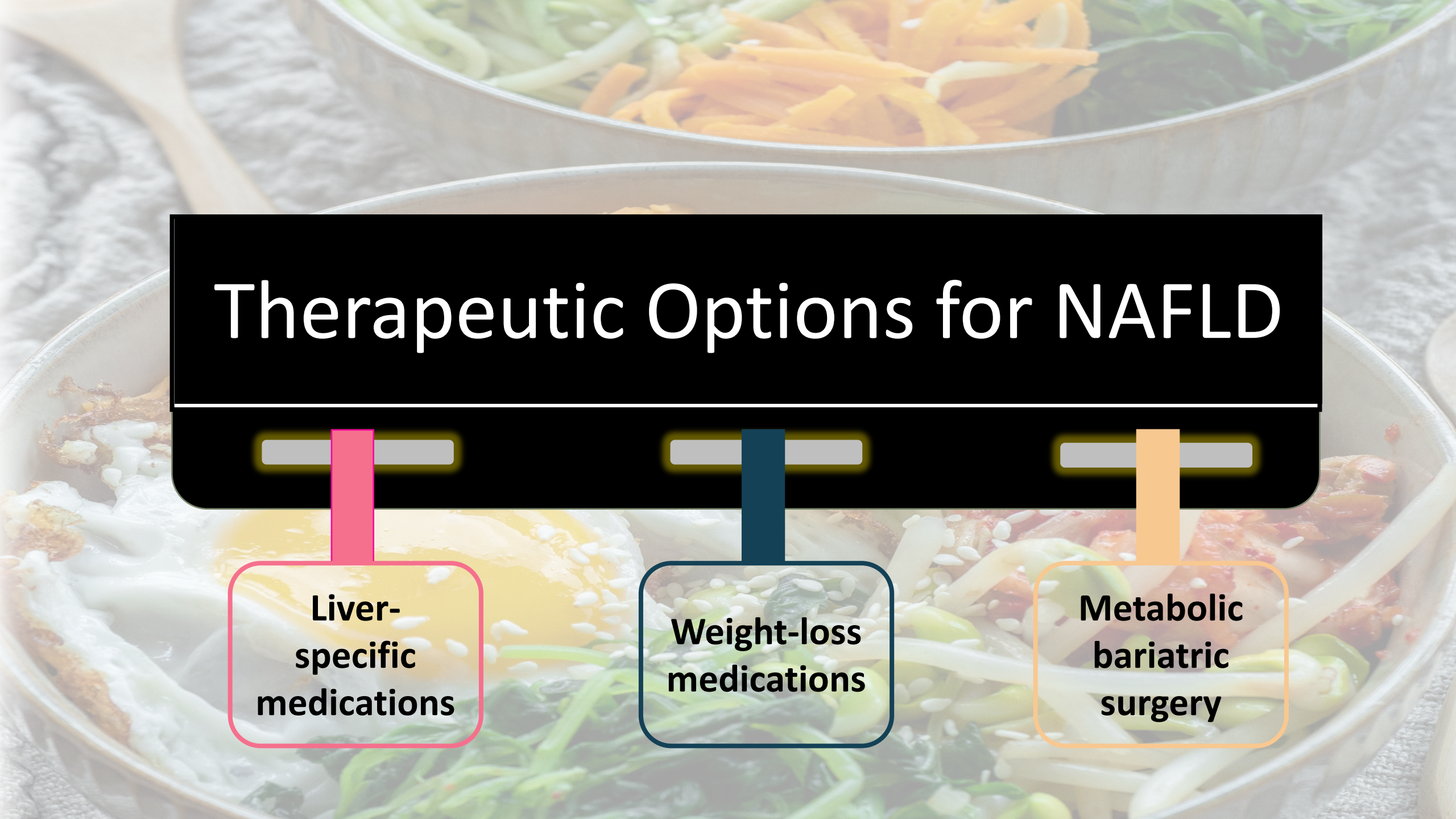
Mean difference
-11 (-14 to -7)



Mean difference
-11 (-14 to -8)

No significant difference in metabolic parameters
(waist circumference, fasting glucose, HOMA-IR, cholesterol)

Yin C, Front Nutr 2021


Therapeutic Options for NAFLD
Liver-specific medications
Weight-loss medications
Metabolic bariatric surgery

More information

https://www.youtube.com/watch?v=nRDgNxQmBIo