2019 12th Paris Hepatology Conference

PHC 2019
14 & 15 January 2019
PARIS - Palais des Congrès

International Conference
on the Management of Liver Diseases

NAFLD/NASH:
Is change of lifestyle councelling efficient?

Prof. Elisabetta Bugianesi MD, PhD
Division of Gastro-Hepatology,
University of Turin, Italy.

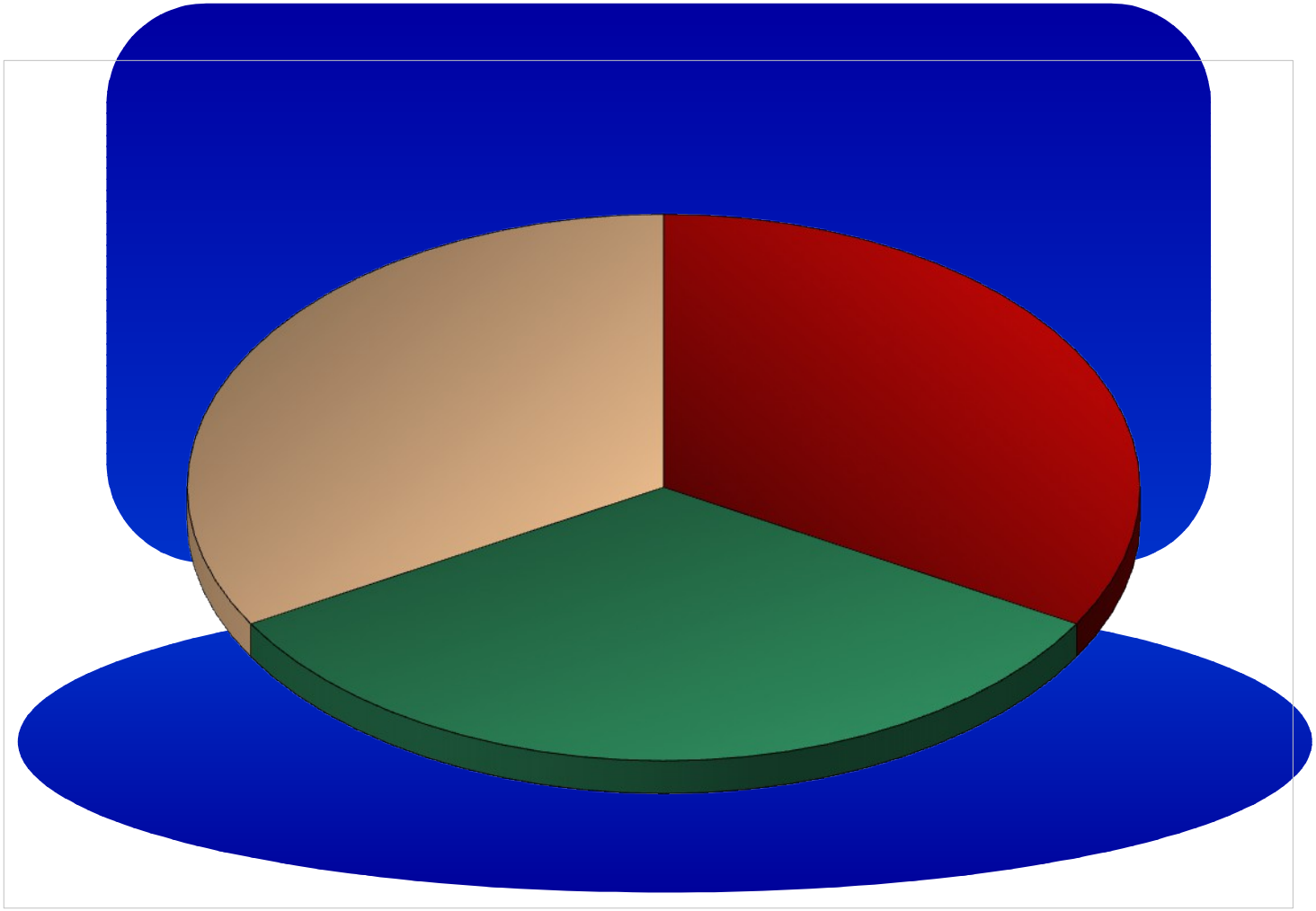
Disclosures

Consulting:

Boehringer Ingelheim, Genfit, GILEAD

Intercept, IBSA, Innova

Lifestyle Modification: three key components

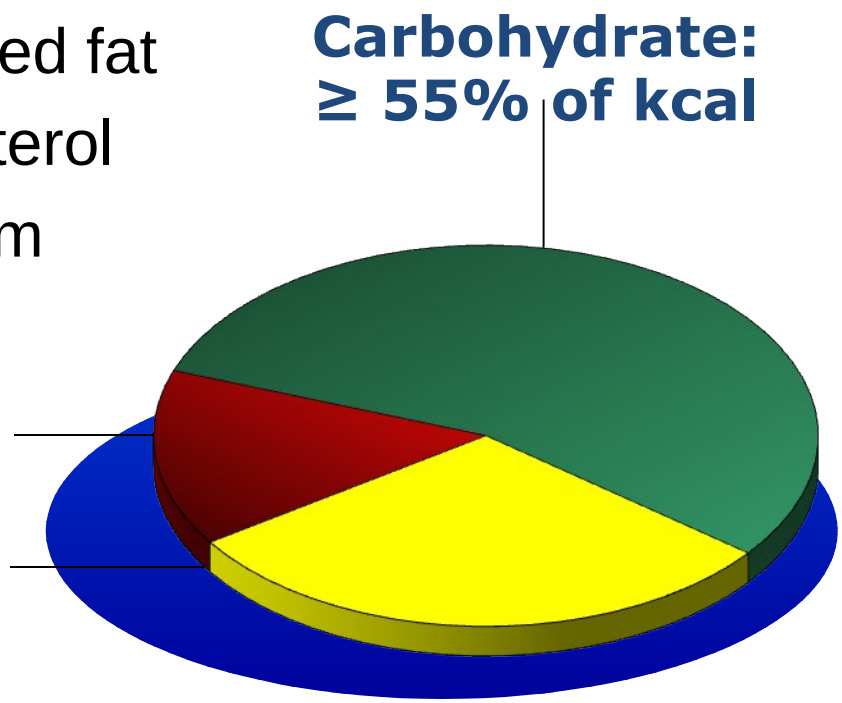


1. Dietary Recommendations

- Reduce intake by 500–1000 kcal/day to lose 0.5–1.0 kg/wk
- Balanced deficit diet with:
  - ≤ 10% kcal from saturated fat
  - < 300 mg/day of cholesterol
  - ≤ 2400 mg/day of sodium
  - ≥ 20–30 g/day of fiber

Protein: ~ 15% of kcal

Fat: ≤ 30% of kcal



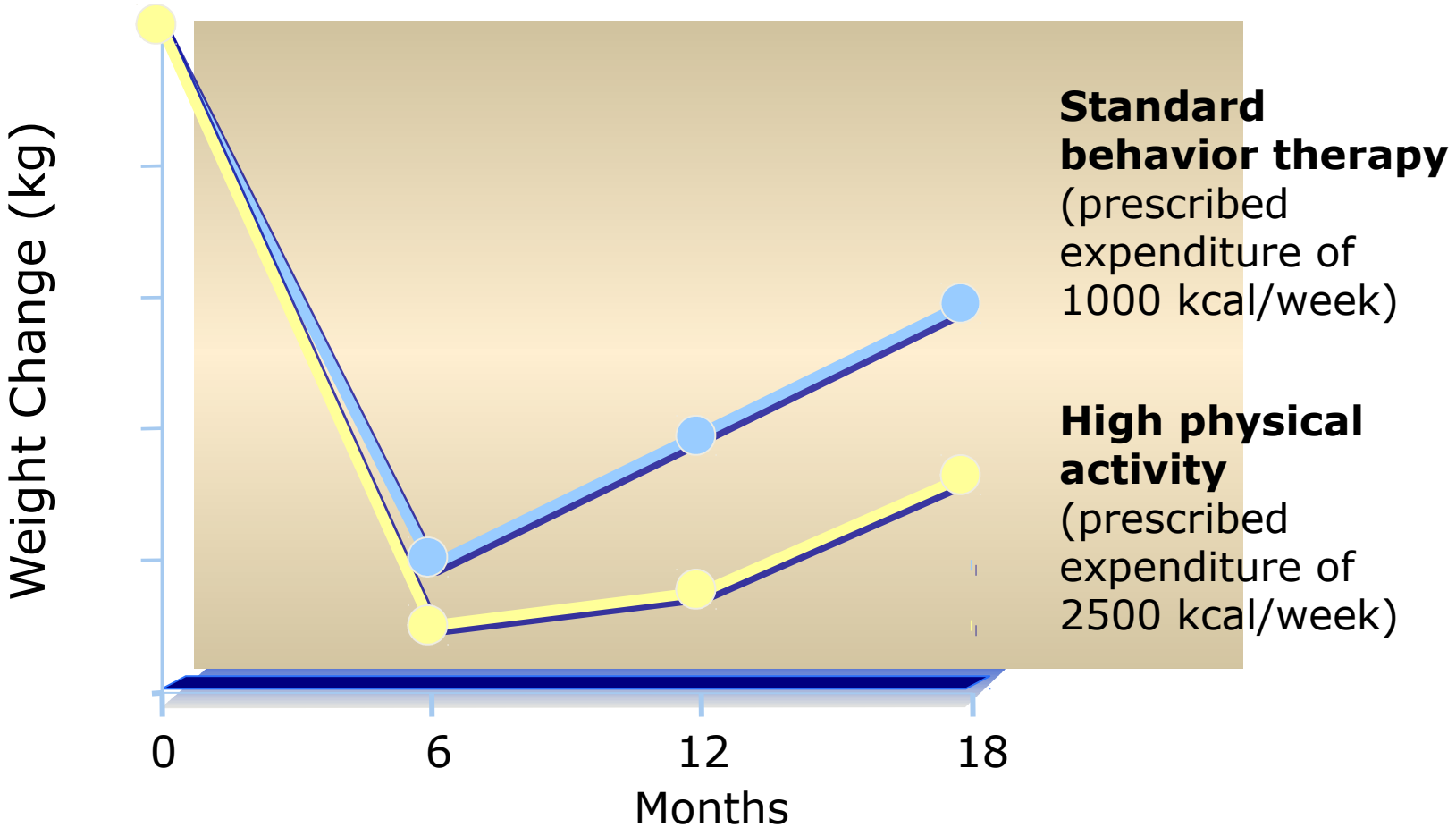
NIH/NHLBI, NAASO. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* Bethesda, MD: NIH, 2000.

2. Physical exercise recommendations

- Moderate-to-vigorous exercise for at least 60 minutes on most days (at least 5 days per week)
- Walking is preferred exercise
  - Target value of 10,000-12,000 steps per day
- Jogging (20-40 min/day), biking or swimming (45-60 min/day) may replace walking.

Physical exercise is intended to produce a calorie deficit of at least 400 kcal/day, favoring weight loss, maintaining muscle mass and preventing weight cycling.

Higher Physical Activity Goals Enhance Long-Term Weight Control



Jeffery RW et al. *Am J Clin Nutr* 2003;78:684-689.

3. Behavior Therapy

Use of psychological techniques to modify maladaptive behaviors

Behavioral techniques :

- ‘Goal Setting’: specific goals, objective measurements.
- Self-monitoring (regular feedback eg: food diary..)
- Stimulus control (move away from barriers to change eg: sources of bad food!)

Butryn et al, Psych Clin North Am 2011

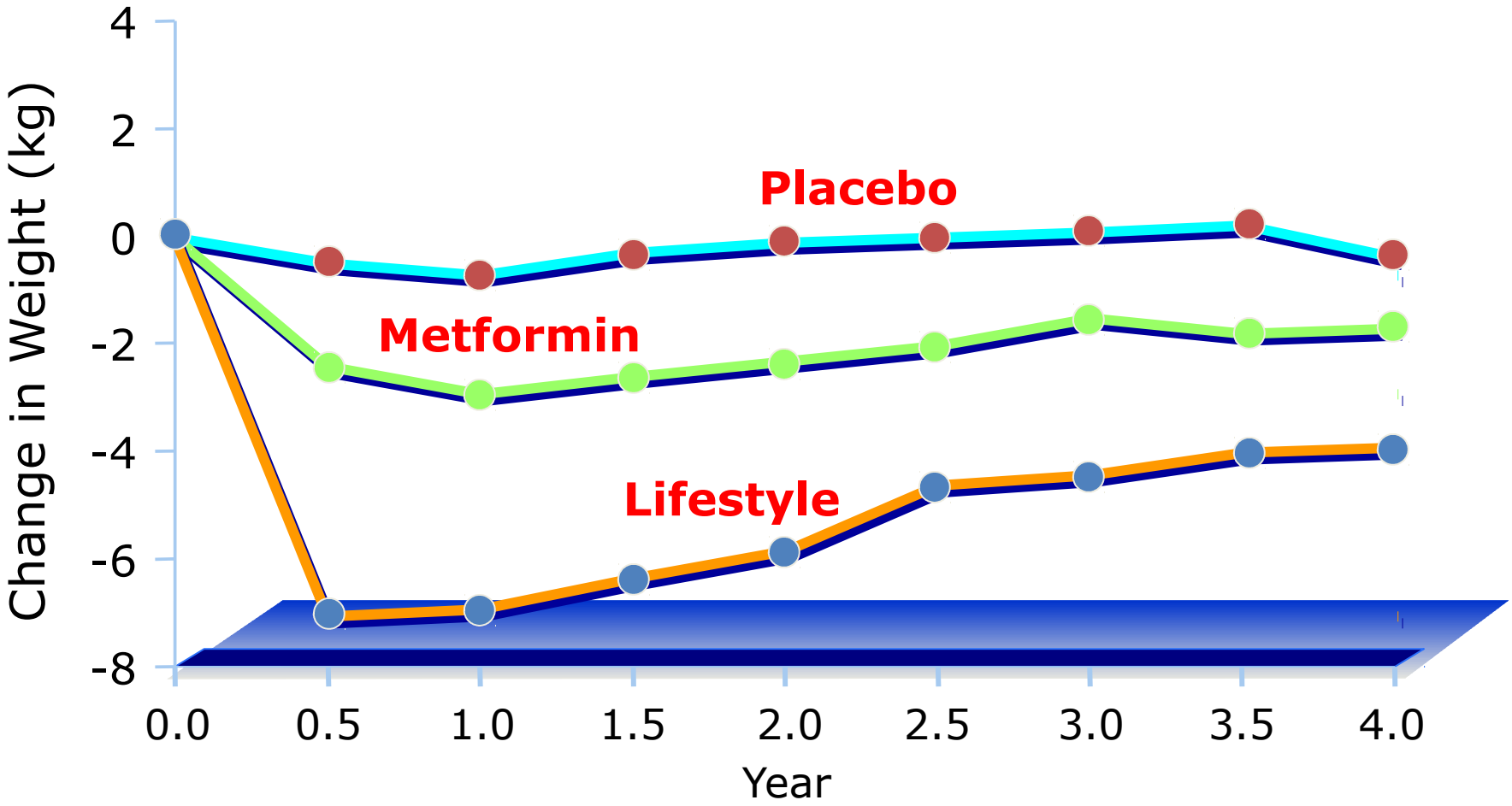
Ways of delivering Lfestyle modifications:

- Groups (10-20 patients) Wadden TA, Foster GD. *Med Clin North Am* 2000.
- Individually with Case Managers The DPP Research Group. *Diabetes Care* 2002.
- Multidisciplinary not eclectic team Bellentani, et al. Hepatology. 2008
    - *Physician :* Assessment, management of medical

Diabetes Prevention Program [NEJM, 2002]

- 3234 overweight pts wt IGT [Defn: fasting BGL 95-125 mg/dL and 2-hour BGL 140-199 mg/dL on OGTT]
- 3 groups: intensive Lifestyle Intervention (LI), metformin daily, control.
- **Initial 3.2 yr F/U**: reduced diabetes incidence by **58% LI** and **31% metformin**, versus placebo.
- **Further 7 years of group-based "quarterly lifestyle advice" provided to <u>all</u> groups – F/U at 10 yrs:** diabetes reduced by **34% in original LI** and 18% original Metformin, versus control. [Lancet, 2009]

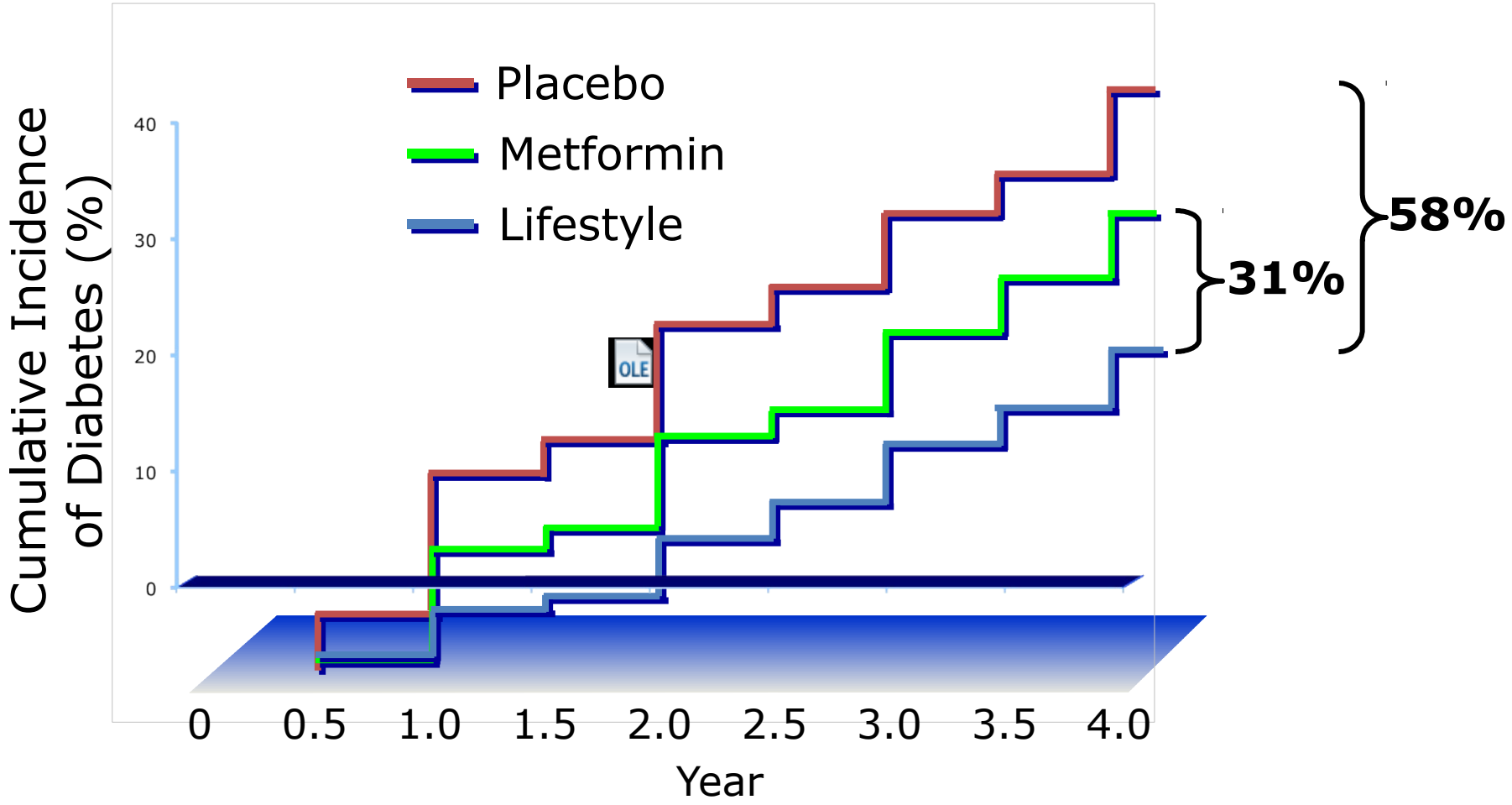
Diabetes Prevention Program: *Weight Loss*



Diabetes Prevention Program Research Group.

N Engl J Med 2002;346:393-403.

Diabetes Prevention Program: *Incidence of Diabetes*



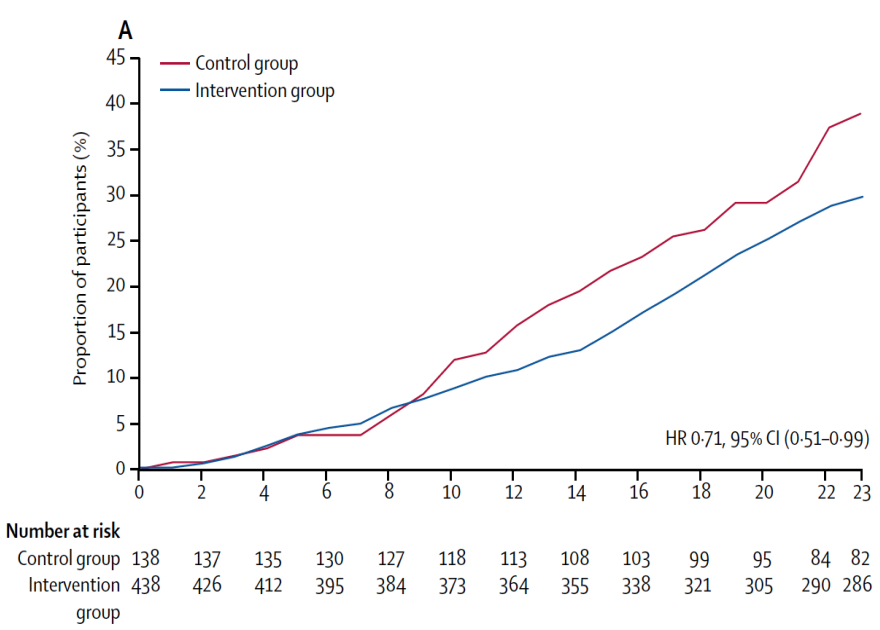
Diabetes Prevention Program Research Group.

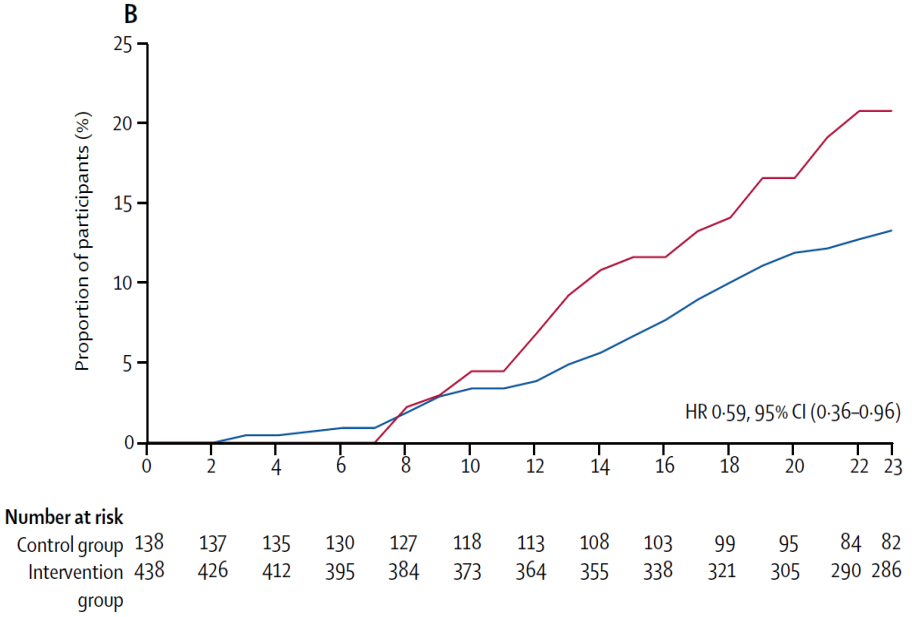
N Engl J Med 2002;346:393-403.

Da Qing Diabetes Prevention Study

[Diabetes Care, 1997]

- 577 Chinese pts, 33 clinics across Da Qing province
- Standard advice, or LI (Ex, Diet, Diet+Ex) over 6 years.
- 20-Yr FU (94% recall!): diabetes incidence 93% vs 80%.
- **23-Yr FU: reduced all-cause, and CVS-related mortality**





[Li et al; Lancet, 2011]

[Li et al; Lancet Diabetes Endocrinol, 2014]

Current guidelines for NAFLD treatment

Lifestyle Interventions

- **Weight Loss 5%–10% of body weight**

Pioglitazone 30–45 mg/day

Vitamin E 800 U/day

- No long-term data on these interventions and clinical outcomes
- No FDA- or EMA-approved therapy

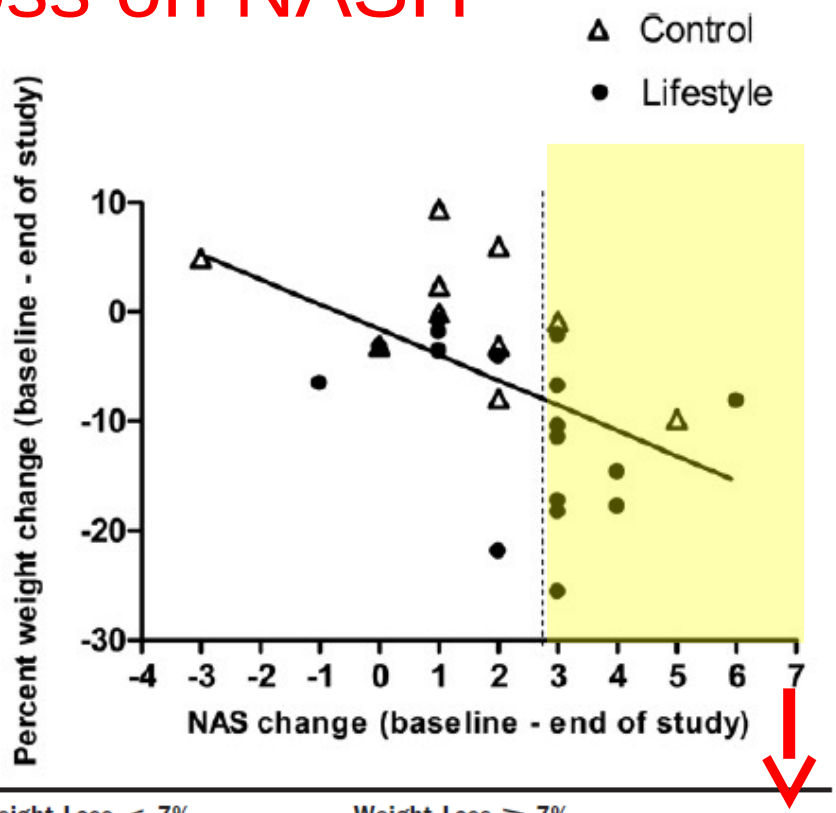
Abbreviations: EMA, European Medical Agency; FDA, U.S. Food and Drug Administration; NASH, nonalcoholic steatohepatitis.

Chalasani N, et al. *Hepatology.* 2012;55:2005-2023.

Studies based on Lifestyle Intervention: Effects of weight loss on NASH

Variable	Group	Baseline	End of Study	*P* Value†
Fat (0-3)	Control	1.9 (0.9)	1.6 (1.0)	0.02
	LS	1.9 (0.7)	0.8 (0.9)	
Parenchymal inflammation (0-3)	Control	1.7 (0.8)	1.3 (0.8)	0.18
	LS	1.4 (0.6)	0.9 (0.5)	
Ballooning injury (0-2)	Control	1.3 (0.5)	0.6 (0.7)	0.22
	LS	1.2 (0.5)	0.3 (0.6)	
Fibrosis (0-4)	Control	1.7 (0.8)	1.4 (1.3)	0.62
	LS	1.4 (1.1)	1.4 (1.0)	
NAS (0-8)	Control	4.9 (1.0)	3.5 (1.8)	0.05
	LS	4.4 (1.1)	2.0 (1.5)	

*Control group, N = 10; LS group, N = 18.
Data expressed as mean (SD).
†*P* value compares the mean difference between the pretreatment and post-treatment changes in the variables between the two groups.



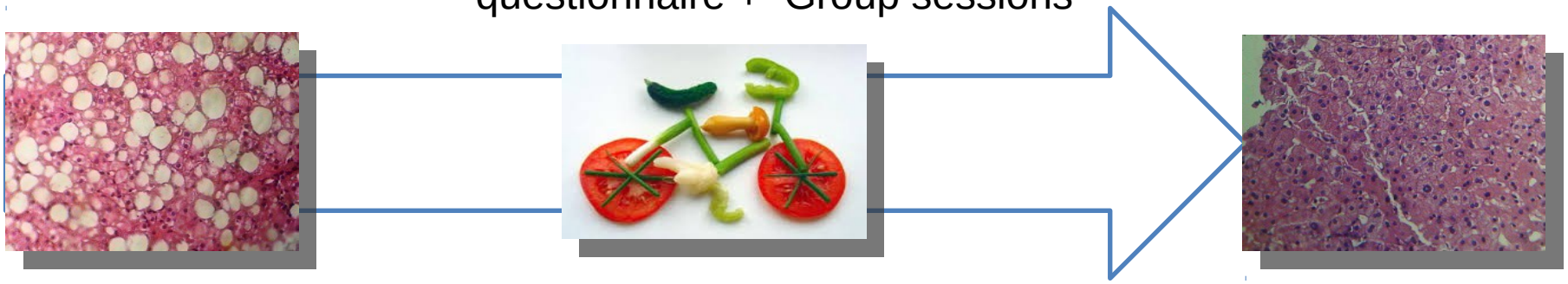
Variable	Weight Loss < 7% (n = 17)	Weight Loss ≥ 7% (n = 11)	*P* Values
Histological parameters			
Fat (0-3)	-0.41 (0.80)	-1.36 (0.67)	<0.001
Lobular inflammation (0-3)	-0.24 (0.75)	-0.82 (0.75)	0.03
Ballooning injury (0-2)	-0.53 (0.80)	-1.27 (0.47)	0.03
Fibrosis (0-4)	+ 0.06 (0.83)	-0.45 (0.93)	0.10
NAS (0-8)	-1.18 (1.59)	-3.45 (1.21)	<0.001
Participants with ≥3 points' improvement in NAS from baseline, N (%)	4 (23.5)	9 (81.8)	0.003
Participants with NAS ≤2 at follow-up, N (%)	4 (23.5)	10 (90.9)	<0.001

Promrat et al., HEPATOLOGY 2010;51:121-129

Weight Loss via Lifestyle Intervention Significantly Reduces Features of Nonalcoholic Steatohepatitis

N=293 NASH proven patients

Low-fat hypocaloric diet + walking 200 min/week + questionnaire + Group sessions



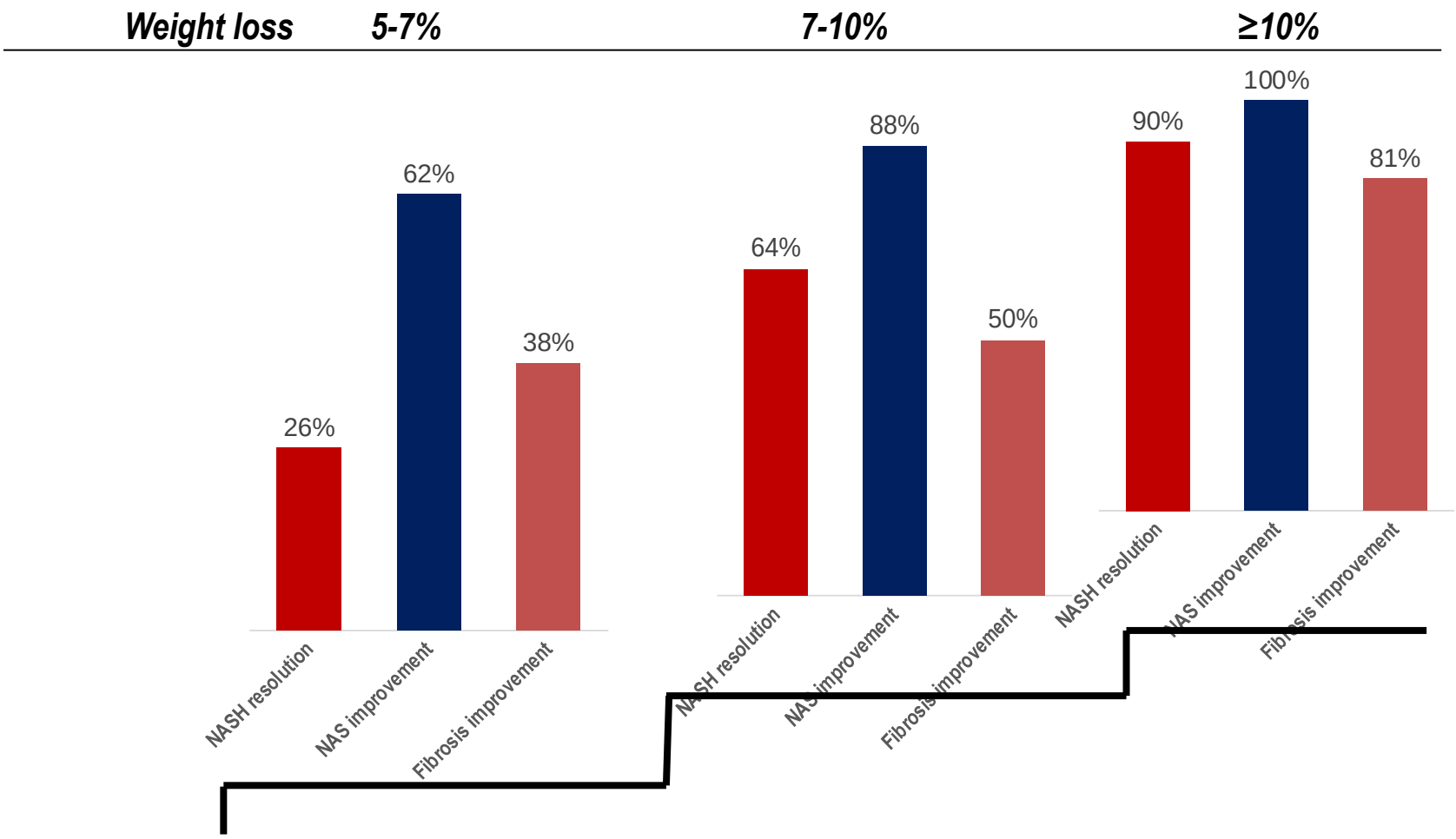
End-point: NASH resolution w/o fibrosis worsening

Conclusion:

WL between 7-10% may improve NAS score and their components.

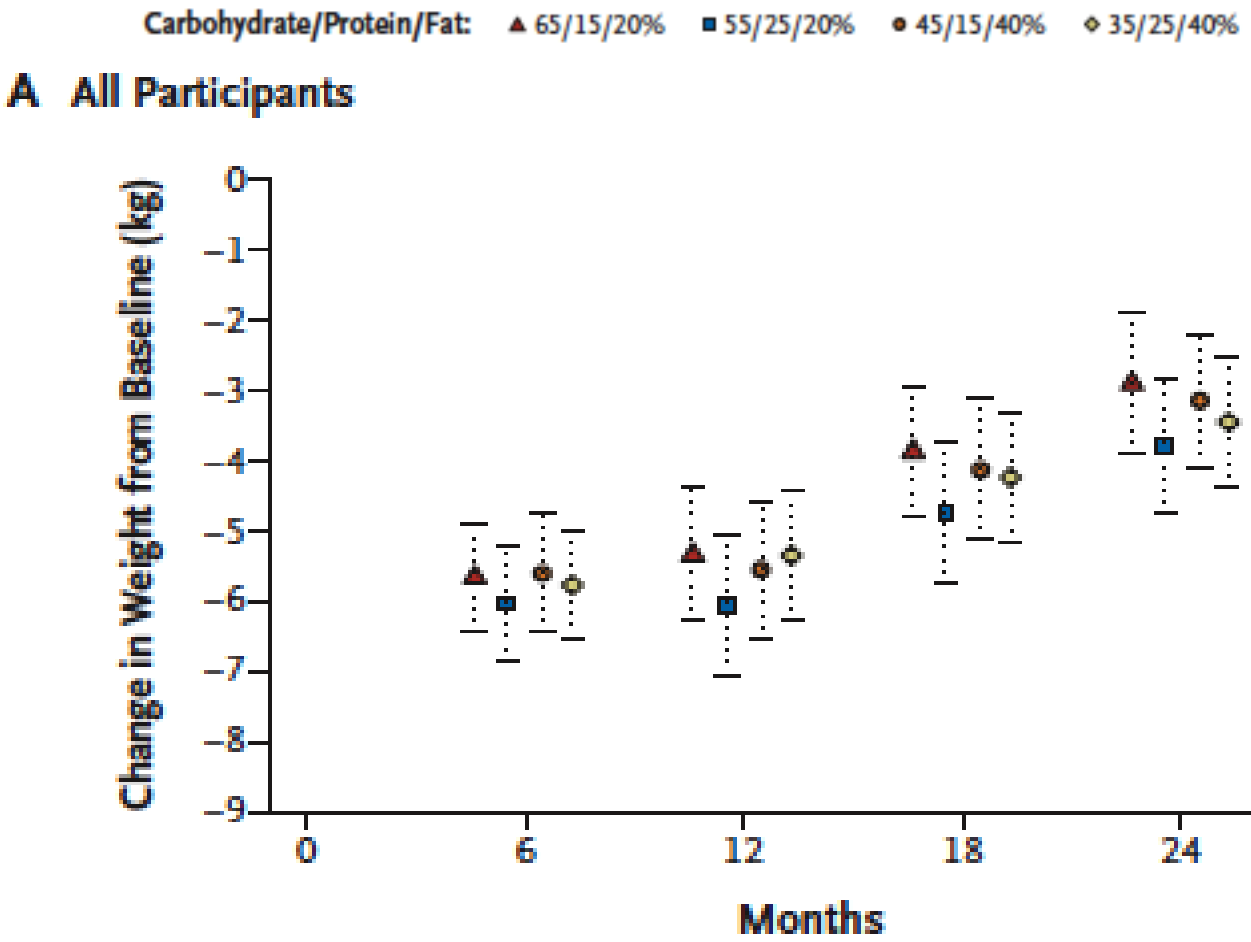
Vilar-Gomez et al, Gastroenterology 2015

Impact in liver histology based on weight loss percentage



Vilar-Gomez, Romero-Gomez, Gastroenterology 2015

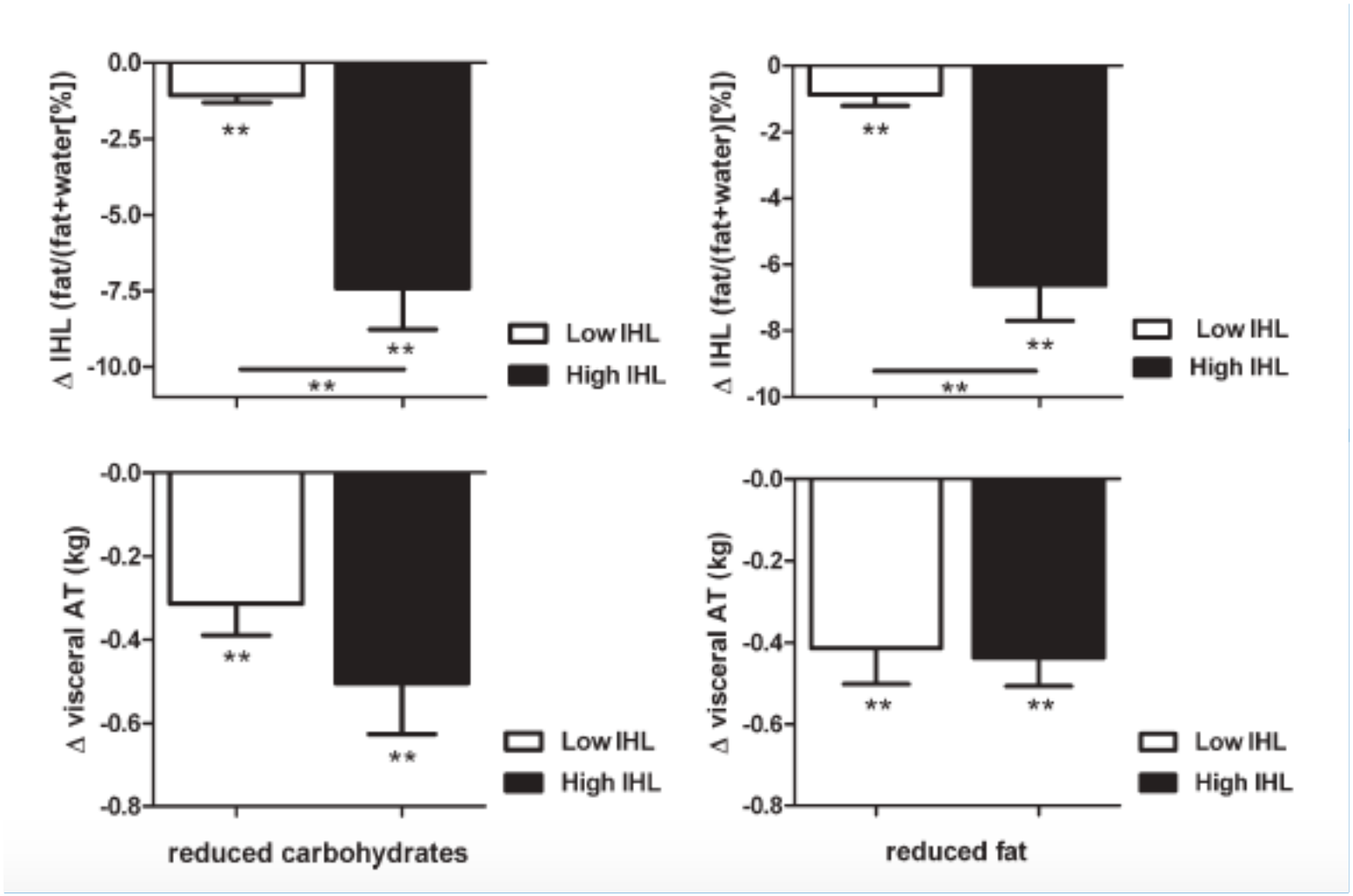
Nutrient composition and Wt loss



N=811 overweight adults
Satiety, hunger, satisfaction with diets, attendance at group sessions: similar across diets

Sacks et al NEJM 2009;360:859-73

Effect of low carb vs low fat diet on intrahepatic and visceral fat

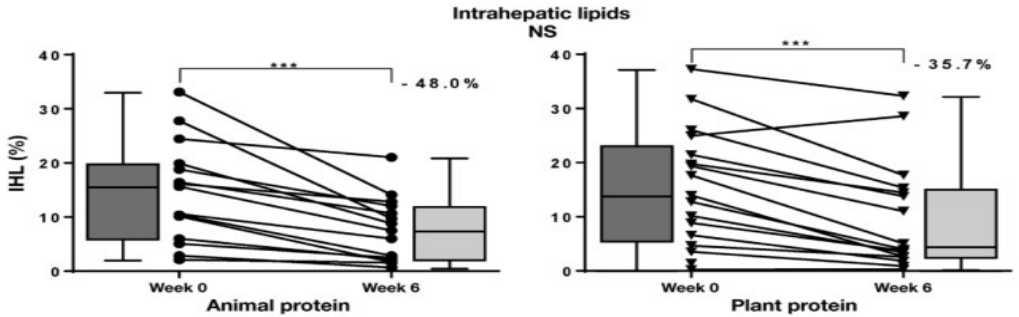


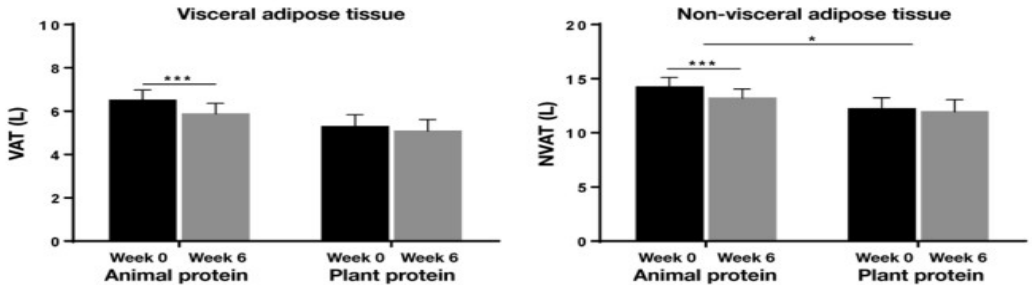
Haufe et al Hepatology 2011

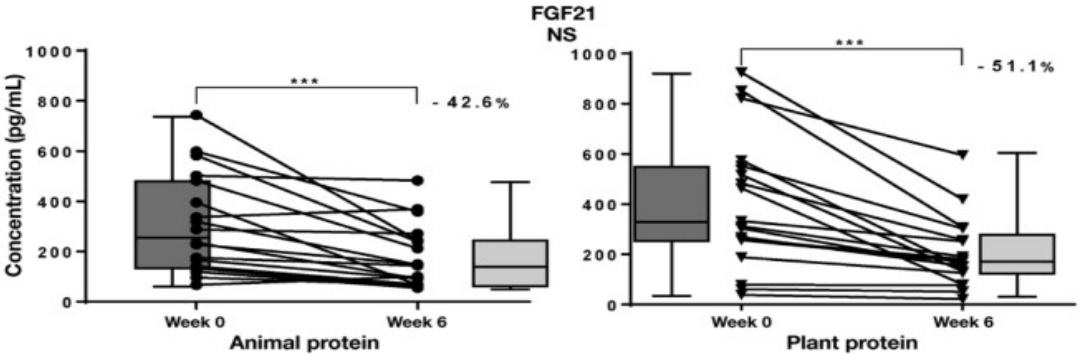
Gastroenterology 2017;152:571–585

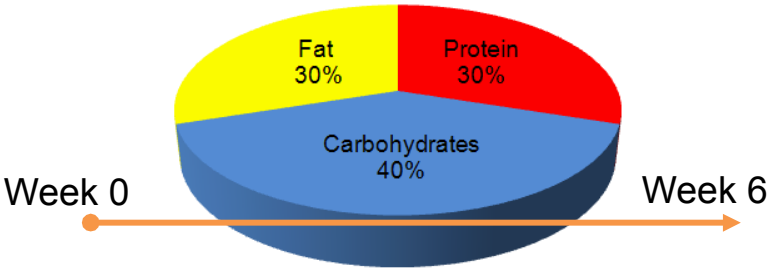
Isocaloric Diets High in Animal or Plant Protein Reduce Liver Fat and Inflammation in Individuals With Type 2 Diabetes

Mariya Markova,[1,2,*] **Olga Pivovarova**,[1,2,3,*] Silke Hornemann,[1,2] Stephanie Sucher,[1,2] Turid Frahnow,[1,2] Katrin Wegner,[4] Jürgen Machann,[2,5,6] Klaus Jürgen Petzke,[1] Johannes Hierholzer,[7] Ralf Lichtinghagen,[8] Christian Herder,[2,9] Maren Carstensen-Kirberg,[2,9] Michael Roden,[2,9,10] Natalia Rudovich,[1,2,3] Susanne Klaus,[1] Ralph Thomann,[11] Rosemarie Schneeweiss,[12] Sascha Rohn,[4,12] and Andreas F. H. Pfeiffer[1,2,3]









Intrahepatic lipids content assessed by MRS significantly decreases in both diets

VF and non-VF significantly decreases only after 6w high-APs diet

The decrease of FGF21 plasma levels, is related to the decrease of intrahepatic lipids content

Markova M et al. *Gastroenterology* 2017

Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease[1–3]

Fare clic per modificare lo stile del titolo

Angela M Zivkovic, J Bruce German, and Arun J Sanyal

Effects of diets on selected indexes important to patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)[1]

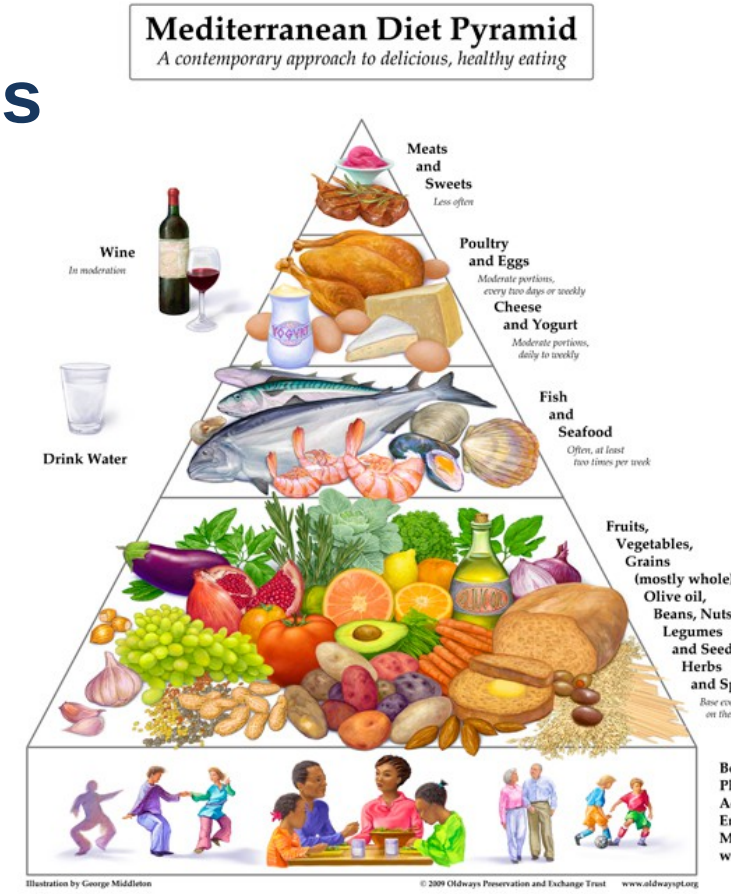
Diet	Weight	Waist circumference	Steatosis	Insulin sensitivity[2]	DNL	Inflammation[3]	TC	TG	HDL	LDL
USDA	↓	↓			↑		↓	↑		↓
AHA	↓	↓			↑	↓	↓	↑	↓	↓
NCEP Step I	↓	↓		↑	↑		↓	↑	↓	↓
DASH	↓	↓		↑	↑		↓	↑	↓	↓
TLC	↓	↓		↑	↑		↓	↑	↓	↓
American Diabetes Association	↓	↓		↑			↓			
American Dietetic Association	↓	↓		↑			↓			
Mediterranean	↓	↓	↓	↑	↓	↓	↓	↓	↑	↓
Ornish	↓	↓		↑	↑	↓	↓	↑	↓	↓
Atkins[4,5]	↓	↓	↑	↓	↓		↑	↓	↑	↑
Zone[5]	↓	↓		↑				↓		↓
South Beach[4,5]	↓	↓					↓	↓		↓
Weight Watchers	↓	↓		↑	↓	↓	↓	↓	↑	↓

Am J Clin Nutr 2007;86:285–300

The Mediterranean is superior to low fat diet in RCTs

High in

- Olive oil≥4 tbsp/day
- nuts handful/day
- Fish ≥3 /wk
- Legumes ≥3 /wk
- Fruits &Vegetables
- Fat - 40% /kcal, mostly MUFA and ω3 PUFA



Low in

- Soda drinks
- Sweets
- Red and processed meats
- Carbohydrate-40% /kcal

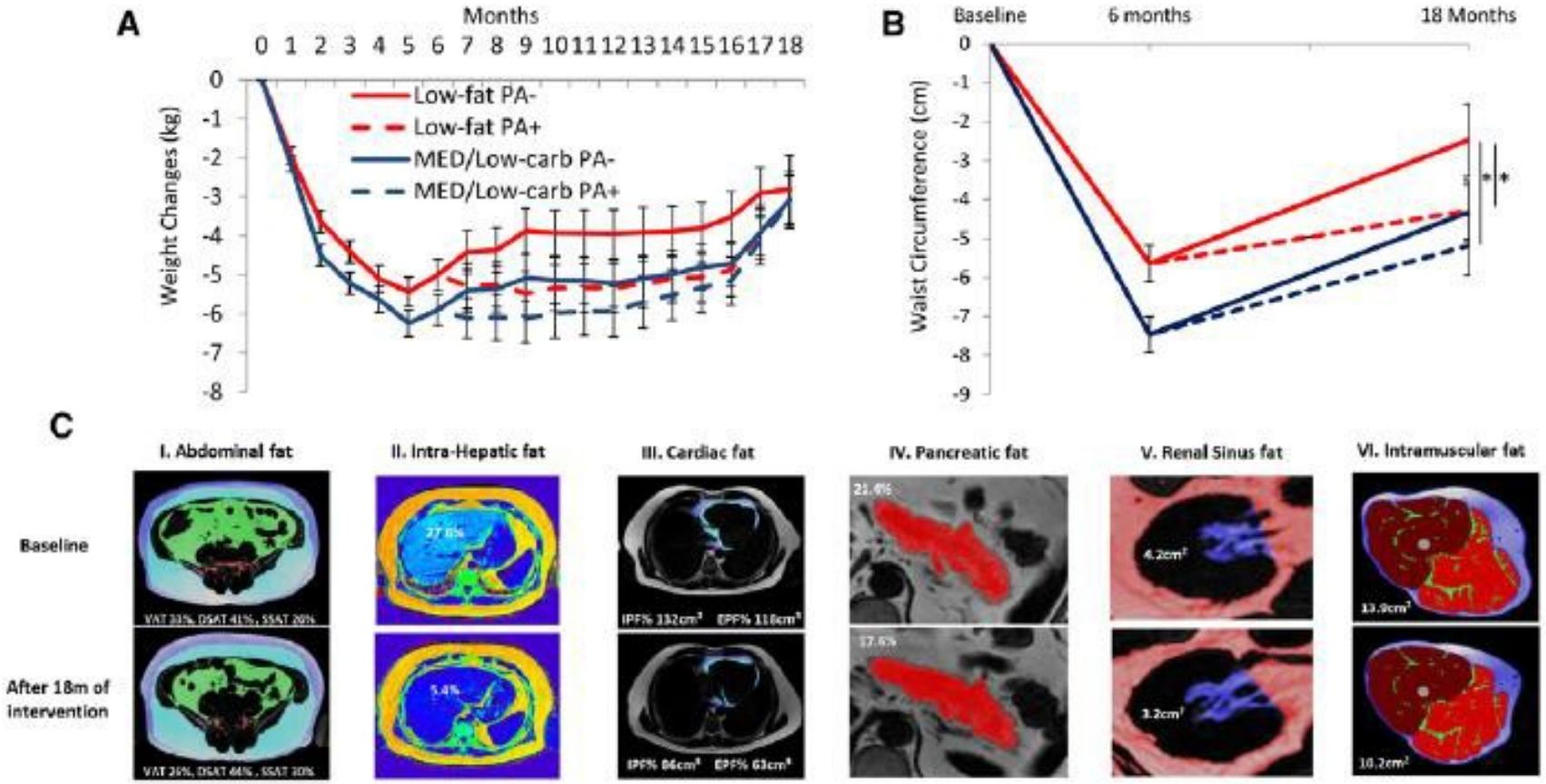
Salas-Salvadó J., Ann Intern Med 2014

Ryan MC., Journal of Hepatology 2013

Nordmann AJ., The American Journal of Medicine 2011

Estruch R., N Engl J Med 2013

Effect of Med Diet and exercise on fat depots



Mediterranean diet, rich in unsaturated fats and low in carbohydrates, is superior to the low-fat diet in mobilizing specific fat depots as hepatic, cardiac and pancreatic fat.

Gepner et al, Circulation 2018

Fructose as bad as Alcohol?

- It remains unclear whether fructose *causes* NAFLD
- Association between sweetened beverage intake and fibrosis in NAFLD *Abdelmalek Hepatology 2010*
- In adolescents:
  - high fructose intake in *obese* 14 year olds increased chances of having NAFLD at 17 years
  - this relationship was not seen in high fructose consuming *lean* 14 year olds *O'Sullivan J Pead Gas Nutr 2014*

Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: The Rotterdam study

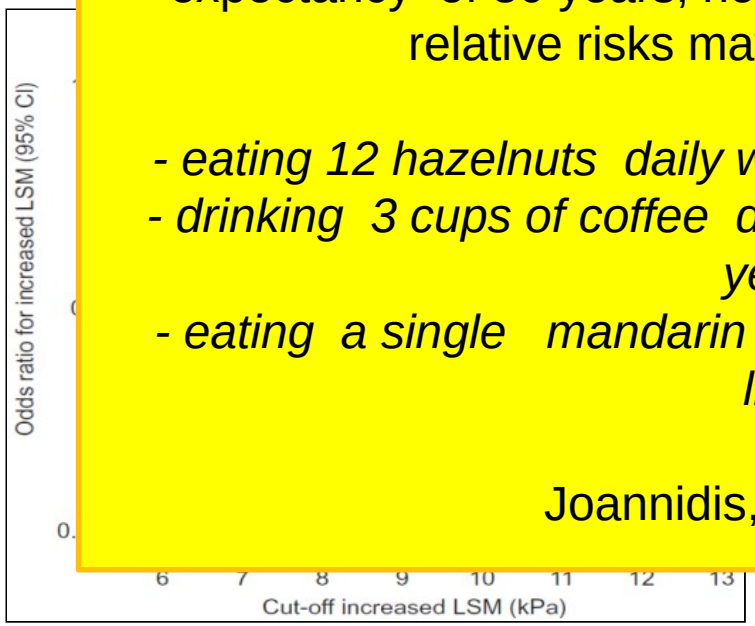
Louise J.M. Alferink[1], Juliana Fittipaldi[1,2], Jessica C. Kiefte-de Jong[2,3], Pavel Taimr[1], Bettina E. Hansen[1,4], Herold J. Metselaar[1], Josje D. Schoufour[2], M. Arfan Ikram[2,5,6], Harry L.A. Janssen[1,4], Oscar H. Franco[2], Sarwa Darwish Murad[1,*]

- Coffee and tea are emerging as promising nutraceuticals for liver health
- Both coffee and tea contain substantial amount of polyphenols, which have been

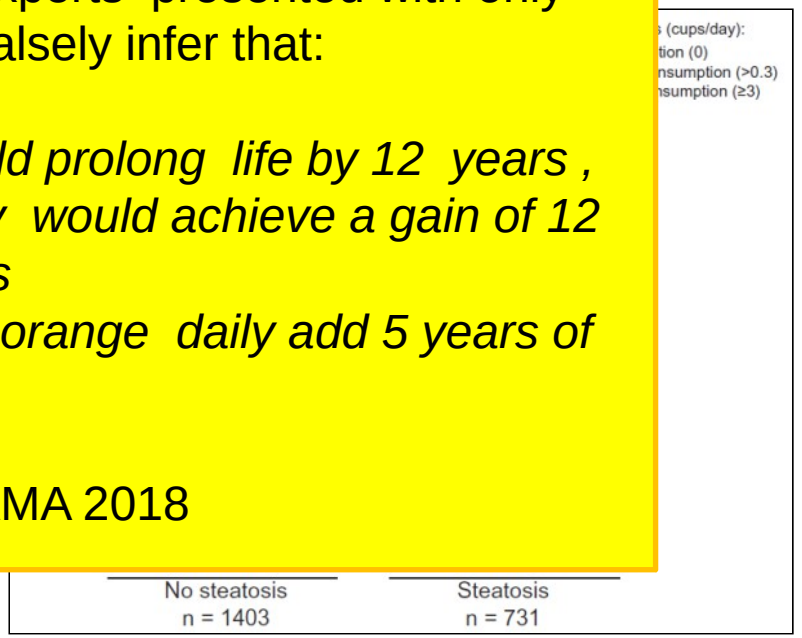
"Assuming the meta-analyzed evidence from cohort studies represents lifespan-long causal associatons , for a baseline life expectancy of 80 years, non experts presented with only relative risks may falsely infer that:

- eating 12 hazelnuts daily would prolong life by 12 years ,
- drinking 3 cups of coffee daily would achieve a gain of 12 years
- eating a single mandarin or orange daily add 5 years of life"

Joannidis, JAMA 2018

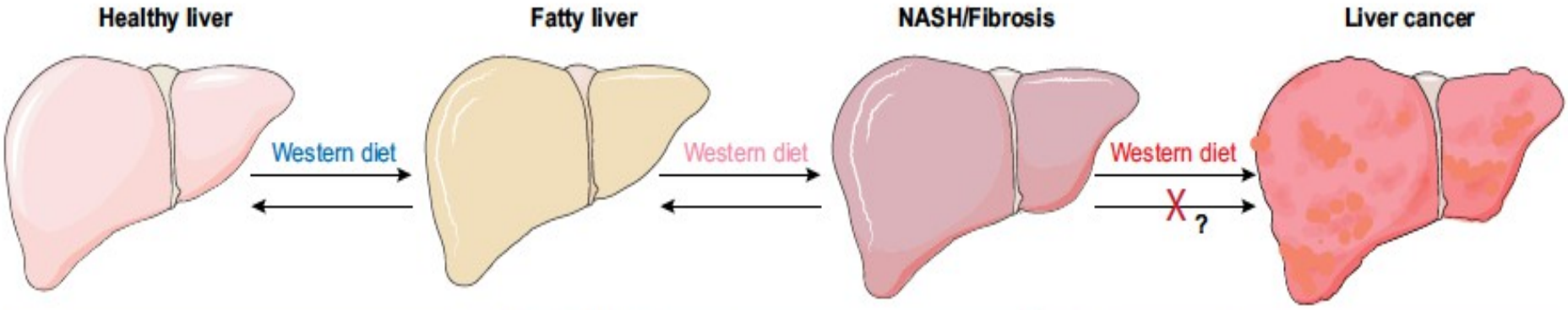


Estimated odds ratio for **moderate** and **frequent** coffee consumers *vs* no coffee consumers



Predicted probabilities (%) of having LS ≥8.0 kPa for the different coffee categories amongst subjects with and without steatosis.

Evidence by clinical stage of NAFLD



Hypocaloric or isocaloric - Mediterranean diet

Aerobic or resistance excercise
(Clinical trials)

≥7-10% Weight reduction
by energy deficit of 500-750 kcal/day through either diet:
- low fat
- low carb
- Mediterranean

(Clinical trials)

Dietary composition modification
Reduced fructose
Mediterranean diet
(Observational studies)

Mediterranean diet
- High fibres
- High fish
- High vegetables
- Low cholesterol
- Low sugar

Drinks
- Coffee ≥2-3 cups/day
- No alcohol in cirrhotics

(Observational studies)

Romero Gomez et al J Hepatol 2017

Lifestyle change and clinical benefit in NAFLD

- ✓ Weight reduction is a well-proven clinical indicator of a meaningful clinical benefit both for the metabolic complications and NASH:
  - 5–8% improve hepatic inflammation ballooning and clear NASH
  - >10% can reduce fibrosis
- ✓ NAFLD is a systemic disorder, other important measures of “success”:
  - Diabetes prevention
  - Reduced CVS, renal events
  - Improved mortality
- ✓ As the development of T2DM is a major determinant of fibrosis progression, its prevention should also result in a better control of the liver disease

5. Lifestyle Management: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S46–S60 | https://doi.org/10.2337/dc19-S005

American Diabetes Association

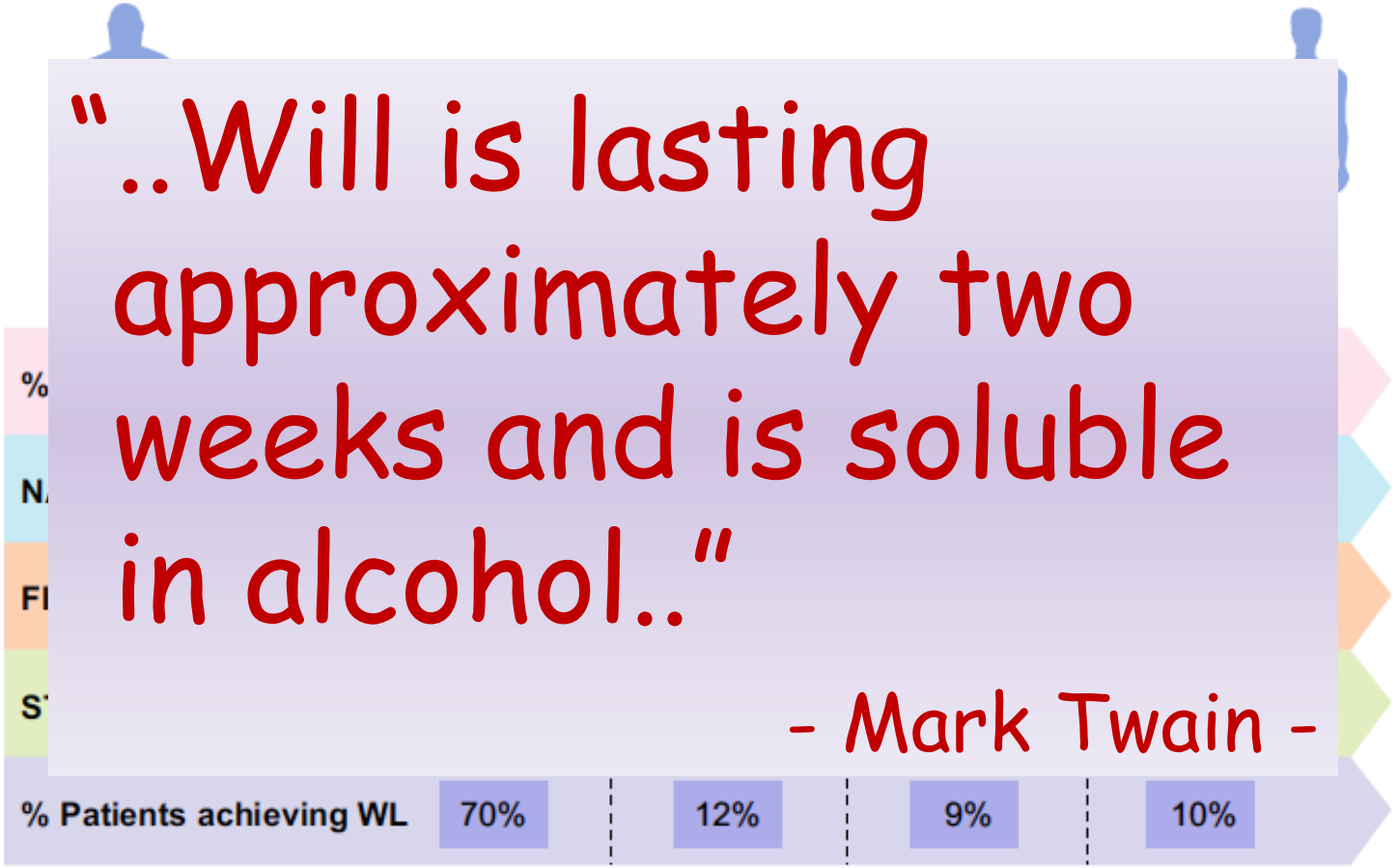
Nonalcoholic Fatty Liver Disease

Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

- ✓ **An individualized medical nutrition therapy program** as needed to achieve treatment goals, preferably provided by a registered dietitian, **is recommended for all people with type 1 or 2 diabetes, prediabetes, and gestational diabetes.**
- ✓ **Weight loss (>5%) achievable by the combination of reduction of calorie intake and lifestyle modification benefits overweight or obese adults** with type 2 diabetes and with prediabetes. Intervention programs to facilitate weight loss are recommended.
- ✓ **There is no single ideal dietary distribution** of calories among carbohydrates, fats, and proteins for people with diabetes; therefore, **meal plans should be individualized while keeping total calorie and metabolic goals in mind**.
- ✓ Data on the ideal total dietary fat content for people with diabetes are inconclusive, so an eating plan emphasizing elements of a **Mediterranean-style diet rich in monounsaturated and polyunsaturated fats** may be considered to improve glucose metabolism and lower cardiovascular disease
- ✓ People with diabetes and those at risk are advised to **avoid sugar-sweetened beverages** (including fruit juices) in order to control glycemia and weight and

Impact in liver histology based on weight loss percentage



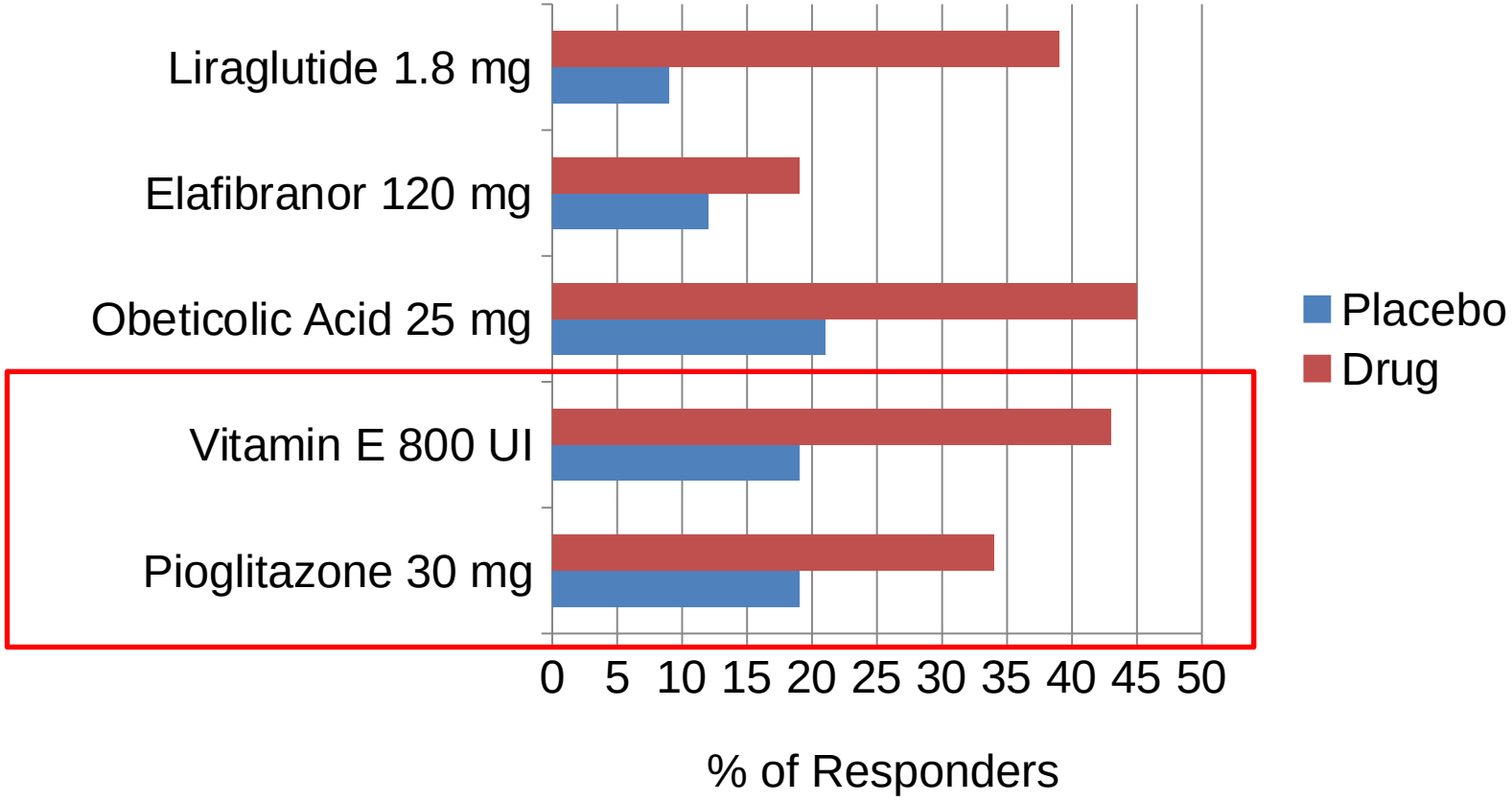
Vilar-Gomez, Romero-Gomez, Gastroenterology 2015; 149:367-378

Factors involved in weight loss and maintenance

- Drop-out
  - Higher weight loss expectancies → Address unrealistic weight loss expectations
- Weight loss
  - Increase of dietary restraint and reduction of dietary disinibition
- Weight maintenance
  - Satisfaction with weight loss and self-efficacy
  - Intensity of Physical Activity
  - Percentage of weight loss during the first year
  - Regular contact with councelling team (physician,

Training the mind to think about the weight control

Resolution of NASH in key clinical trials



Differences in:
time points, populations,
rate of improvement in the placebo arm

Summary

- ✓ **Lifestyle change is an effective treatment modality for curing/controlling NAFLD/NASH.** Traditional measure of success = weight loss, but other important endpoints independent of weight: diabetes incidence & complications, CVS events, mortality, and cancer.
- ✓ **Lifestyle change is difficult to achieve and maintain**
- ✓ **Three essential components**: Cognitive behavioural Therapy + dietary modifications + physical activity changes ➔ ALL required for successful outcomes
- ✓ **MULTIDISCIPLINARY, HOLISTIC, INDIVIDUALISED approach is key**
- ✓ Societal efforts to change an **"obesigenic environment"** is needed

Thank you for your attention!

University of Torino, Italy
Dr Chiara Rosso
Dr. Ramy Younes
Dr. Alessandro Musso
Dr. Maria Lorena Abate
Dr. Antonella Olivero
Prof. M. Rizzetto
Prof. Giorgio Maria Saracco
Prof. Antonina Smedile

Grants to E. Bugianesi:
H2020 EPoS, GA 634413.
IMI2 LITMUS, GA 777377

IFC-CNR, Pisa, Italy
Prof. Amalia Gastaldelli
Dr. Melania Gaggini
Dr. Emma Buzzigoli
Dr. Demetrio Ciociaro

University of Bologna, Italy
Prof. Giulio Marchesini Reggiani