פתופיזיולוגיה של הכבד השומני 2022 – מהן ההשפעות הסביבתיות מעבר לקלוריות?

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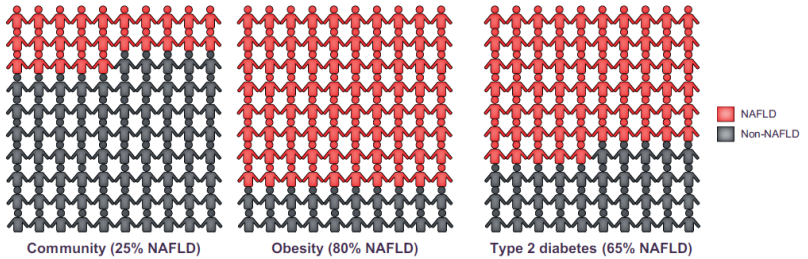
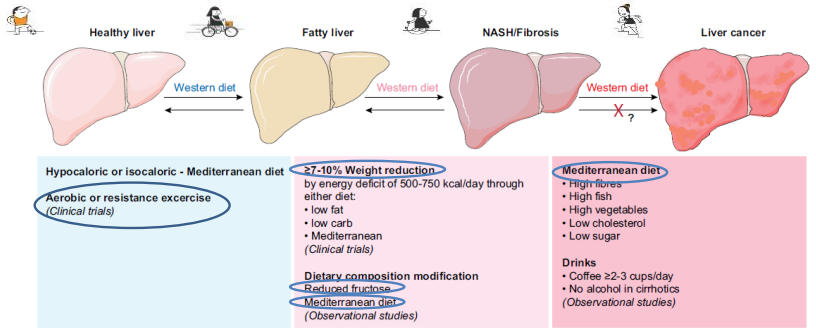
הפקולטה למדעי הרווחה והבריאות

NAFLD prevalence and high-risk groups



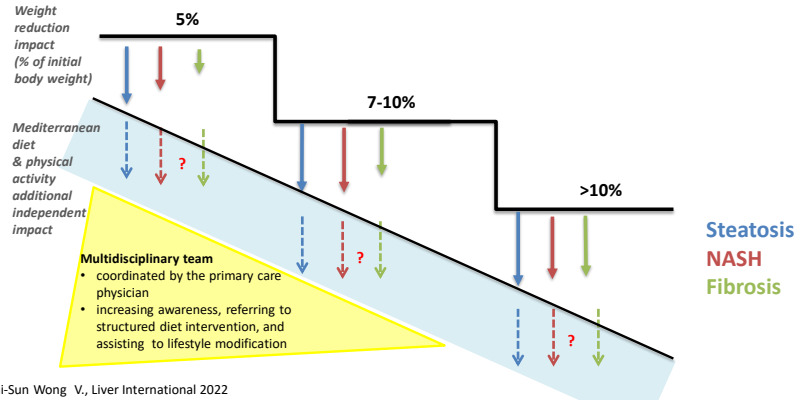
Francque SM., JHEP Reports 2021

NAFLD is a lifestyle oriented and treated disease



Romero-Gómez M., Zelber-Sagi S., Trenell M., Journal of Hepatology 2017

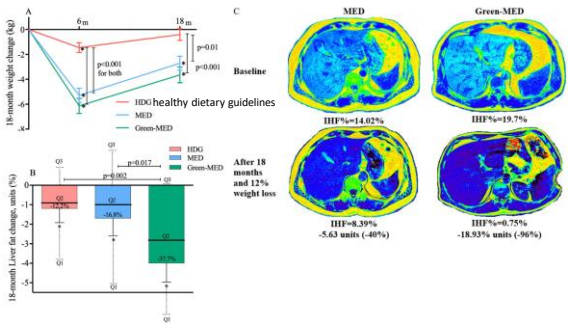
The dose-response effect of weight reduction on features of NAFLD and the added independent impact of the Mediterranean diet and physical activity



Wai-Sun Wong V., Liver International 2022

Effect of green-Mediterranean diet on intrahepatic fat RCT

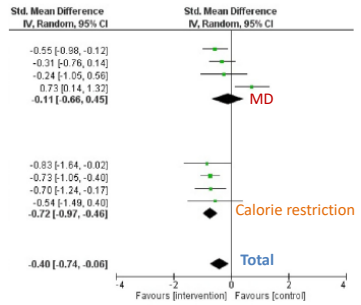
- 18-month
- 294 people with abdominal obesity or dyslipidemia
- Two isocaloric MED groups
- Green-Mediterranean diet enriched with green plants and polyphenols
  - green tea (3–4 cups/day)
  - Mankai (aquatic plant strain) green shake



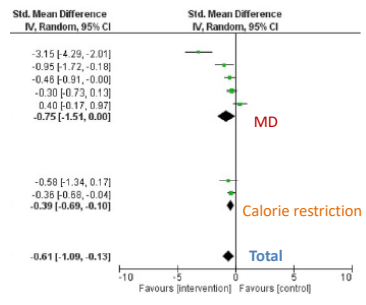
Yaskolka Meir A., Gut 2021

Mediterranean diet and calorie restriction in NAFLD Meta-analysis of RCTs and CCTs

Hepatic steatosis



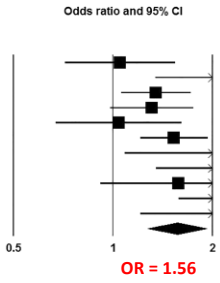
Liver stiffness measurement (LSM)



Haigh L., Clinical Nutrition 2022

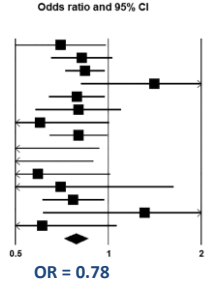
Relationship between dietary patterns and NAFLD: A meta-analysis of observational studies

Western dietary patterns



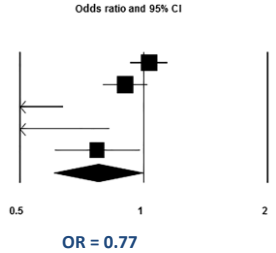
OR = 1.56

Prudent dietary patterns



OR = 0.78

Mediterranean dietary patterns



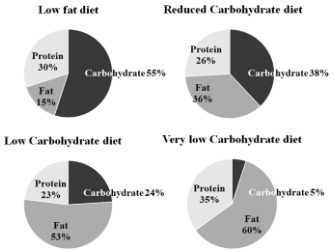
OR = 0.77

Hassani Zadeh S., Journal of Gastroenterology and Hepatology 2021

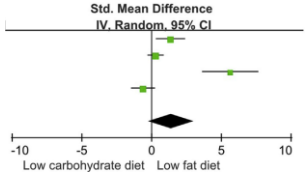
Low-carbohydrate diet in NAFLD: Meta-analyses

- 11 trials (7 RCTs)
- Small sample-sizes

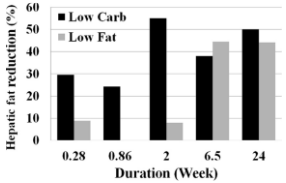
The classification of low carbohydrate diet



% change in hepatic fat content by low carbohydrate diet and low fat diet in NAFLD patients

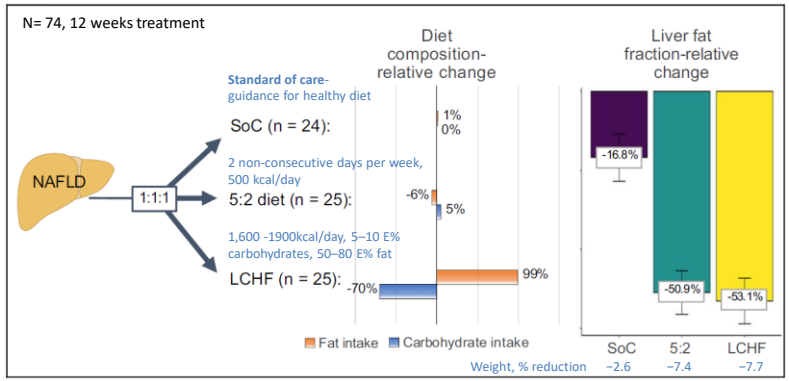


The relation between the duration of low-carbohydrate diet and hepatic fat reduction.



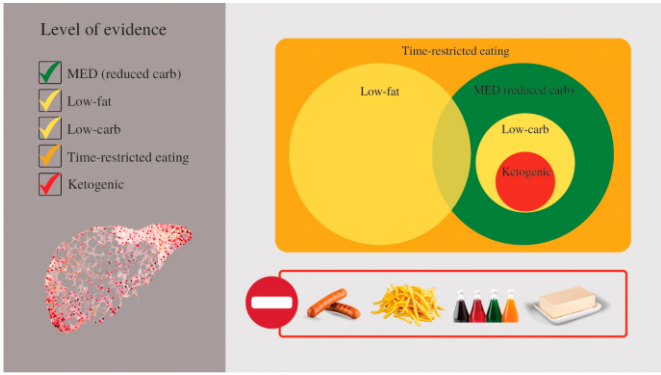
Ahn J., Clinical Nutrition 2019

Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet RCT



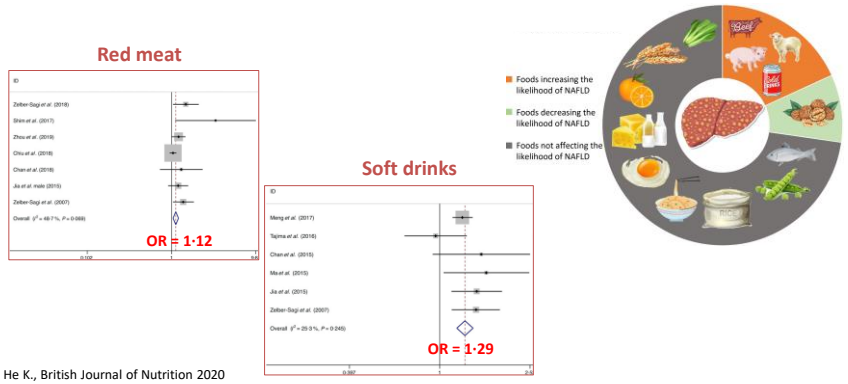
Holmer M., JHEP Reports 2021

A conceptual summary of the level of evidence of each type of diet for the treatment of NAFLD and suggested combinations



Zelber-Sagi S., Liver International 2022

Food groups and the likelihood of NAFLD: meta-analysis of cross-sectional and case-control studies



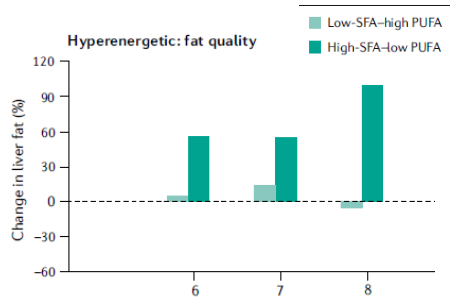
He K., British Journal of Nutrition 2020

Differential effects of dietary saturated and unsaturated fats on liver fat content

- Short-term (couple of weeks) randomized trials

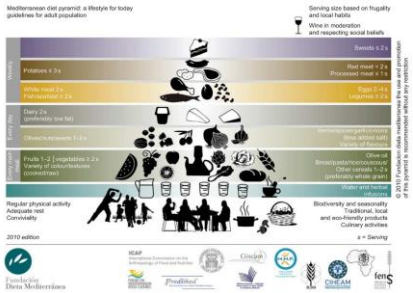
Saturated fat consistently increase IHTG more than polyunsaturated or monounsaturated fat

The evidence supports the Mediterranean diet
low in saturated fat high in monounsaturated fat



Yki- Järvinen H., Nature Reviews Gastroenterology & Hepatology 2021

Mediterranean



Dream

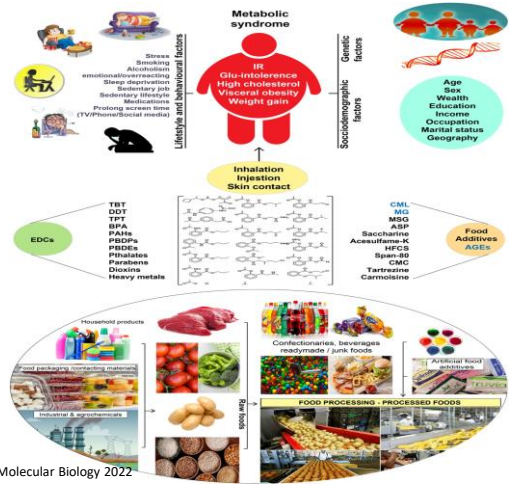
vs.

Western

- Ultra processed food and drinks (UPF) **>50% of daily calories**

Reality

Source, exposure, and impacts of environmental chemicals and food additives



EDC, endocrine disrupting chemicals

- Human food is composed of loads of chemicals
  - naturally / intentionally
  - unintentionally through environmental sources

Ravichandran G., Journal of Steroid Biochemistry and Molecular Biology 2022

A Worldwide Consumption of Ultra-Processed Foods

Country	Population	UPF Consumption of total energy intake
Brazil	Adolescents/ Children	24-50%
	Adults	21-51%
USA	Adolescents/ Children	65%
	Adults	36-60%
France	Adults	17-33%
UK	Adolescents/ Children	65-68%
	Adults	49-54%

Marino M., Nutrients 2021

Ultra-processed food (UPF)

Formulations of ingredients made by **industrial processes**, and **sophisticated packaging, usually with plastic and other synthetic materials**

Designed to create highly **profitable products** (low-cost ingredients, long shelf life), ready-to-consume, **hyper-palatable products**

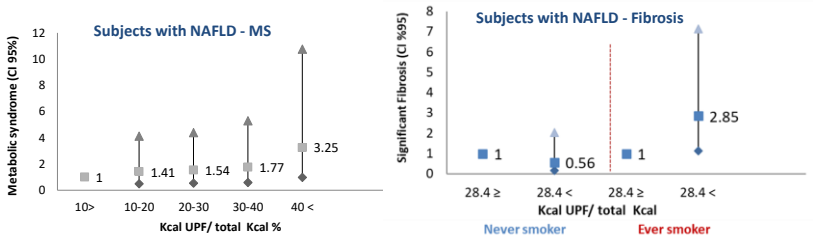
Low nutritional quality, high energy density, contains many ingredients (≥5), such as sugars, oils, fats, salt, anti-oxidants, stabilizers, and preservatives

Monteiro CA., FAO 2019

Martinez S., Popul Health Metr 2017

Dose-response association between UPF consumption and metabolic syndrome & significant fibrosis by smoking status

- Cross-sectional study, 789 volunteers
- AUS, FibroMax
- UPF defined by NOVA classification

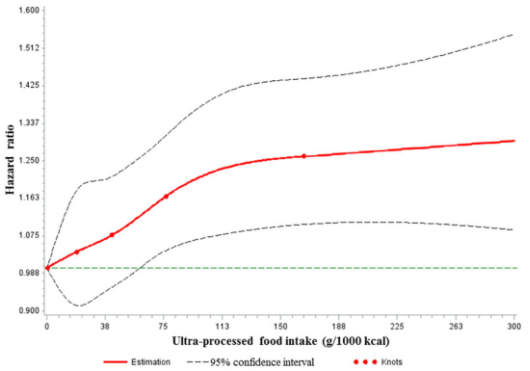


Adjusted for: age, gender, BMI, saturated fatty acids and protein intake, physical activity, coffee and fibers

Ivancovsky-Wajcman D., & Zelber-Sagi S., Liver International 2021

Dose-response association between ultra-processed food consumption (g/1000 kcal) and risk of NAFLD

- Prospective cohort study
- N=16,168
- NAFLD defined by US

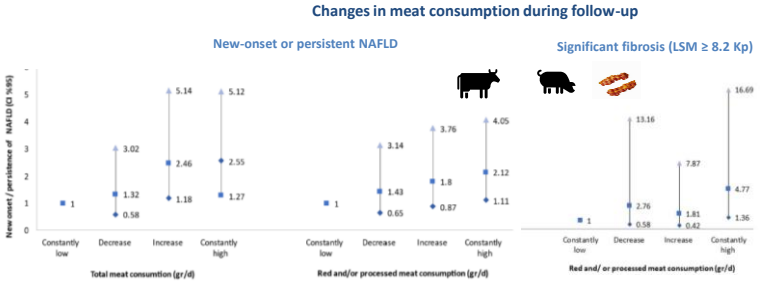


Adjusted for age, sex, BMI, smoking, alcohol, education, income, physical activity, total energy intake, healthy diet score, hypertension, hyperlipidaemia and diabetes

Zhang S., International Journal of Epidemiology 2022

High meat consumption is prospectively associated with risk of NAFLD and presumed significant fibrosis

- Prospective cohort, 6.8 y follow-up
- N=316 subjects
- US or CAP, FibroScan



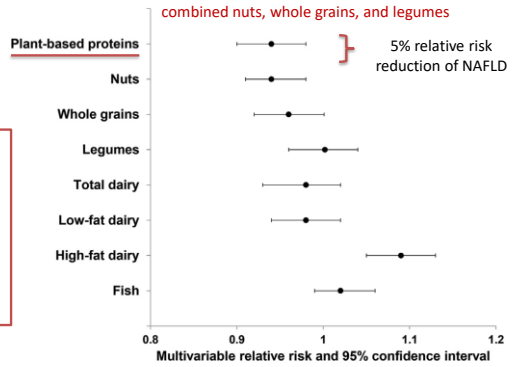
Adjusted for baseline age (years), gender, BMI (Kg/m2), energy, (Kcal), protein (% total Kcal), and cholesterol intake (mg/day)

Ivancovsky-Wajcman D., Nutrients 2022

Relative risk of NAFLD associated with replacement of 1 serving/day of red meat with other protein sources

- Prospective cohort study
- N= 77,795 women, Nurses' Health Study
- A physician-confirmed NAFLD

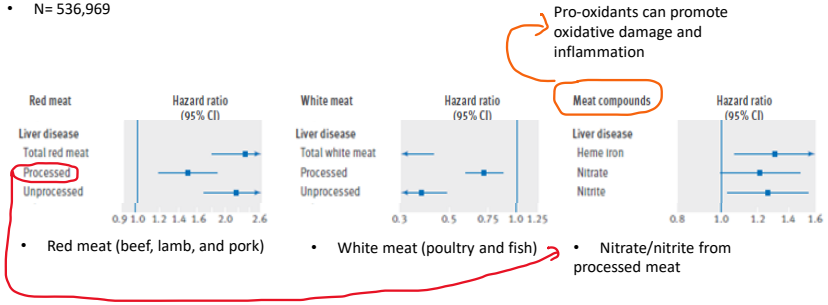
- Red meat (processed & unprocessed) related with NAFLD 1.41 (95% CI 1.13-1.75)/1 serving/day vs. ≤1 week
- Mediation of the association between red meat consumption and NAFLD:
  - Heme-iron 23%
  - Cholesterol 26%
  - BMI 66%



Kim MN., Clinical Nutrition 2022

Association between intake of different types of and meat-associated compounds and liver-related mortality

- Population-based cohort study from six states in the US
- 16-year follow-up data
- N= 536,969

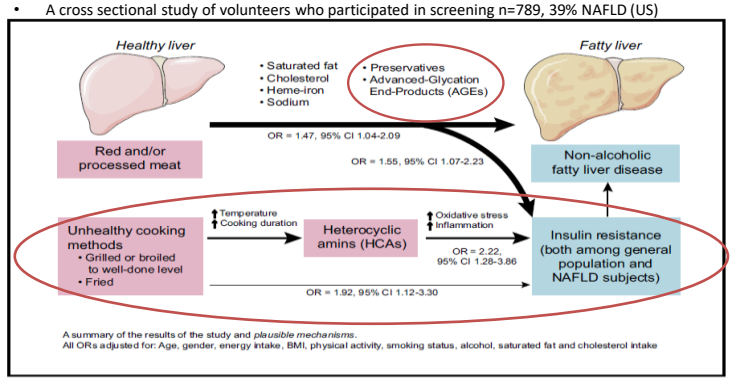


- Red meat (beef, lamb, and pork)
- White meat (poultry and fish)
- Nitrate/nitrite from processed meat

Etemadi A., BMJ 2017

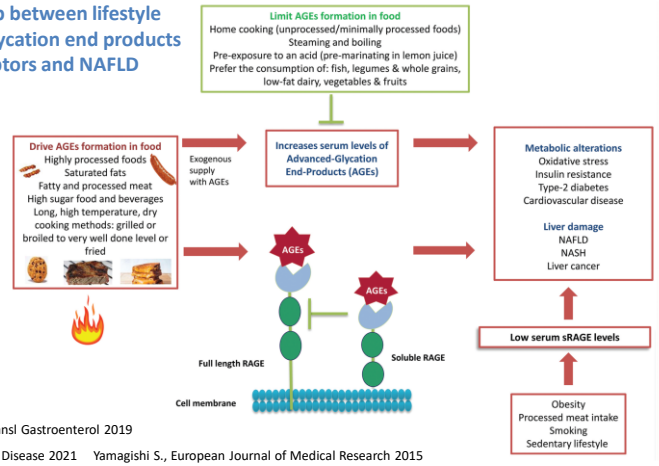
High red and processed meat consumption is associated with NAFLD and insulin resistance

- A cross sectional study of volunteers who participated in screening n=789, 39% NAFLD (US)



Zelber-Sagi S., Journal of Hepatology 2018

The interrelationship between lifestyle factors, advanced glycation end products (AGEs), and its receptors and NAFLD



Ivancovsky-Wajcman D., Clin Transl Gastroenterol 2019

Zelber-Sagi S., Seminars in Liver Disease 2021 Yamagishi S., European Journal of Medical Research 2015

VS.

Pasta with tomato sauce	100 gr (12 min cooked)
AGEs (Ku)	250
Energy (Kcal)	128
Carbohydrate (g)	20
Protein (g)	4
Fat (g)	3

Beef steak	100 gr (7 min cooked)
AGEs (Ku)	6,973
Energy (Kcal)	187
Carbohydrate (g)	0
Protein (g)	30
Fat (g)	7

Role of bisphenol A as an environmental factor in the promotion of NAFLD

- An endocrine-disrupting chemical associated with T2DM, CVD and liver abnormalities
- A building block of **plastics** and of the lining in **food and beverage containers**
- Disrupts pancreatic b-cells function and whole-body glucose homeostasis

Dallio M., Aliment Pharmacol Ther 2018

Rules to follow bisphenol A free diet

BPA-FREE DIET

Avoid Metal Cans

Soft drinks in cans (Coca-Cola, Fanta, etc.), preserved food (tomato sauce, corn, vegetables, tuna, etc.).

Avoid plastic bottles and containers

It is better to store and buy food and liquids in glass containers. Avoid, if possible, disposable plastic plates, cutlery and cups.

Check the marking on all plastic containers

Avoid plastics number "3" and "7".

3 7

Limit the cooking in microwave

Especially if you use plastic containers to heat food! This process could accelerate and increase BPA release in food!

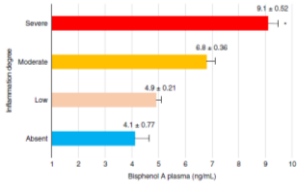
If possible, prefer fresh food not stored in containers

It is recommended to follow the above diet for one month

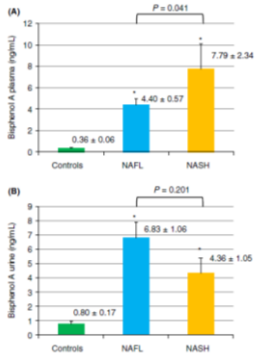
Role of bisphenol A as an environmental factor in the promotion of NAFLD

- N=60, NAFLD with **histological diagnosis** vs. controls

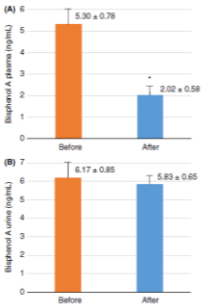
Bisphenol A plasma levels and hepatic inflammation



Bisphenol A urine (A) and plasma (B) levels

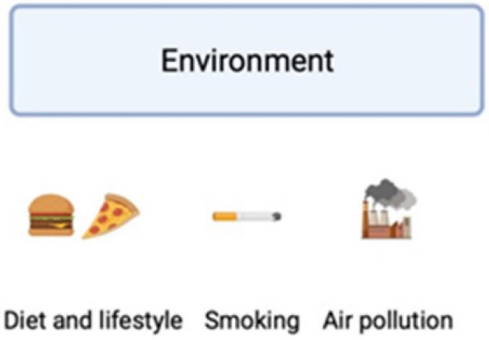


Bisphenol A levels of NAFLD before and after bisphenol A free-diet for 1 month



Dallio M., Aliment Pharmacol Ther 2018

Should hepatologists care about air pollution?



Juanola O., Int. J. Environ. Res. Public Health 2021

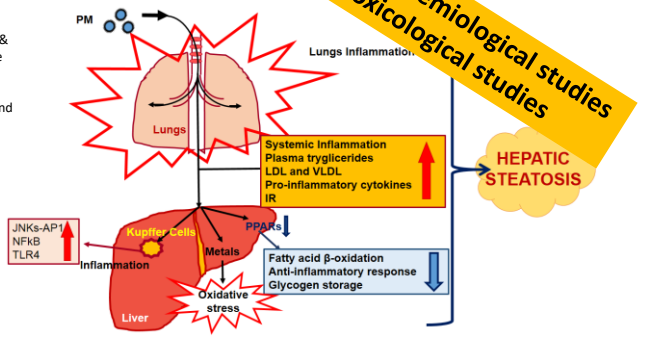
Environmental Pollution: A Tangible (?) Risk for NAFLD Pathogenesis

Very few- Epidemiological studies
Mostly - Toxicological studies

Inhaled particulate matter pr… …atosis through inflammation and metab…

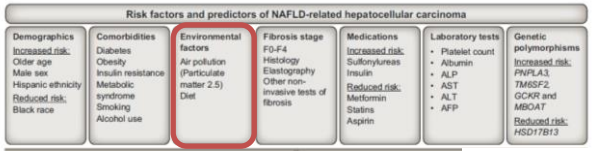
Phase1: systemic inflammation & dyslipidemia & insulin resistance

Phase 2: particles arrive in the liver and activate Kupffer cells and promote inflammation & alter lipid and glucose metabolism



Arciello M., Int. J. Mol. Sci. 2013

Environmental exposure to particulate matter air pollution (PM2.5)

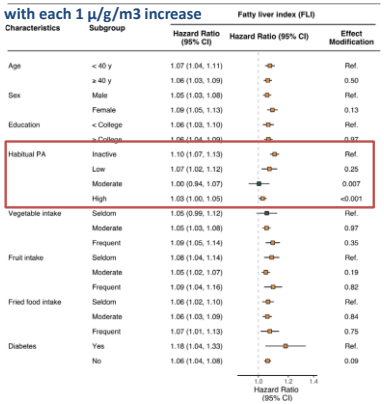


- PM2.5 chemicals primarily originating from fossil fuel combustio
- Associated with HCC (16 US population-based cancer registries: 26% increased risk per 10 µg/m3)

VoPham T., Cancer Causes Control 2018
Ioannou GN., Journal of Hepatology 2021

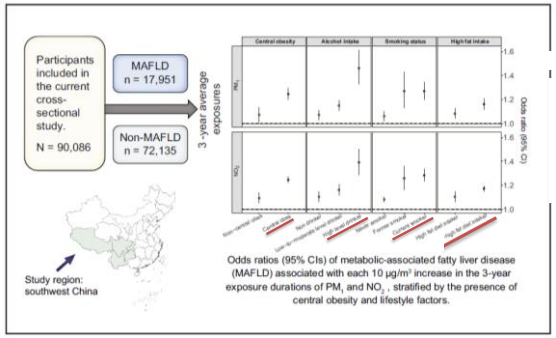
Long-term exposure to fine particulate matter (PM2.5) and NAFLD markers Prospective cohort study

- N=58026 undergoing medical screening in Taiwan
- Incident Fatty liver index (FLI)>30
- Annual PM2.5 levels at participants' residential addresses

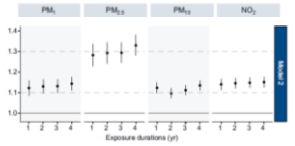


Sun S., Gut 2022

Exposure to air pollution increase the risk of MAFLD and interacts with alcohol, smoking, high-fat diet and central obesity



OR of MAFLD associated with each 10 lg/m3 increase in the 1-4-year exposure durations of the air pollutants

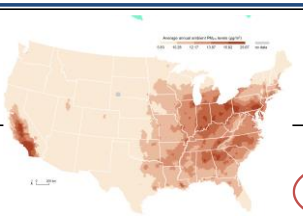


Adjusted for age, sex, ethnicity, study region, education, income, smoking, alcohol intake, diet, physical activity, second-hand smoke, and indoor air pollution

Guo B., Journal of Hepatology 2022

Air pollution PM2.5 exposure and NAFLD among hospitalized patients in nationwide inpatient sample in the United States

- Cross-sectional analysis
- Hospital discharge diagnosis codes
- N= 269,705 NAFLD /N= 45,433,392 hospitalizations

$PM_{2.5}$ exposure (per 10 µg/m^3 increase)		Fully adjusted[b] OR (95% CI)	p
Overall analysis			
$PM_{2.5}$		1.24 (1.15–1.33)	<0.01

Adjusted for age, sex, race/ethnicity, income, urbanicity, region, obesity, diabetes, metabolic syndrome, dyslipidemia, hypertension, obstructive sleep apnea, and smoking

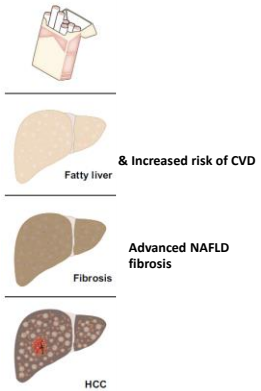
VoPham T., Environmental Research 2022

Lifestyle and NAFLD: an umbrella review of observational studies and RCTs

Exposure	Measure	Studies (n)	Subjects (n)	Cases (n)	Random effect model	Effect sizes (95% CI)	I^2 (%)
Smoking	NAFLD	20	92125	20149		OR, 1.43 (1.02, 1.84)	98.50
Passive smoking	NAFLD	2	NA	NA		OR, 1.32 (1.16, 1.50)	59.41
Former smoking	NAFLD	4	2210	784		OR, 1.38 (1.20, 1.59)	0.00
Sugar sweetened beverages	NAFLD	4	5241	1150		OR, 1.40 (1.07, 1.82)	31.00
Sugar-Sweetened Soda	NAFLD	7	4639	NA		RR, 1.53 (1.34, 1.75)	0.00
Soft drinks	NAFLD	7	32788	9947		OR, 1.33 (1.18, 1.49)	23.11
Hypercaloric fructose diet	IHLC	6	NA	NA		OR, 1.13 (1.02, 1.45)	0.00
Red meat	NAFLD	8	NA	8115		OR, 1.26 (1.08, 1.47)	63.73
Short sleep duration	NAFLD	6	59094	NA		RR, 1.19 (1.04, 1.36)	0.00
Obesity	NAFLD	21	381655	NA		RR, 3.53 (2.48, 5.03)	94.50
Per 1-unit increase in WC	NAFLD	11	37941	10454		OR, 1.07 (1.03, 1.10)	73.90
Per 1-unit increase in BMI	NAFLD	11	37941	10454		OR, 1.25 (1.13, 1.38)	88.70
WHR	NAFLD	3	1063	387		OR, 4.10 (1.53, 10.79)	65.70
Hyperuricemia	NAFLD	11	100725	18303		OR, 1.92 (1.66, 2.23)	80.00
Hyperuricemia	NAS	5	777	NA		RR, 2.17 (1.51, 3.12)	16.00

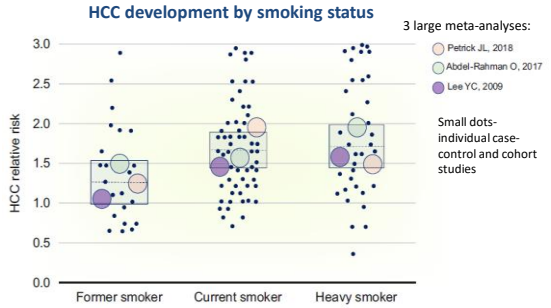
Peng X., BMC Endocrine Disorders 2022

Effects of cigarette smoking across the spectrum of liver disease



& Increased risk of CVD

Advanced NAFLD fibrosis

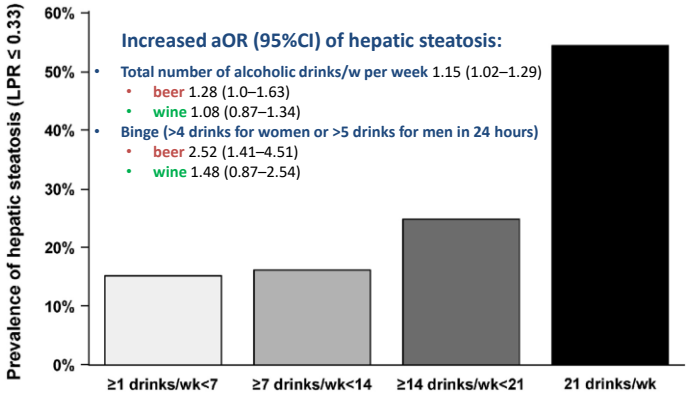


- No studies specifically examined the association between smoking and NAFLD-related HCC

Marti-Aguado D., Journal of Hepatology 2022

Hepatic steatosis by "normal" alcohol consumption

- Cross-sectional Framingham Heart Study
- N = 2475
- Hepatic steatosis by CT
- Excluded women>14 & men>21 alcohol drinks/w



Increased aOR (95%CI) of hepatic steatosis:

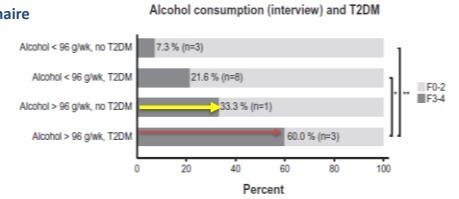
- **Total number of alcoholic drinks/w per week** 1.15 (1.02–1.29)
  - beer 1.28 (1.0–1.63)
  - wine 1.08 (0.87–1.34)
- **Binge (>4 drinks for women or >5 drinks for men in 24 hours)**
  - beer 2.52 (1.41–4.51)
  - wine 1.48 (0.87–2.54)

Long MT., Clinical Gastroenterology and Hepatology 2020

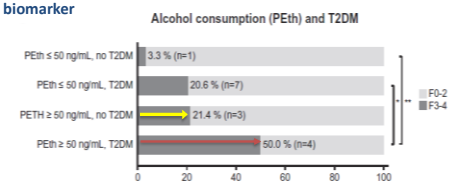
Moderate alcohol consumption is associated with advanced fibrosis in NAFLD and shows a synergistic effect with type-2 diabetes mellitus

- Cross-sectional study
- 86 patients with **biopsy-proven NAFLD**
- All participants reported alcohol consumption <140 g/week

Questionnaire

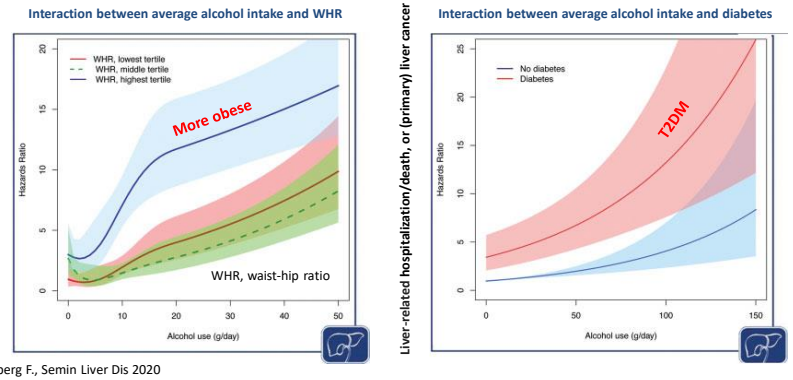


Serum PEth, Phosphatidyl ethanol - biomarker



Blomdahl J., Metabolism Clinical and Experimental 2021

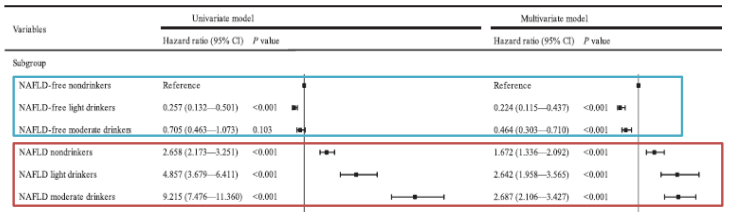
Drinking and Obesity & DM Interactions in the development of incident clinical liver disease in the Finnish general population



Åberg F., Semin Liver Dis 2020

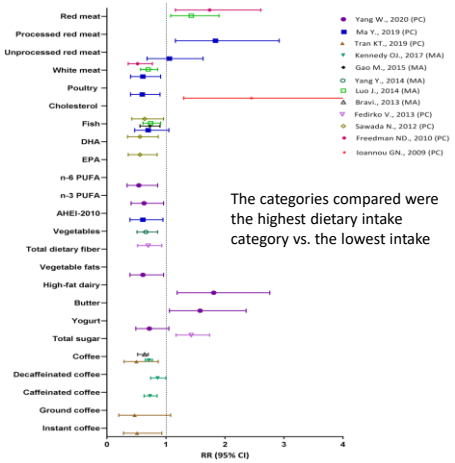
Light-to-moderate alcohol consumption is associated with increased risk of type-2 diabetes in individuals with NAFLD

- A 9-year cohort study
- Chinese men
- N=7,079
- NAFLD by US



Xu. L., The American Journal of Gastroenterology 2020

Lifestyle parameters related with risk for HCC, in large prospective cohort studies and meta-analyses



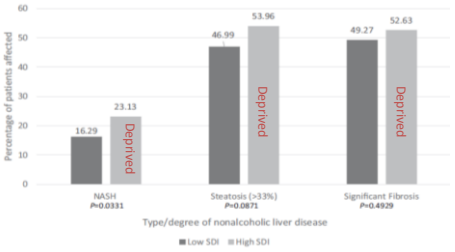
The categories compared were the highest dietary intake category vs. the lowest intake

Zelber-Sagi S., Seminars in Liver Disease 2021

Community socioeconomic deprivation predicts NASH

- Electronic medical records of 1,430 patients in tertiary health care network in New York
- Patients with evidence of NAFLD/NASH on liver biopsy

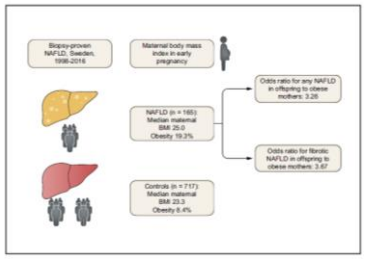
Degree and severity of liver injury between high- versus low-social deprivation index (SDI) groups



Giammarino AM., Hepatology Communications 2022

Maternal obesity and low socioeconomic level increase the risk and severity of NAFLD in offspring

- Register-based nationwide case-control study, Swedish Medical Birth Register
- Individuals ≤ 25 years of age with biopsy verified NAFLD matched by age, sex, and calendar year with up to 5 controls



Multivariable prediction for biopsy-proven NAFLD based on parameters other than BMI

Parameter	OR (95% CI)	P
Maternal age (continuous)	0.99 (0.95–1.02)	0.46
Nordic country of birth of mother	0.35 (0.22–0.57)	<0.001
Maternal smoking in early pregnancy **≥10 cig/day vs. Non-smoking**	2.13 (1.07–4.25)	0.03
Highest level of education in parents **≤ 9 years vs. more**	2.22 (0.94–5.26)	0.07

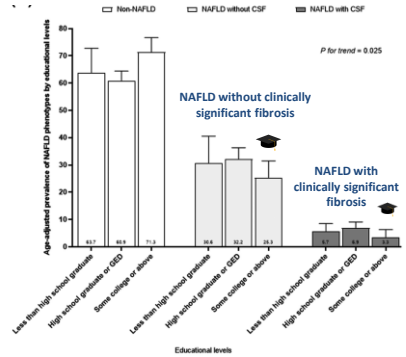
Hagström H., Journal of Hepatology 2021

College education is associated with a low risk of NAFLD among the US population

- A cross-sectional analysis of the NHNES 2017–2018
- 3589 participants with transient elastography

- The total effect of education on NAFLD risk was partially mediated by
  - high diet quality - 29%
  - high physical activity - 8%

Age-adjusted prevalence of NAFLD phenotypes by Educational levels



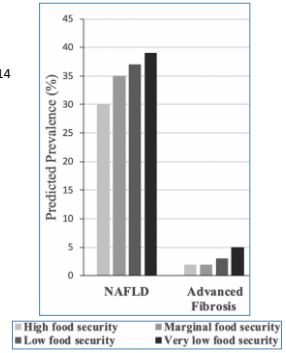
Vilar-Gomez E., Hepatology 2022

Food insecurity associated with NAFLD among low-income adults in the US

Food Insecurity definition (USDA): reduced quality, variety, or desirability of diet without or with hunger

Food-insecurity ⇒ **Affordability of energy-dense, high-fat / sugar foods and an overall decline in dietary quality**

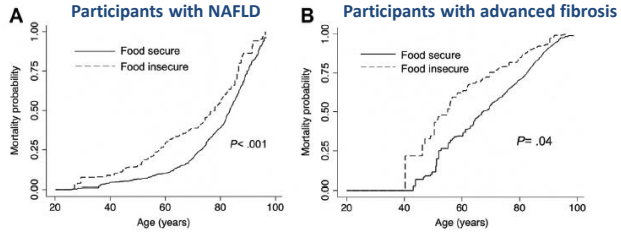
- Cross-sectional
- NHANES 2005–2014
- 2627 adults
- NAFLD by US
- Advanced fibrosis by NAFLD fibrosis score



Golovaty I., J Nutr 2019

Food insecurity is associated with all-cause mortality among U.S. adults with NAFLD and Advanced Fibrosis

- Cross-sectional
- NHANES
- N=4816 NAFLD
- n=1654 advanced fibrosis
- NAFLD by US
- Advanced fibrosis by NAFLD fibrosis score
- Food insecurity in 28%

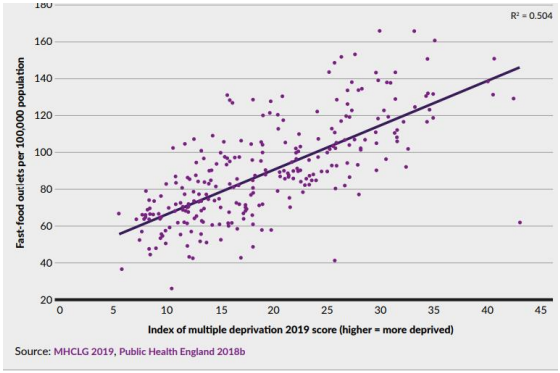


- Adjusting for demographics & BMI, smoking, alcohol
- Food insecurity was independently associated with higher all-cause mortality
  - **NAFLD: HR 1.46 (95% CI 1.08, 1.97)**
  - **Advanced fibrosis: HR 1.37 (95% CI 1.01, 1.86)**

Kardashian A., Clinical gastroenterology and hepatology 2021

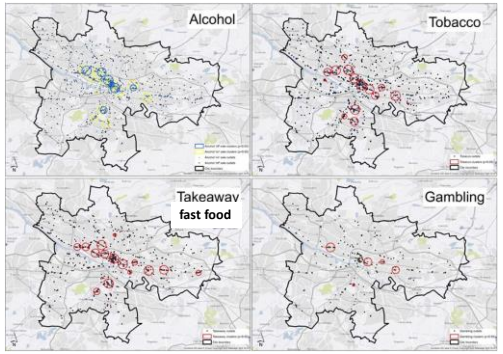
Density of fast-food outlets per 100,000 population by local authority and deprivation in England

Unhealthy food environments are more prevalent in more deprived areas

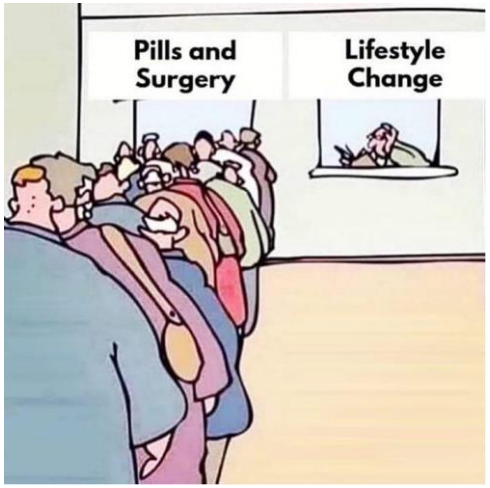


Published by The King's Fund 2021

'Environmental bads' (alcohol, fast food, tobacco) outlets cluster in more deprived areas in Glasgow City, Scotland



Laura Macdonald L., Health & Place 2018



A call for action

- Public health interventions with a particular emphasis on children

- School education for healthy diet and lifestyle
- Use taxations to subsidize healthy food
- Legislation to restrict advertising and aggressive marketing, especially among children
- Encouraging healthy food reformulation

Jim O'Hara et al.
Center for Science in the Public Interest

Karlsen TH., EASL–Lancet Liver Commission, Lancet 2021

Thank you!