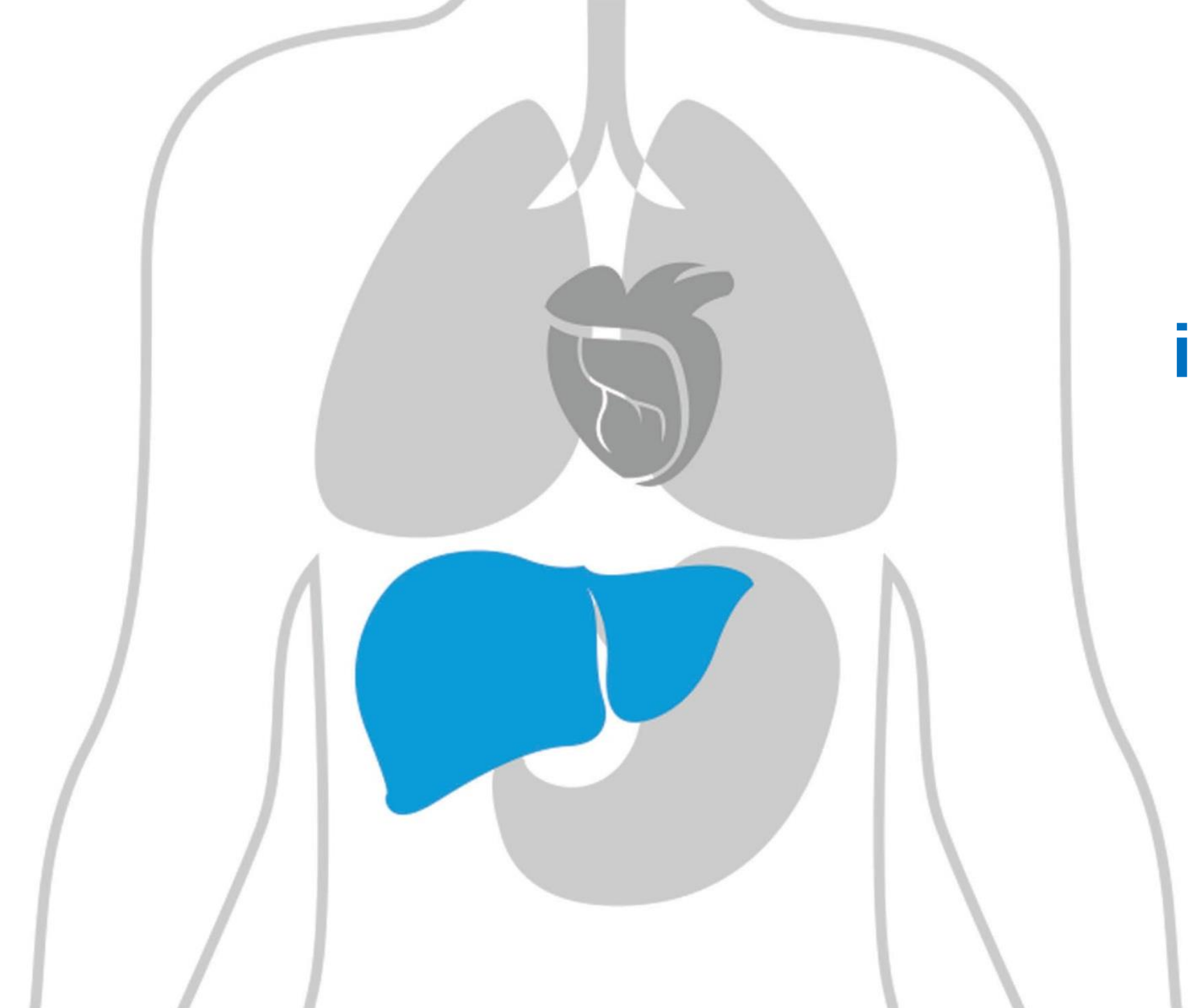

Effectiveness of lifestyle interventions in NAFLD

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PhD in nutrition & sport physiology
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INFLUENCE OF DIETARY MACRONUTRIENTS ON NON-ALCOHOLIC FATTY LIVER DISEASE

- Several studies have confirmed the role of specific **macronutrients** in the **onset** and **progression** of NAFLD.
- However, it is very difficult to separate the role of each separate macronutrient, in relation to the amount of energy provided, their proportion in the diet and the food they contain.
- The macronutrient composition of a diet is associated with NAFLD/NASH, **independent of energy intake**.
- Macronutrients such as saturated fatty acids (SFA), trans fats, simple sugars (sucrose and fructose) and animal proteins **damage** the liver.
- These modulate the **accumulation of triglycerides** and **antioxidant activity** in the liver, which affects insulin sensitivity and postprandial triglyceride metabolism.
- **In contrast**, monounsaturated fatty acids (MUFA), PUFA ω3 fats, plant-based proteins and dietary fibers appear to be **beneficial** to the liver.

The Western diet is associated with NAFLD

This type of diet contains excessive amounts of

1. refined and processed foods
2. red meat,
3. processed meat,
4. sugary drinks,
5. snacks,
6. cakes, biscuits,
7. eggs and butter.

It involves an excess of calorie consumption, saturated fats, animal protein, sugar, cholesterol and salt.

The Mediterranean diet has beneficial effects on NAFLD

This diet is based on the **high** intake of:

1. extra virgin olive oil,
2. vegetables,
3. fruits,
4. cereals,
5. nuts and legumes;

moderate intakes of:

1. fish and other meats, dairy products
2. red wine

low intakes of:

1. eggs and sweets.

So, it provides a large amount of monounsaturated fatty acids, polyunsaturated fatty acids, vegetable proteins, fiber and antioxidants; and low amounts of sugar, cholesterol and saturated fats.

Dietary approach to stop hypertension has beneficial effects on NAFLD

This diet is rich in:

1. fruits,
2. vegetables,
3. whole grains,
4. fish, poultry,
5. nuts, legumes
   low-fat dairy
   products

DASH has low levels of sodium, added sugars and fat.
this diet emphasizes on the consumption fresh food.
It provides low intakes of total fat, salt, sugar and cholesterol; and high intakes of vegetable protein, fiber, and antioxidants.

The role of fats

We can distinguish three types of fats at a nutritional level:

1. Saturated
2. Monounsaturated
3. polyunsaturated.

Despite a general consensus that the intake of saturated fats should be reduced, the issue of dietary fatty acid composition remains controversial.

The **SFA** diet was associated with a **marked increase in liver fat**, probably because of an increase in de novo liver lipogenesis and an increase in lipolysis of adipose tissue.

In contrast, **unsaturated fat** intake was associated with a **decrease in lipolysis**, preventing the accumulation of fat in the liver.

The SFA diet has also been linked to impaired glutathione metabolism and an increase in oxidative stress, which leads to the progression of NAFLD.

However …

The role of fats

at present, it is **not clear** whether **different sources of SFA** (for example, dairy vs meat) can have **different effects** on liver fat content.

On the other hand, it is also important to consider that the effects of saturated fats seem to depend on a patient's **genetic background**.

The specific effects of trans fats on the human liver have not been adequately evaluated because most studies have been performed in **mice** models.

The role of fats

Studies on MUFA have reported different, sometimes contradictory conclusions. This may be because of both differences in methodology and the origin of MUFAs.

MUFA consumption  **the progression of NAFLD**

the origin of MUFA
?????

The role of fats

Polyunsaturateds, including mainly ω3 and ω6 fats have also been evaluated in the progression of NAFLD in particular the essential PUFAS, α-linolenic acid (ALA; ω3) and linoleic acid (LA; ω6).

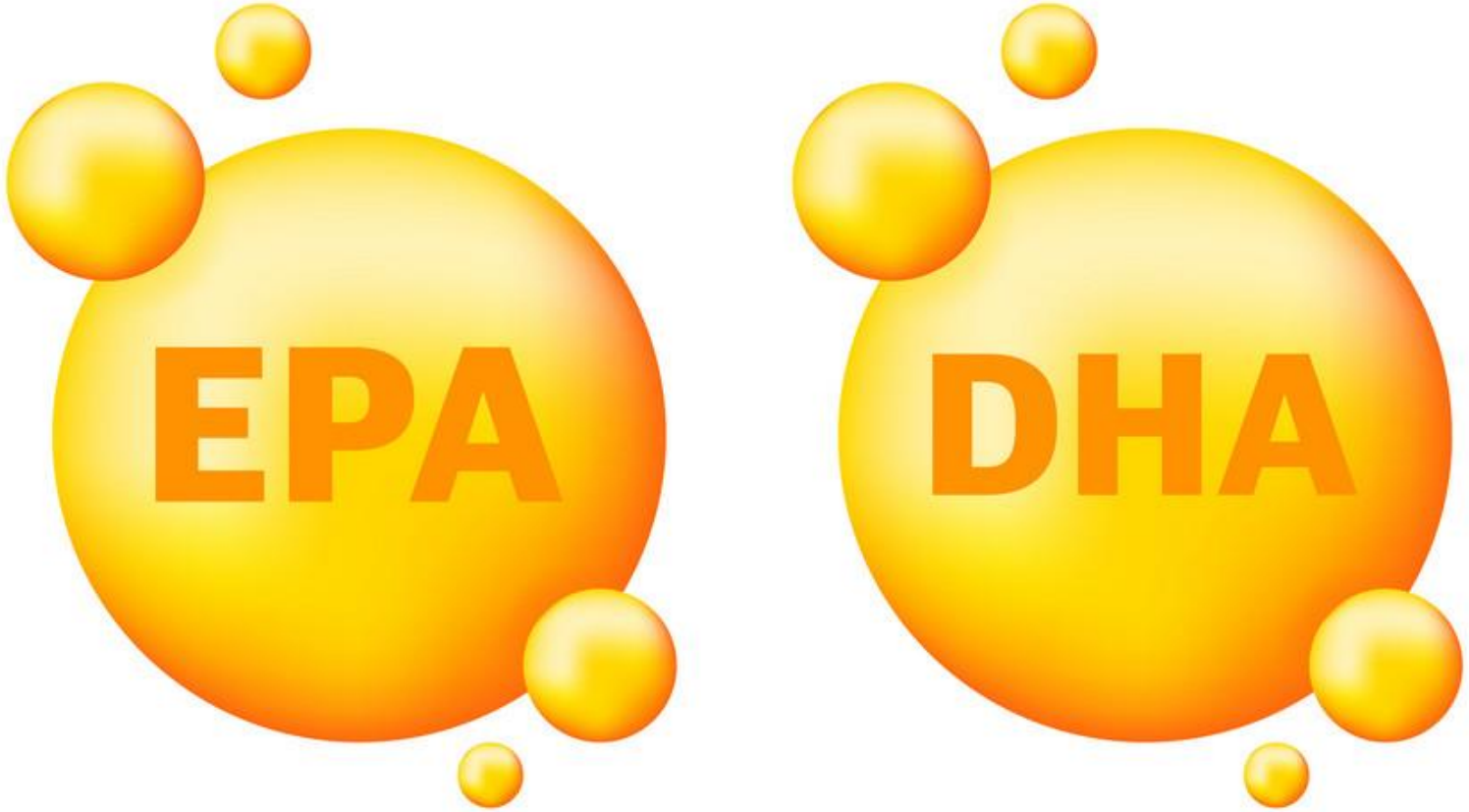
LA is metabolized to → arachidonic acid (AA; 20:4 n-6)

ALA is metabolized to → eicosapentanoic acid (EPA; 20:5 n-3) & docosahexanoic acid (DHA; 22:6 n-3)

The metabolic products of AA are proinflammatory, prothrombotic and proaggregatory

The role of fats

On the other hand, EPA and DHA modulate the liver's lipid composition, **increasing** anti-inflammatory mediators and **decreasing** insulin resistance.



low EPA and DHA liver values could tilt the balance towards liver fatty acid lipogenesis, instead of fatty acid beta-oxidation.

The role of fats

Therefore, the ratio ω6/ω3 fats plays an important role in increasing the prevalence of chronic metabolic diseases (mostly a ω6/ω3 imbalance).

Nevertheless, a double-blind randomized trial showed that a **long-term hypercaloric diet** rich in ω6 PUFA intake prevents liver fat accumulation in overweight individuals.

Several clinical trials have addressed the **potential benefits** of omega-3 PUFAs on NAFLD/NASH. A systematic review and meta-analysis of controlled intervention studies on the effects of ω3 PUFAs in NAFLD patients indicates that supplementation with ω3 **decreases liver fat content** and the **steatosis score**.

However, the effects of ω3 supplementation on improving severe liver injury markers, such as inflammation and fibrosis are not well-established.

The role of fats

It is important to consider that the **controversial results** on ω3 could be because of differences in:

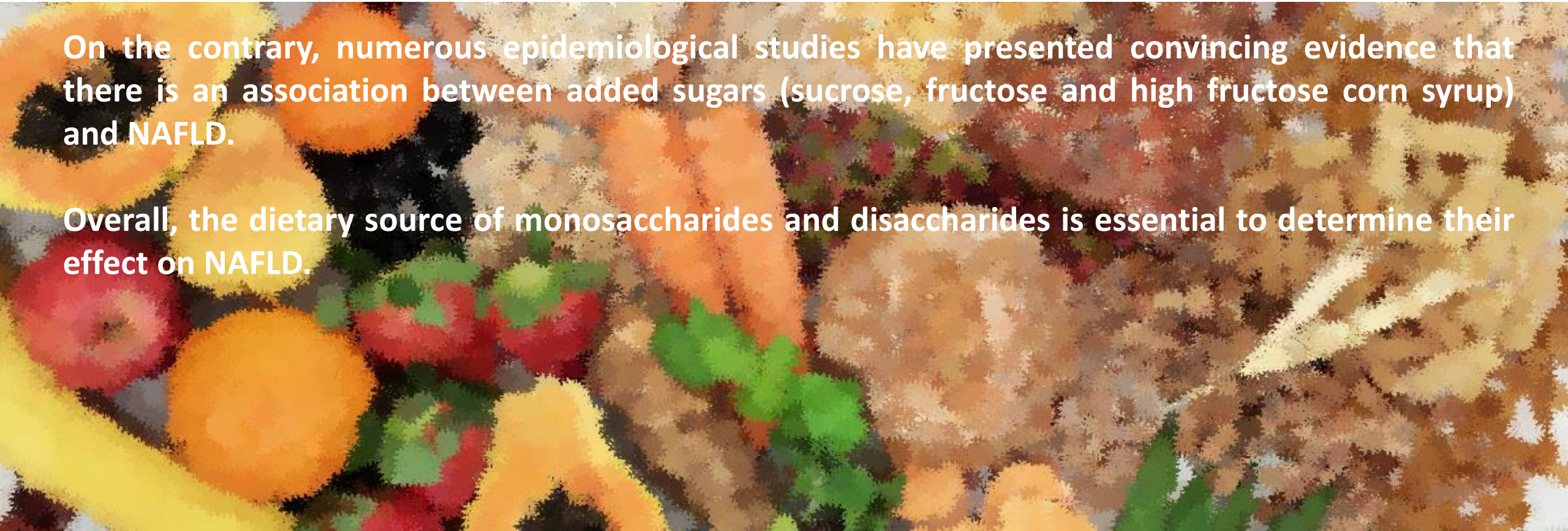
1. Methodology
2. the duration of the nutritional intervention
3. levels of intake
4. their sources
5. the EPA/DHA relationship
6. the chemical composition of ω3
7. the patient's genetic background.

The contribution of dietetic cholesterol in NAFLD is not clear. Certain nutritional studies suggest that high-cholesterol diets are involved in the development of NAFLD. However, the same studies show that patients had high fat intake.

The role of carbohydrates

In the past twenty years, there has been substantial evidence to confirm the adverse metabolic effects of over consumption of simple carbohydrates.

However, studies have cast doubts on the real role of monosaccharides and disaccharides when they are naturally contained in foods in NAFLD.



On the contrary, numerous epidemiological studies have presented convincing evidence that there is an association between added sugars (sucrose, fructose and high fructose corn syrup) and NAFLD.

Overall, the dietary source of monosaccharides and disaccharides is essential to determine their effect on NAFLD.

The role of carbohydrates

Numerous studies have found a **positive association** between the risk of NAFLD and high-fructose products (cakes, soft drinks and sugary snacks).

The liver is the primary site of fructose metabolism, with nearly **60%** oxidation of fructose ingestion.

fructose metabolization in the liver is **much higher** than that of glucose.

The hepatic metabolism of fructose stimulates **de novo lipogenesis** in the liver, increasing liver fat.

The role of carbohydrates

The most recent meta-analysis of controlled clinical trials concluded that the isocaloric exchange of carbohydrates for glucose does not induce NAFLD. However, when fructose is the source of a hyper caloric diet, patients with NAFLD have increased liver fat and plasma alanine aminotransferases. In addition, Abdel mark et al showed that in adult patients with NAFLD, an increase in fructose consumption increased fibrosis and swelling.

The role of carbohydrates

The role of non-digestible carbohydrates (fiber) in NAFLD has **not** been extensively studied.

A **decrease** in fiber consumption is thought to be related to NAFLD.

The proposed rationale is that **low fiber intake**, along with other dietary patterns induces dysbiosis, which modifies the microbiota inducing endotoxemia, **systemic inflammation**, **insulin resistance** and **liver inflammation** and damage.

An **alteration** of gut microbiota has been observed in NAFLD patients.

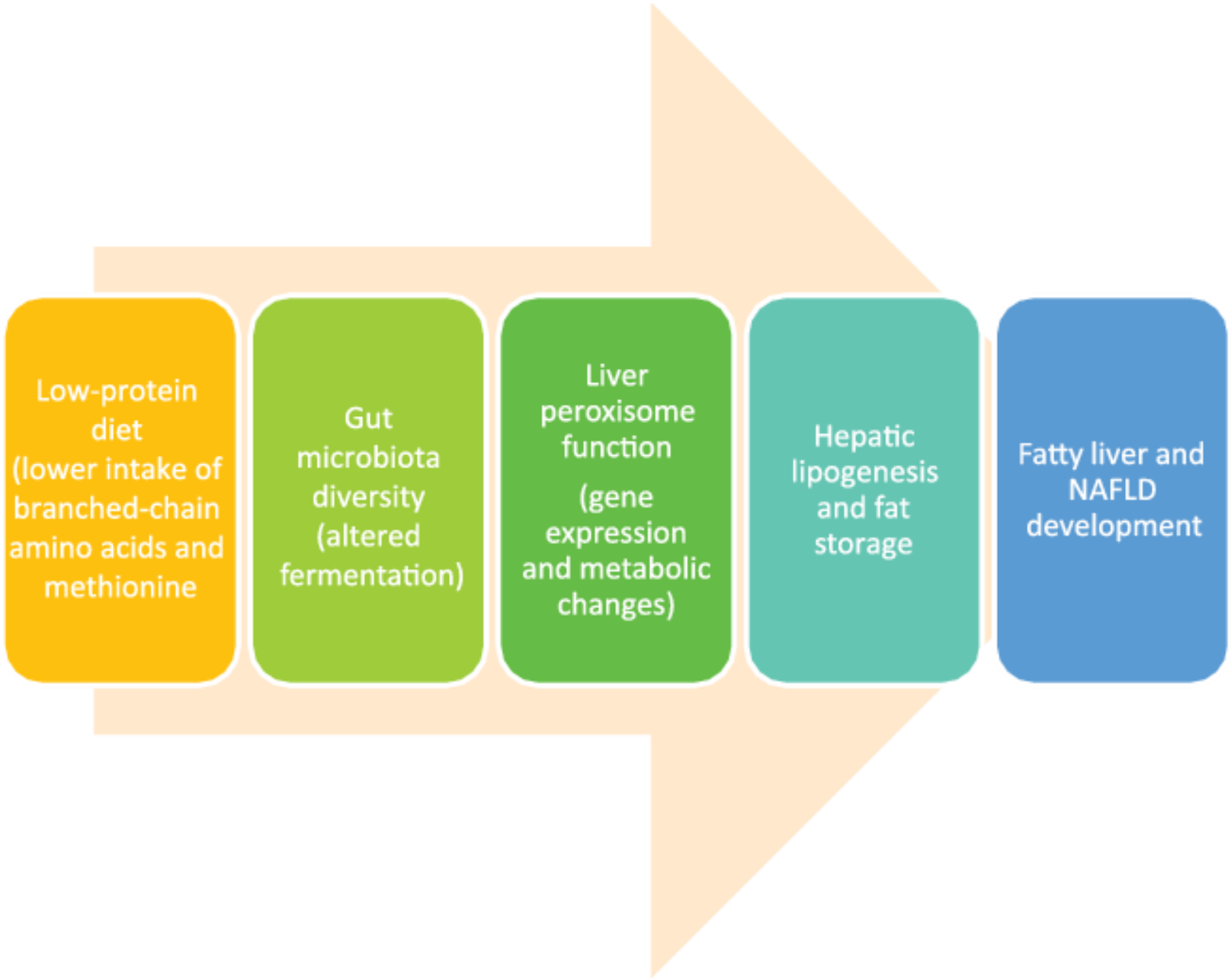
Prebiotic intake has also been shown to **improve liver phenotype** in NAFLD patients.

The role of protein

The role of protein intake in the development of NAFLD is **unclear**.

Existing studies do **not** provide evidence **for or against**.

This may be because of the methodology used in the different studies, the origin of the protein source used (vegetable or animal), as well as the foods containing it.



CONTRIBUTION OF MICRONUTRIENTS TO NON-ALCOHOLIC FATTY LIVER DISEASE

Micronutrients are important for the development of.

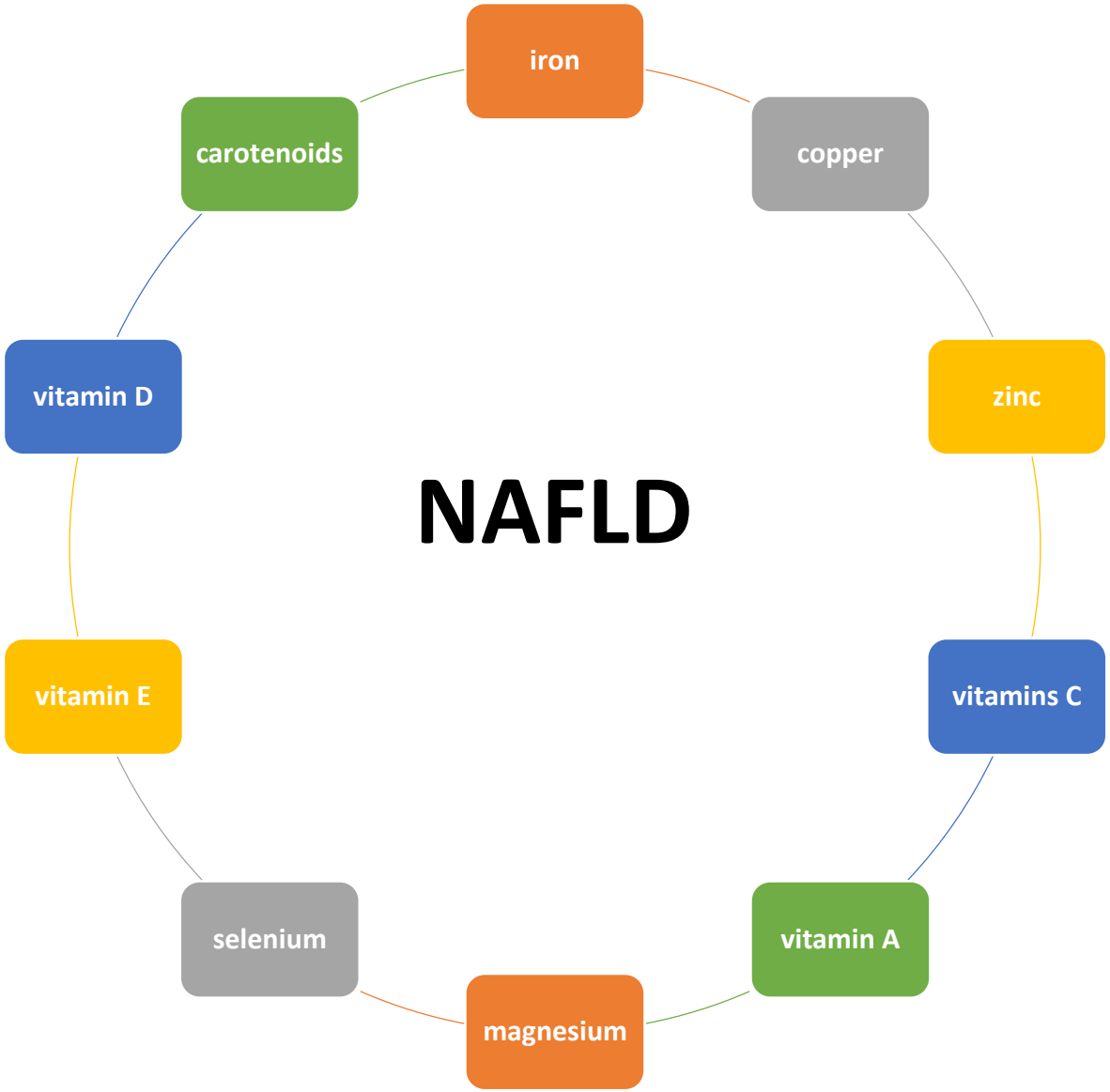
The proposed mechanisms of action are their:

1. Antioxidant
2. antifibrotic,
3. Immunomodulatory
4. lipoprotective

effects.

Non-alcoholic fatty liver disease patients have been shown to have **decreased levels** of serum zinc, copper, vitamins A, C, D, E and carotenoids.

Moreover, an iron and selenium **excess** have been reported to play a role in the severity of NAFLD.



CONTRIBUTION OF MICRONUTRIENTS TO NON-ALCOHOLIC FATTY LIVER DISEASE

Lipid soluble vitamins have been linked to NAFLD, mainly **low serum levels of vitamin A**.

Because vitamin A may be beneficial, there are some concerns about supplementation. Vitamin A has many other effects.

Treatment with **vitamin E** showed a **decrease** in:

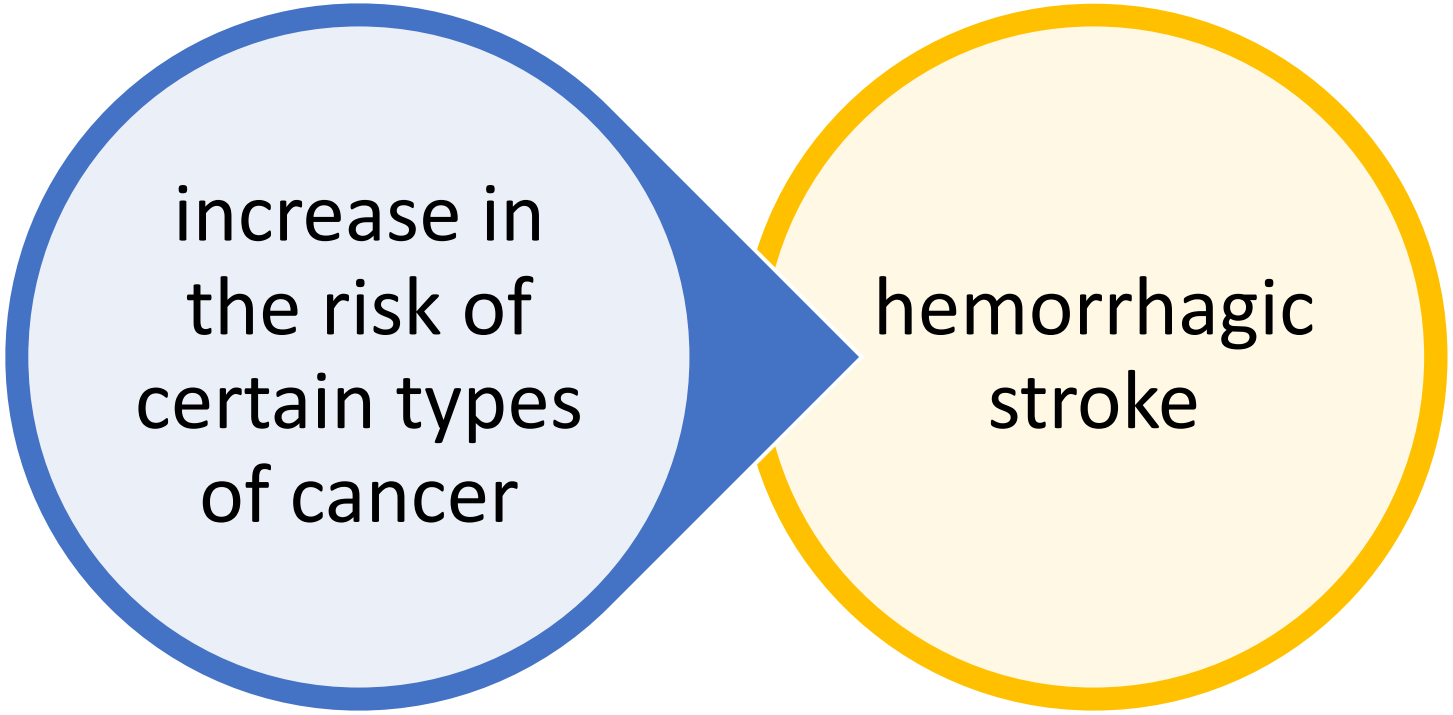
1. transaminase levels
2. liver lobular inflammation
3. improved liver fibrosis
4. reduced steatosis

Vitamin E supplementation is a common practice in AFLD patients.

Vitamin E has antioxidant effects and NAFLD patients present with increased oxidative stress.

CONTRIBUTION OF MICRONUTRIENTS TO NON-ALCOHOLIC FATTY LIVER DISEASE

vitamin E supplementation could have different **side effects**



CONTRIBUTION OF MICRONUTRIENTS TO NON-ALCOHOLIC FATTY LIVER DISEASE

A mix of micronutrients could be proposed to help in the treatment of NAFLD. However, the interactions between different vitamins and between vitamins and macro/micronutrients must be taken into consideration.

Moreover, identifying the contribution of specific micronutrients is difficult because **human diets are complex** and vary and may not correspond to experimental dietary models. Thus, it is difficult to recommend diets with specific micronutrients.

Relationship between food group intake and non-alcoholic fatty liver disease

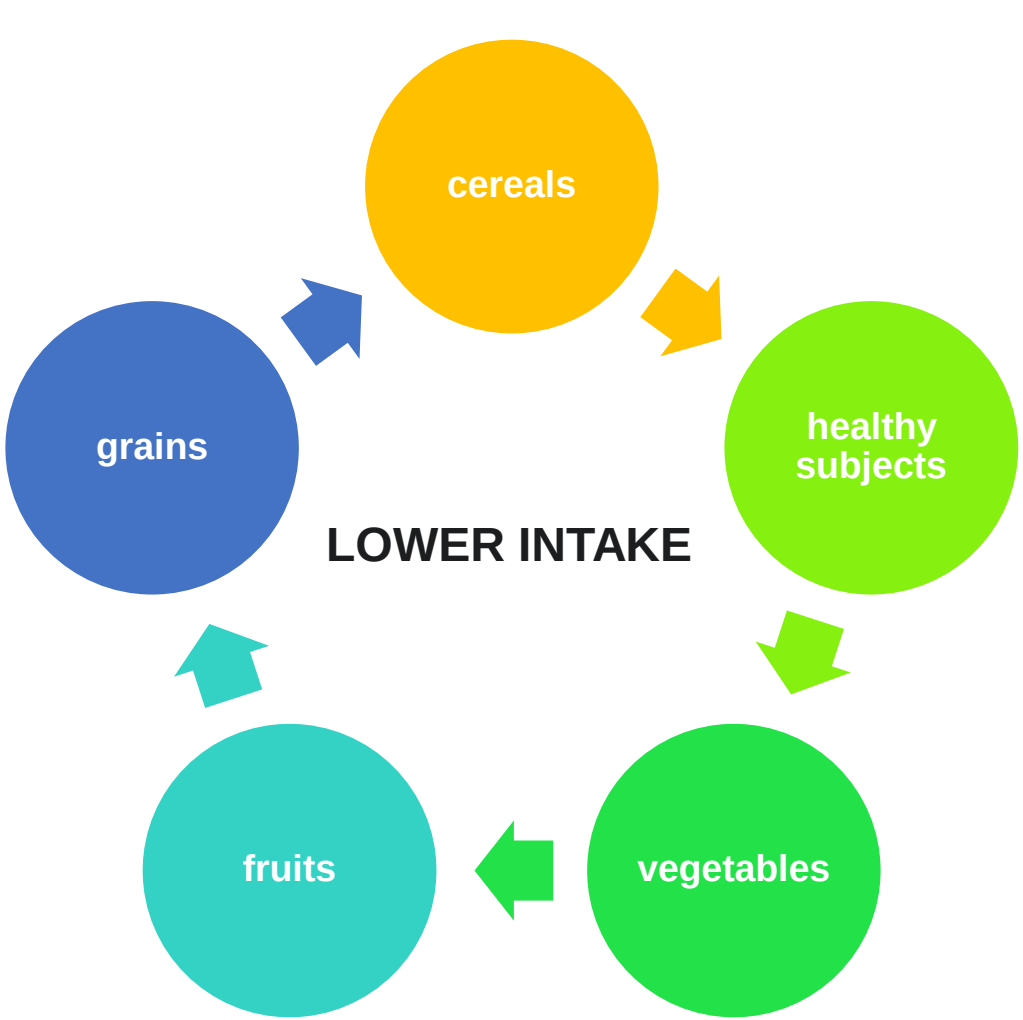
Nutrients are contained in the foods that people eat, thus a more physiological approach is an analysis of the intake of food groups and their relationship with NAFLD.

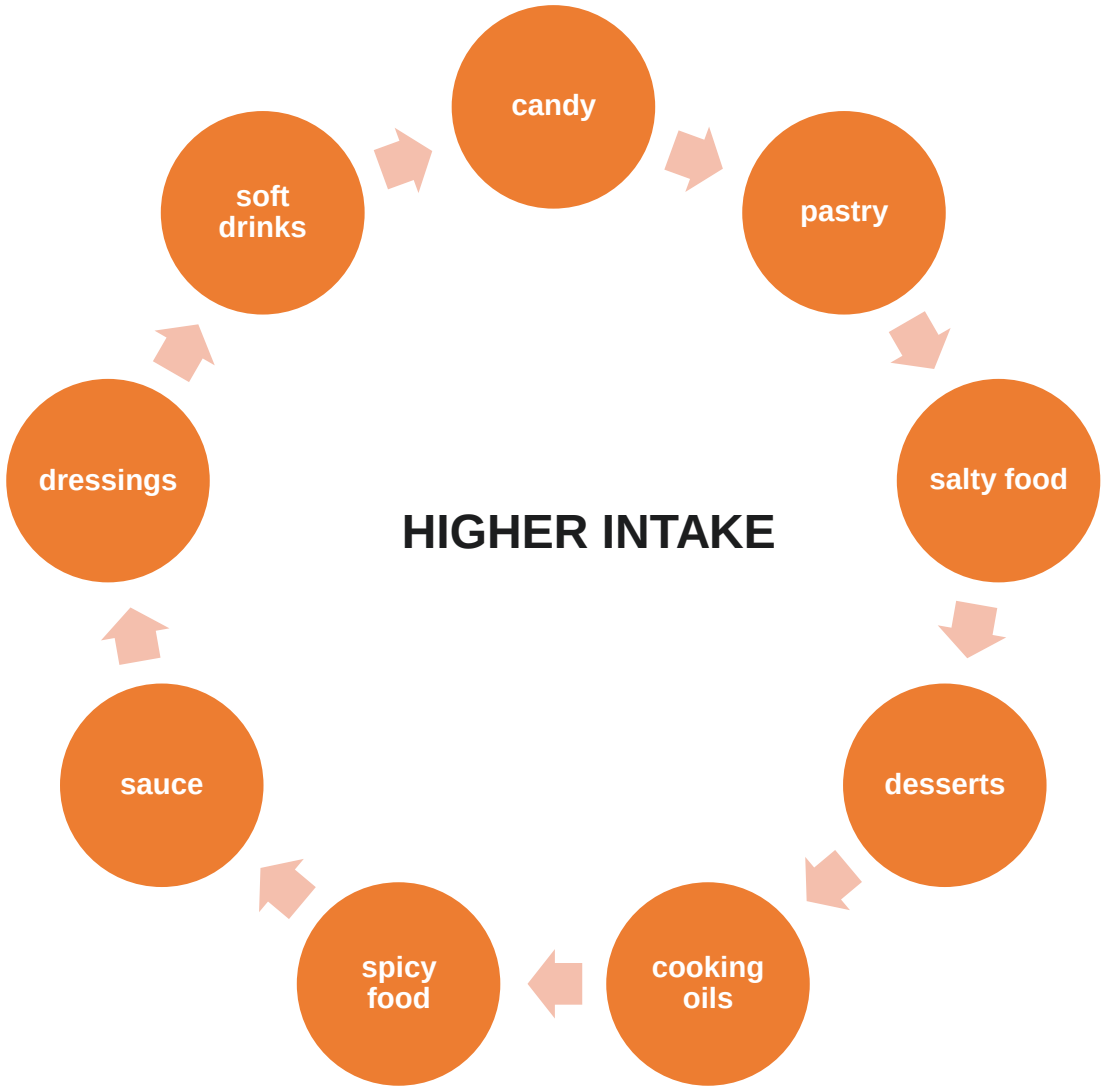
There is a general consensus that the intake of a variety of foods is important to prevent the development of NAFLD.

The foods that are considered to be beneficial for the prevention and progression of NALFD are whole grain cereals, fruits and vegetables, fatty fish (mainly high in ω3) and EVOO.

On the other hand, foods that are considered to adversely effect NALFD include red meat and processed meats, soda, processed foods, cakes and biscuits.

Relationship between food group intake and non-alcoholic fatty liver disease





Relationship between food group intake and non-alcoholic fatty liver disease

A recent study showed that patients with NAFLD had a higher intake of red and processed meats. The effect was **independent** of saturated fat and cholesterol intake. Moreover, cooking meat at **high temperatures** for a long period could be an important factor.

Extra virgin olive oil is a '**protective**' food and exerts its healthy effects through MUFAs (especially oleic acid) and phenolic compounds. It has been suggested that EVOO should be included in the diets of NAFLD patients since it reduces insulin resistance and blood triglycerides, thus inducing downregulation of lipogenic genes.

In a randomized, double-blind clinical trial, the consumption of 20 g/d of olive oil attenuated the fatty liver grade in NAFLD patients. Finally, a randomized trial in prediabetic patients with an isocaloric diet rich in EVOO, reported a decrease in liver fat and an improvement in both hepatic and total insulin sensitivity.

Relationship between food group intake and non-alcoholic fatty liver disease

Because people consume different amounts of various food groups and because of the limited number of large clinical trials, in some cases the impact of different foods are **not clear**, for example dairy products, coffee and rice.

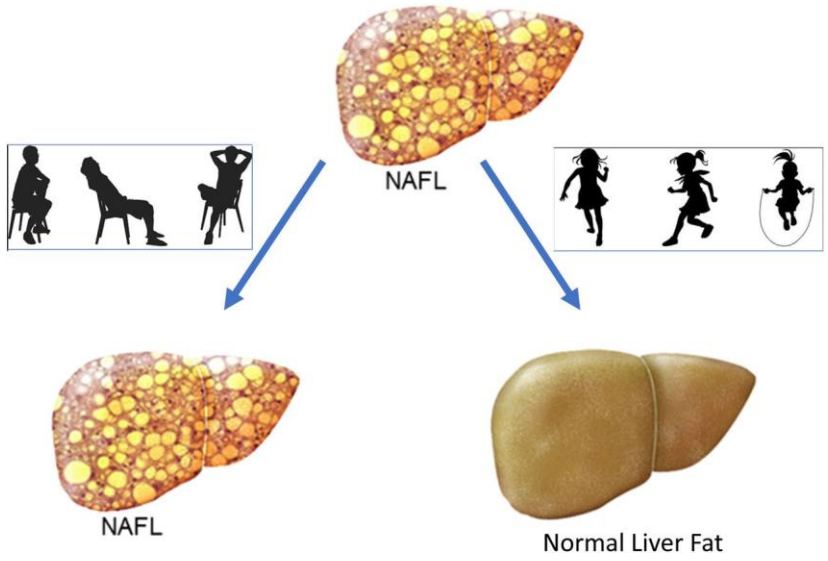
The results of studies on the consumption of dairy products were inconclusive in relation to NAFLD while those on coffee were **contradictory**.

Effect of Exercise on NAFLD and Its Risk Factors

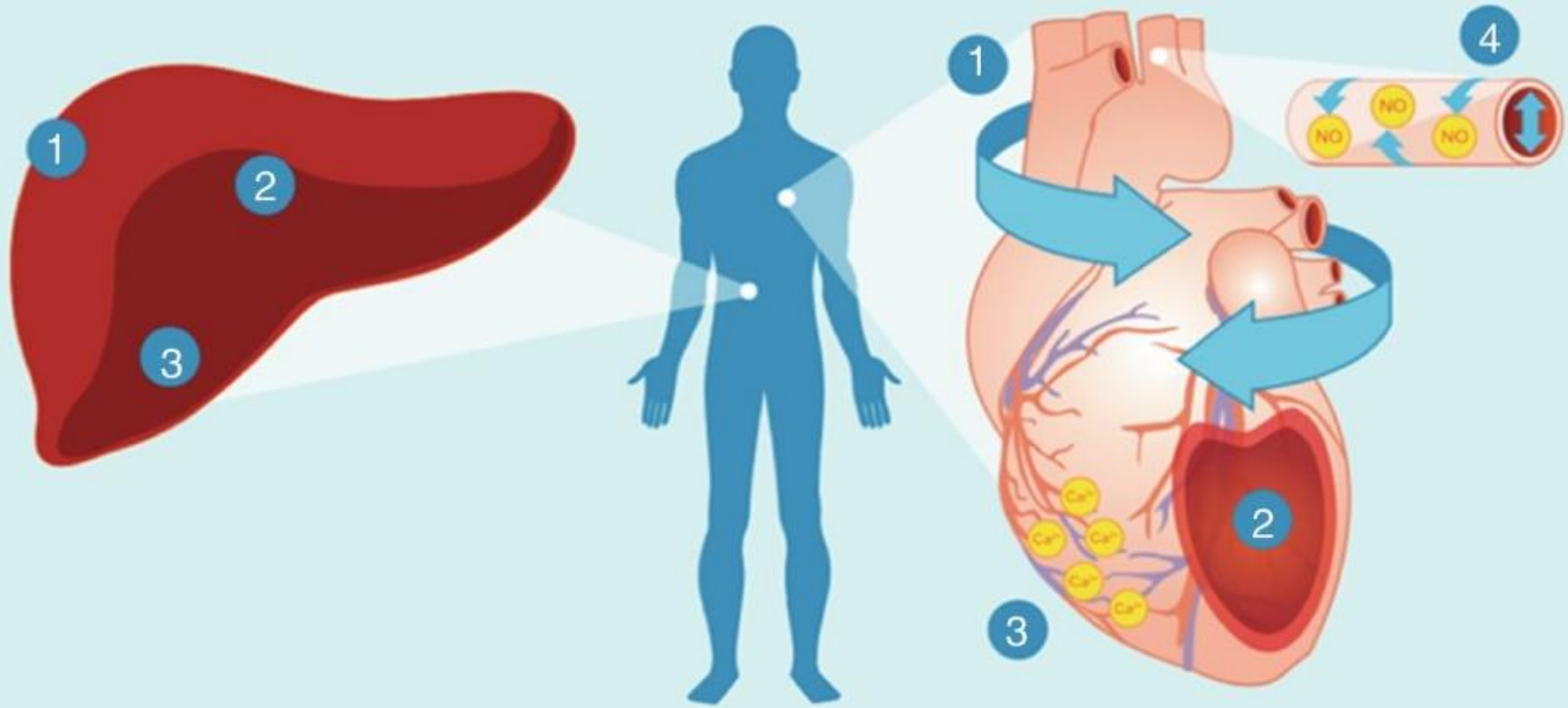
Exercise is a major component of **treatment** for NAFLD, as recommended by the American Gastroenterological Association, the American Association for the Study of Liver Diseases and the European Association of Study of Liver.

As compared to type 2 diabetes mellitus, there is a paucity of data supporting the role of physical activity in management of NAFLD.

This may be due to the **invasive nature of grading hepatic steatosis** by needle biopsy and histology, which limits the capacity for repeated measurement of hepatic steatosis and degree of necroinflammation.



Benefits of exercise in NAFLD



Changes in the liver

1. Peripheral insulin sensitivity ↑ = de novo lipogenesis ↓
2. Visceral fat ↓ = lipid supply to liver ↓
3. VLDL clearance ↑ = lipid storage ↓

Changes to cardiovascular system

1. Torsion ↓ = myocardial damage ↓
2. EDV ↑ = preload ↑
3. Ca^{2+} handling ↑ = SV ↑ + EV ↑
4. FMD ↑ = O^2 supply ↑

Effect of Exercise on NAFLD and Its Risk Factors

The federal guidelines of the USA's Department of Health and Human Services and the USA's Department of Agriculture recommend that:

1. adults should perform 150 min or more of moderate-intensity physical activity per week

2. 75 min or more of vigorous intensity physical activity per week, or a combination

to improve and maintain health.

The Centers for Disease Control and Prevention and the World Health Organization recommendations are also the **same**.

For additional health benefits, the amount of physical activity recommended should be **doubled**. However, **controversy** remains over the role of **exercise intensity** and **total volume of exercise** responsible for final health outcomes.

Effect of Exercise on NAFLD and Its Risk Factors

The effect of exercise with or without hypocaloric diet on NAFLD patients has been studied in various clinical trials.

Most of these studies had smaller number of subjects, absence of measurement of volume (calorie) and intensity of exercise, and some lacked histological endpoints.

All trials showed significant **improvement** in BMI, serum enzymes (AST/ALT), and degree of fatty liver.

There are several studies that have demonstrated a dose-dependent improvement in liver histology and intrahepatic triglycerides dependent on the degree of weight loss achieved.

However, the improvement in transaminases, HOMA-IR, FLI and resolution of ultrasonographic fatty change in liver was **independent of the degree of weight loss** in some study.

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Supplementary Table 1. Comparison of various studies assessing effect of exercise on NAFLD

Study	Year	No of subjects	Mean age	Mean BMI	Sex (male %)	Duration of intervention (physical activity)	Effect on AST/ALT	Primary outcome
Uneno *et al.*[19]	1997	10	39± 13	31±5	52	12-weeks	Decreased	Improvement in liver histology
Huang *et al.*[20]	2005	15	47.8± 12	33.8± 6	48	12-months	Decreased	Improvement in liver histology
Nobili *et al.*[21]	2008	25	11.7	26.8	82.1	24-months	Decreased	Improvement in liver histology
Gomez *et al.*[22]	2009	30	49± 10	31.5±4	53	6-months	Decreased	Improvement in NAS and fibrosis score
Promrat *et al.*[8]	2010	10	48.9± 11	33.9±5	66	48-weeks	Decreased	
Kistler *et al.*[23]	2011	813	48±12	NA	37.1	Physical activity self-reported	NA	Association of physical activity intensity and NAFLD severity
George *et al.*[24]	2009	141	47.5±12.4	31.9±6.0	61.7	3-months	Decreased	Improvement in liver enzymes
Wong *et al.*[25]	2013	154	51±9	25.5±3.9	46.8	12-months	Decreased	Remission of NAFLD by 1H-MRS
Houghton *et al.*[26]	2017	24	59±12	35±5	NA	12-weeks	No change	Improvement in hepatic triglyceride content
Vilar-Gomez *et al.*[27]	2015	293	48.5±9.6	31.3±5.3	41	12-months	Decrease in NAS score	Improvement in liver histology
Our study	2015-16	29	46.8±9.8	26.4±2.1	100	6-months	Decreased	Improvement in liver enzymes

Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; NA, not available; NAS, NAFLD activity score; 1H-MRS, magnetic resonance spectroscopy.

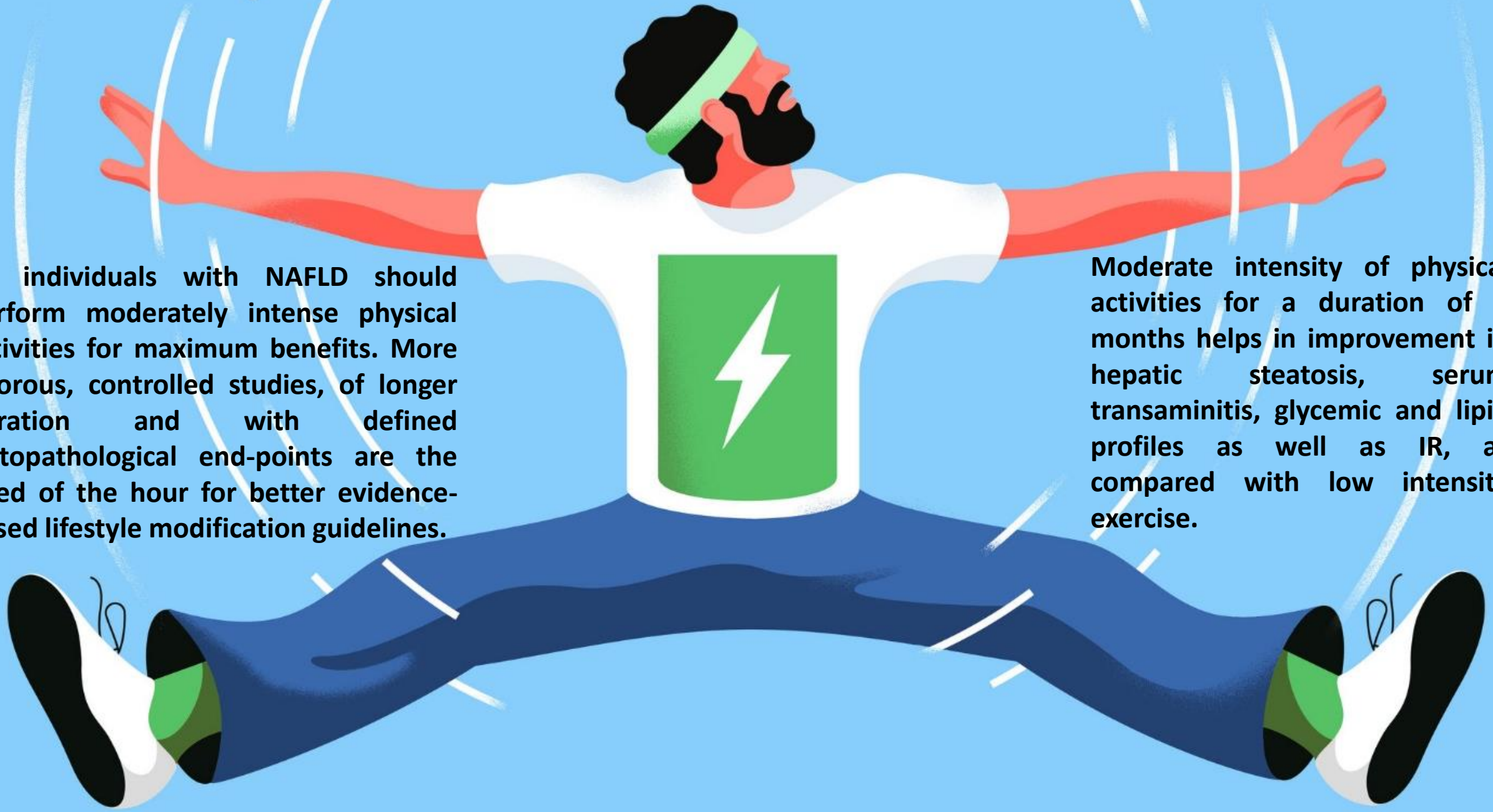
Effect of Exercise on NAFLD and Its Risk Factors

Recently, the intensity rather than duration of exercise and total calorie expenditure during physical activity has caught the attention of researchers. Kistler *et al.*

in a retrospective study examined the effect of exercise intensity on histological severity of NAFLD. In this study, the exercise volume and intensity was calculated by self-reported physical activity data from adult patients with biopsy-proven NAFLD enrolled in the Nonalcoholic Steatohepatitis Clinical Research Network, and the NAFLD patients were classified into moderate and vigorous exercise groups as per the federal recommendations.

The study demonstrated an **inverse relationship** between the **intensity of physical activity** and **severity of NAFLD**. However, this study was limited by its cross-sectional nature, measurement limitations, and misclassification due to reporting and recall bias. On the contrary, in our study, we measured the exercise intensity prospectively with objective methods (by accelerometers).

Effect of Exercise on NAFLD and Its Risk Factors



All individuals with NAFLD should perform moderately intense physical activities for maximum benefits. More rigorous, controlled studies, of longer duration and with defined histopathological end-points are the need of the hour for better evidence-based lifestyle modification guidelines.

Moderate intensity of physical activities for a duration of 6 months helps in improvement in hepatic steatosis, serum transaminitis, glycemic and lipid profiles as well as IR, as compared with low intensity exercise.