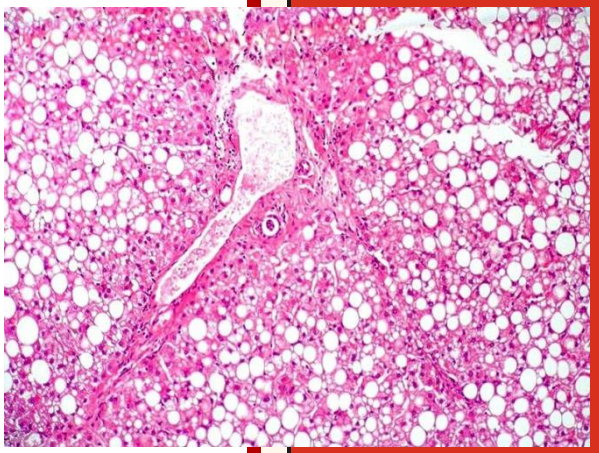
La NAFLD: malattia del benessere e grave malessere

Dott.ssa Sara Traini

U.O.C. Gastroenterologia

Area Vasta 4

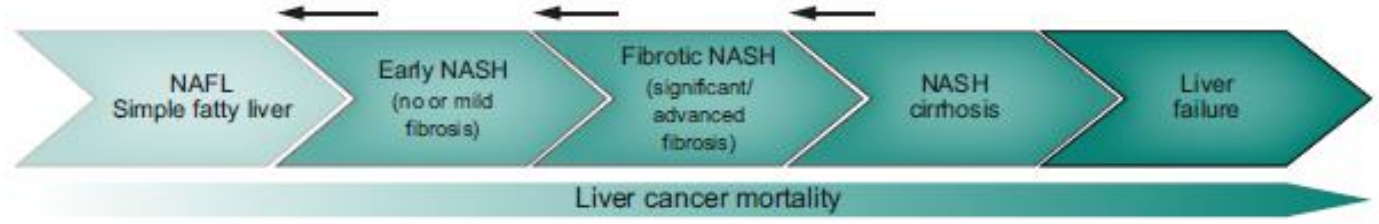
Ospedale «A. Murri» Fermo



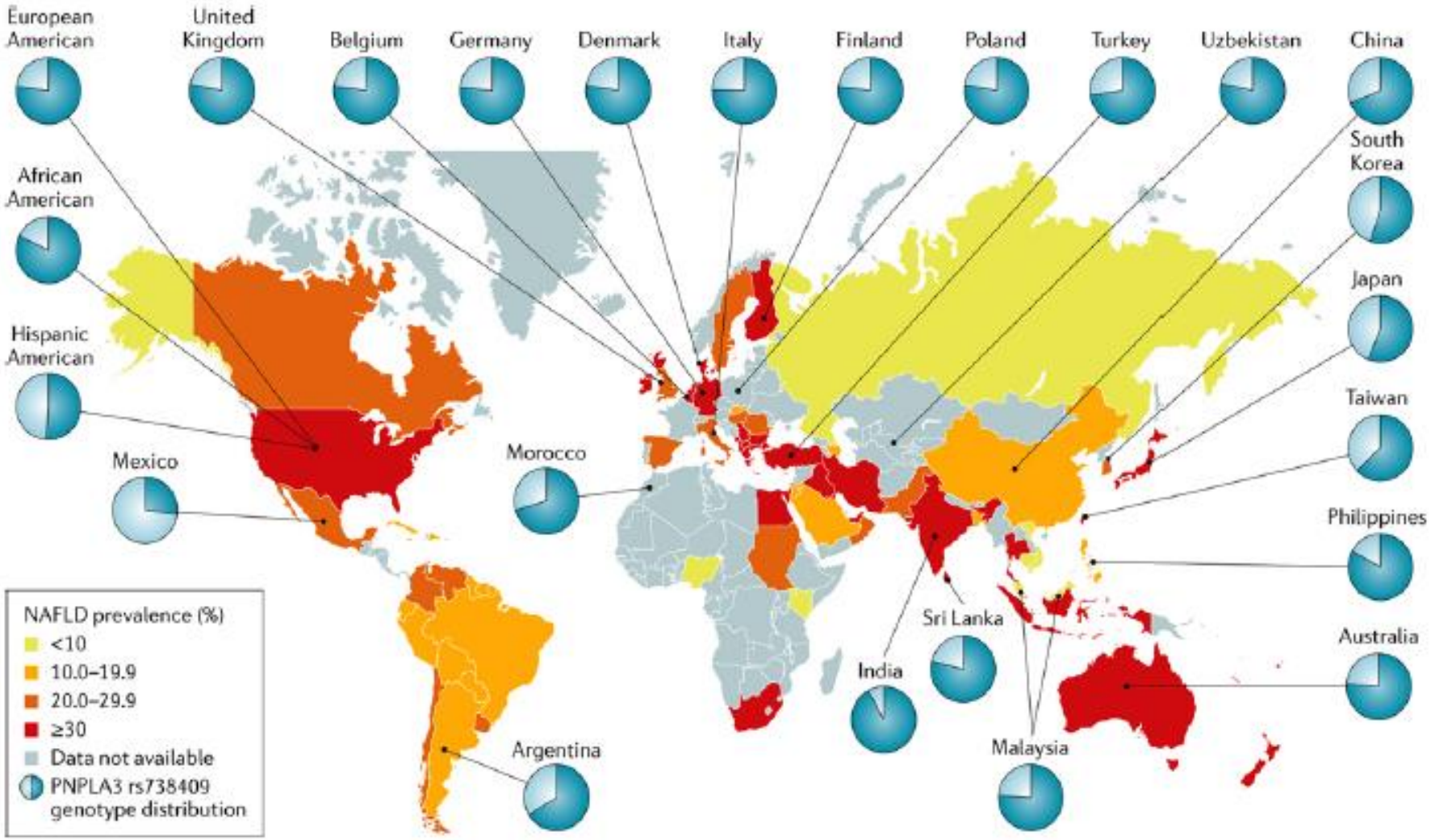
SM Francque et al. JHEP Reports 2021

NAFLD: malattia lentamente progressiva

- Nella maggior parte dei casi la progressione è lenta, sia negli adulti che nei bambini; nel 20% dei casi la fibrosi progredisce rapidamente;
- Tra uno stadio di fibrosi e il successivo il tasso di progressione è di circa 14 anni in NAFL e di circa 7 anni in NASH;
- La presenza di ipertensione arteriosa raddoppia la velocità di progressione.



EASL-EASD-EASO Guidelines for the management of NAFLD – Journal of Hepatology 2016



Younossi, Z. *et al.* (2017) **Nature Reviews** | Gastroenterology & Hepatology

Table 1. Model forecasts – 2016 & 2030.

	China	France	Germany	Italy	Japan	Spain	UK	US
2016 Country population (000)	1,382,300	64,700	80,700	59,800	126,800	46,100	64,200	324,100
2030 Country population (000)	1,415,500	68,000	79,300	59,100	120,600	45,900	68,600	355,800
Adult obesity prevalence (BMI)	≥25 kg/m^2	≥30 kg/m^2	≥30 kg/m^2	≥30 kg/m^2	≥25 kg/m^2	≥30 kg/m^2	≥30 kg/m^2	≥30 kg/m^2
2016	26.9%	15.9%	25.2%	10.9%	23.9%	18.0%	26.9%	39.6%
2030	28.4%	17.7%	26.1%	11.4%	24.5%	18.9%	28.6%	41.7%
NAFLD								
2016 Total cases	243,661,000	13,982,000	18,447,000	15,217,000	22,666,000	10,532,000	14,079,000	85,266,000
2016 Prevalence (all ages)	17.6%	21.6%	22.9%	25.4%	17.9%	22.9%	21.9%	26.3%
2030 Total cases	314,580,000	16,046,000	20,945,000	17,421,000	22,735,000	12,653,000	16,921,000	100,901,000
2030 Prevalence (all ages)	22.2%	23.6%	26.4%	29.5%	18.8%	27.6%	24.7%	28.4%
NAFL								
2016 Total cases	211,049,000	11,676,000	15,122,000	12,611,000	18,904,000	8,728,000	11,476,000	67,949,000
2016 Prevalence (all ages)	15.3%	18.1%	18.7%	21.1%	14.9%	18.9%	17.9%	21.0%
2030 Total cases	266,318,000	12,657,000	16,206,000	13,675,000	18,415,000	9,966,000	13,168,000	73,898,000
2030 Prevalence (all ages)	18.8%	18.6%	20.4%	23.1%	15.3%	21.7%	19.2%	20.8%
NASH								
2016 Total cases	32,612,300	2,305,800	3,325,400	2,605,700	3,761,900	1,803,700	2,602,700	17,316,700
2016 Prevalence (all ages)	2.4%	3.6%	4.1%	4.4%	3.0%	3.9%	4.1%	5.3%
2030 Total cases	48,262,200	3,388,900	4,739,000	3,746,400	4,320,400	2,687,300	3,753,300	27,002,800
2030 Prevalence (all ages)	3.4%	5.0%	6.0%	6.3%	3.6%	5.9%	5.5%	7.6%
Incident NAFLD								
2016 Total cases	10,139,100	467,600	513,200	498,500	436,700	337,000	476,700	3,444,900
2016 Prevalence (all ages)	7.3	7.2	6.4	8.3	3.4	7.3	7.4	10.6
2030 Total cases	10,348,100	347,900	479,500	417,800	436,700	330,500	464,200	2,500,000
2030 Prevalence (all ages)	7.3	5.1	6.0	7.1	3.6	7.2	6.8	7.0
NASH mortality								
2016 Total cases	25,580	2,490	5,180	4,870	4,720	3,260	4,870	30,240
2016 Prevalence (all ages)	103,840	5,460	8,350	6,870	11,790	4,530	7,240	46,720
2030 Total cases	55,740	7,030	12,510	10,490	8,130	7,590	10,390	78,310
2030 Prevalence (all ages)	163,920	9,890	13,660	11,220	15,700	7,850	11,960	83,280

BMI, body mass index; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis.

C. Estes et al. – Journal of Hepatology 2018

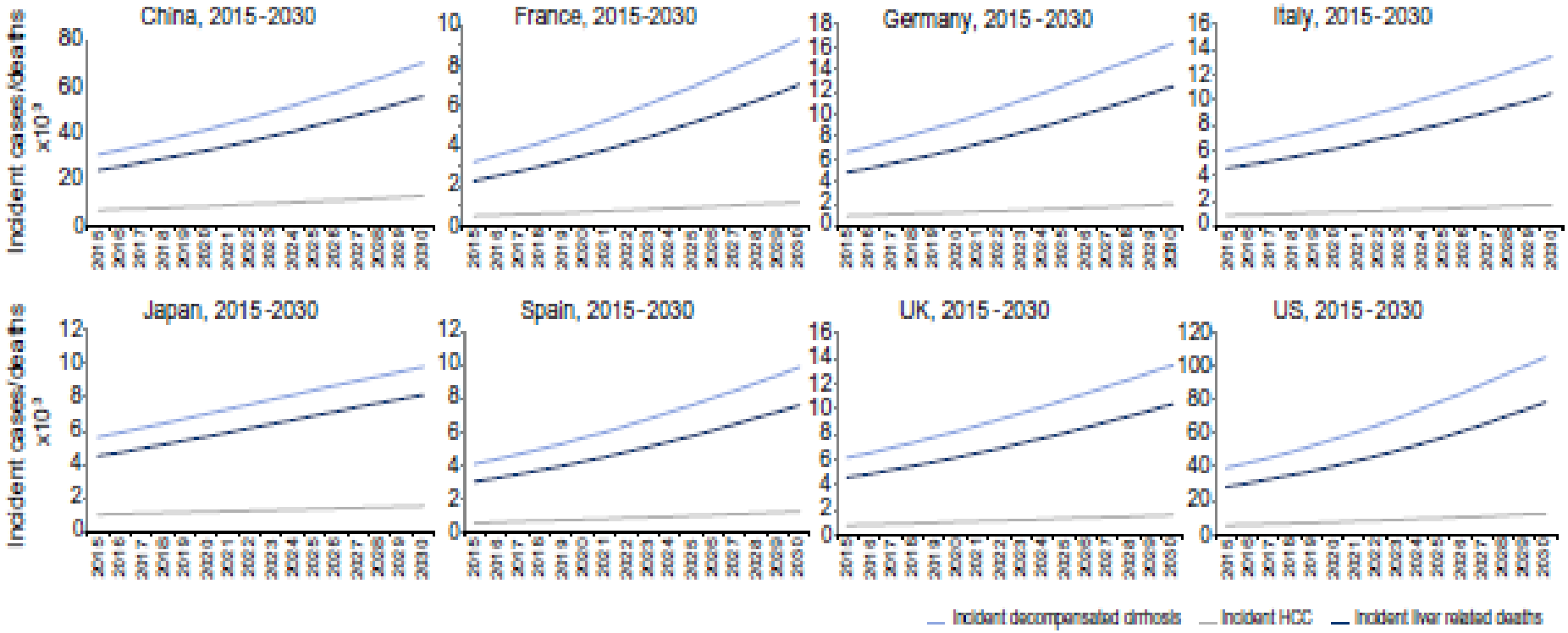
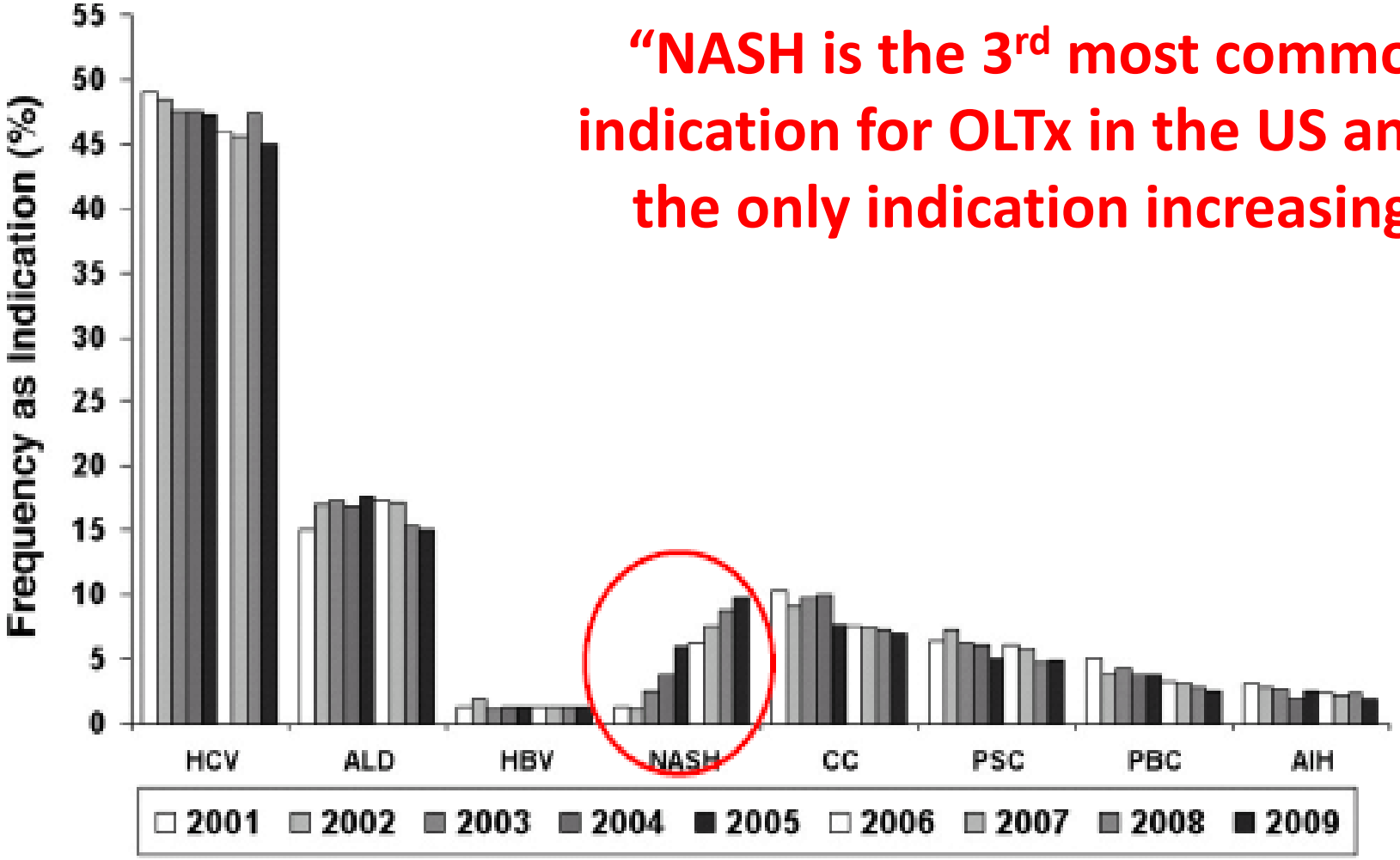


Fig. 3. Incident decompensated cirrhosis, HCC and liver-related deaths among prevalent NAFLD population – 2015–2030. HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.

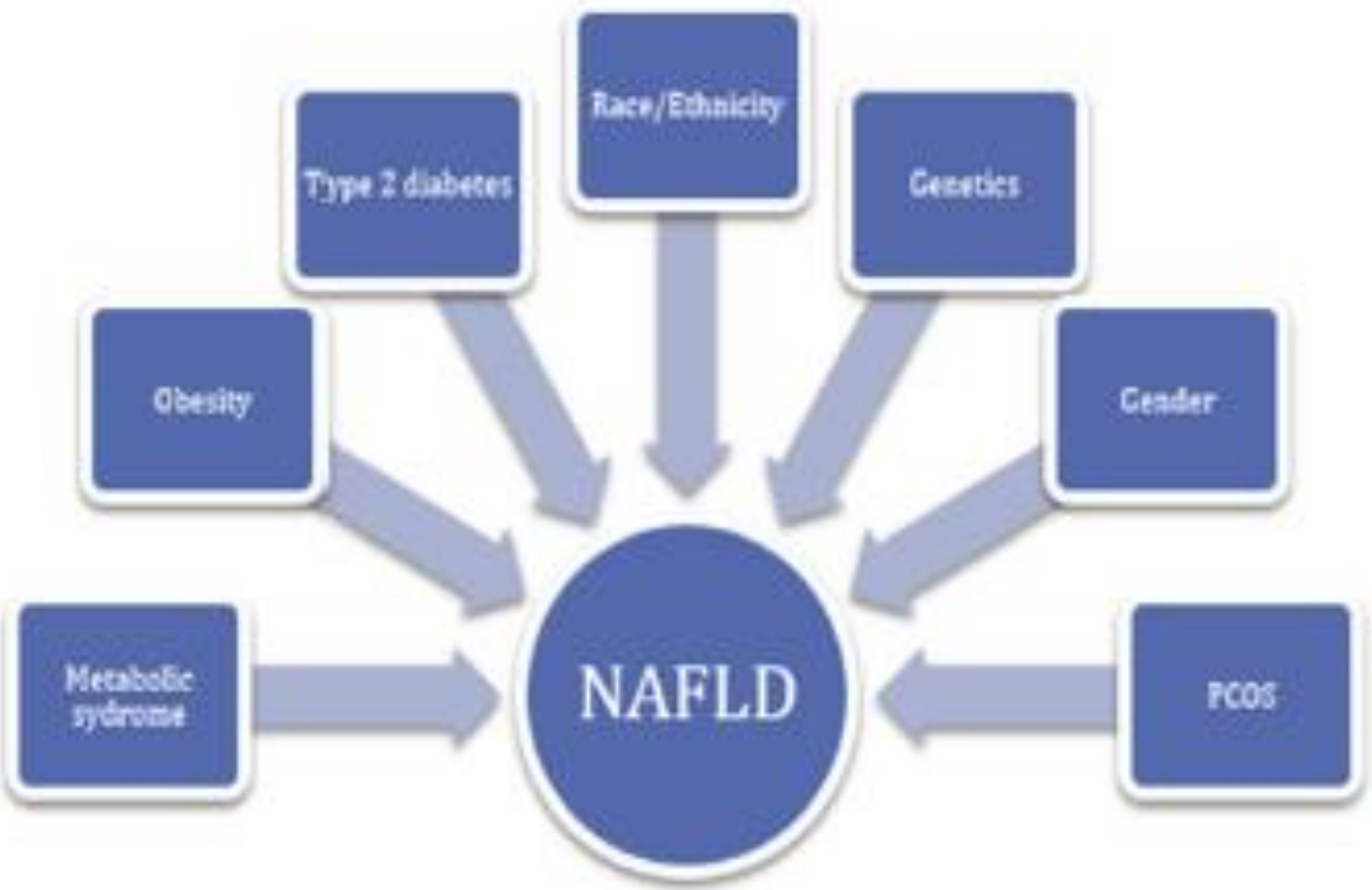
C. Estes et al. – Journal of Hepatology 2018

"NASH is the 3rd most common indication for OLTx in the US and is the only indication increasing"



Data Source: SRTR

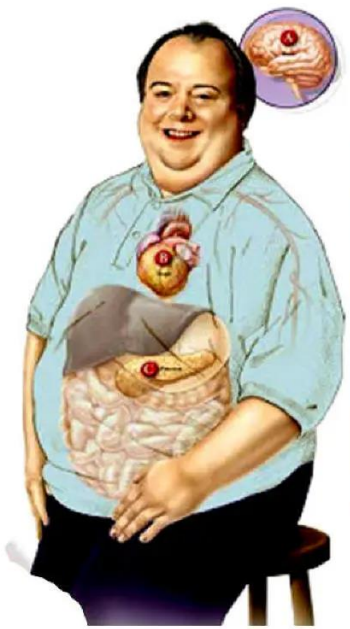
Charlton Gastroenterology 2011



HW Lim et al. Clin Liver Dis 2018

Fenotipi di pazienti con NAFLD:

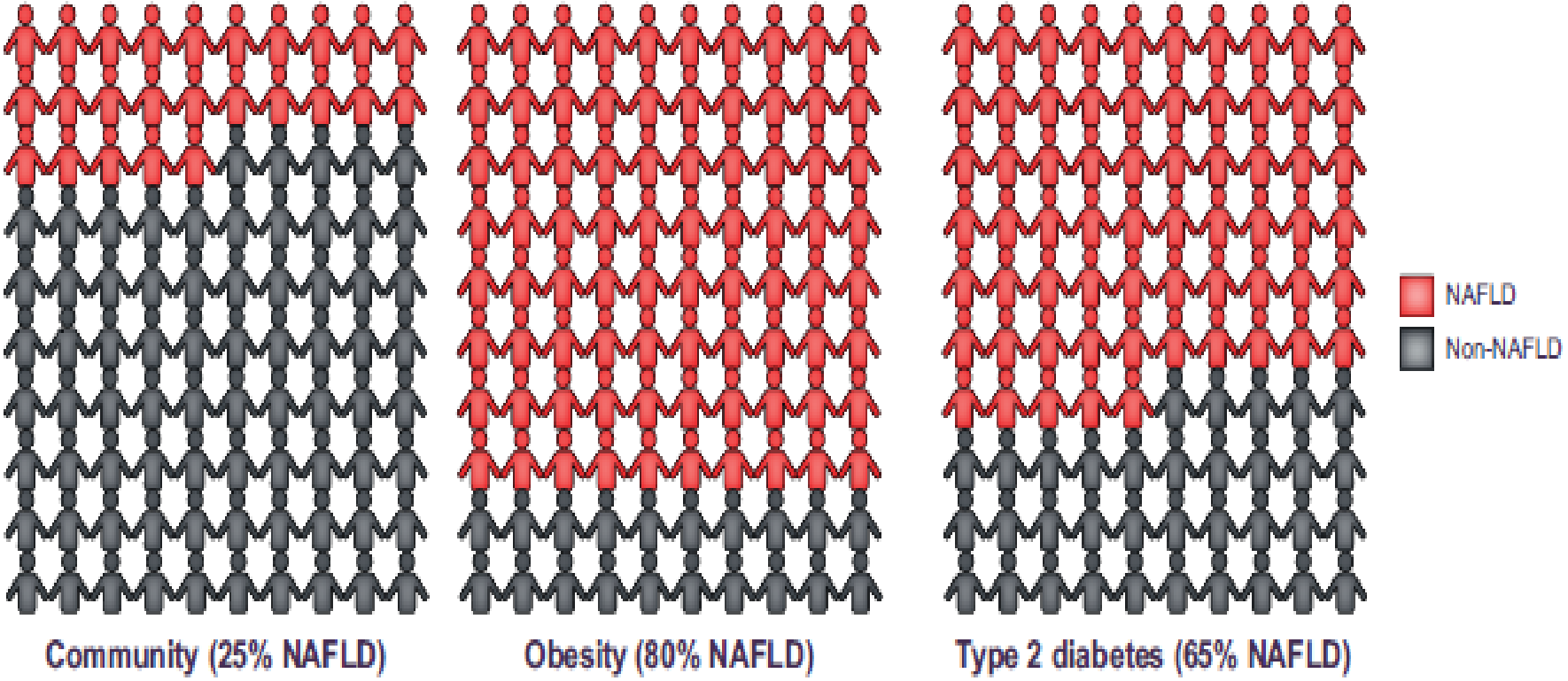
- Pazienti obesi;
- Pazienti con diabete mellito di tipo 2;
- Pazienti con sindrome metabolica;
- Pazienti «magri».



Sindrome metabolica

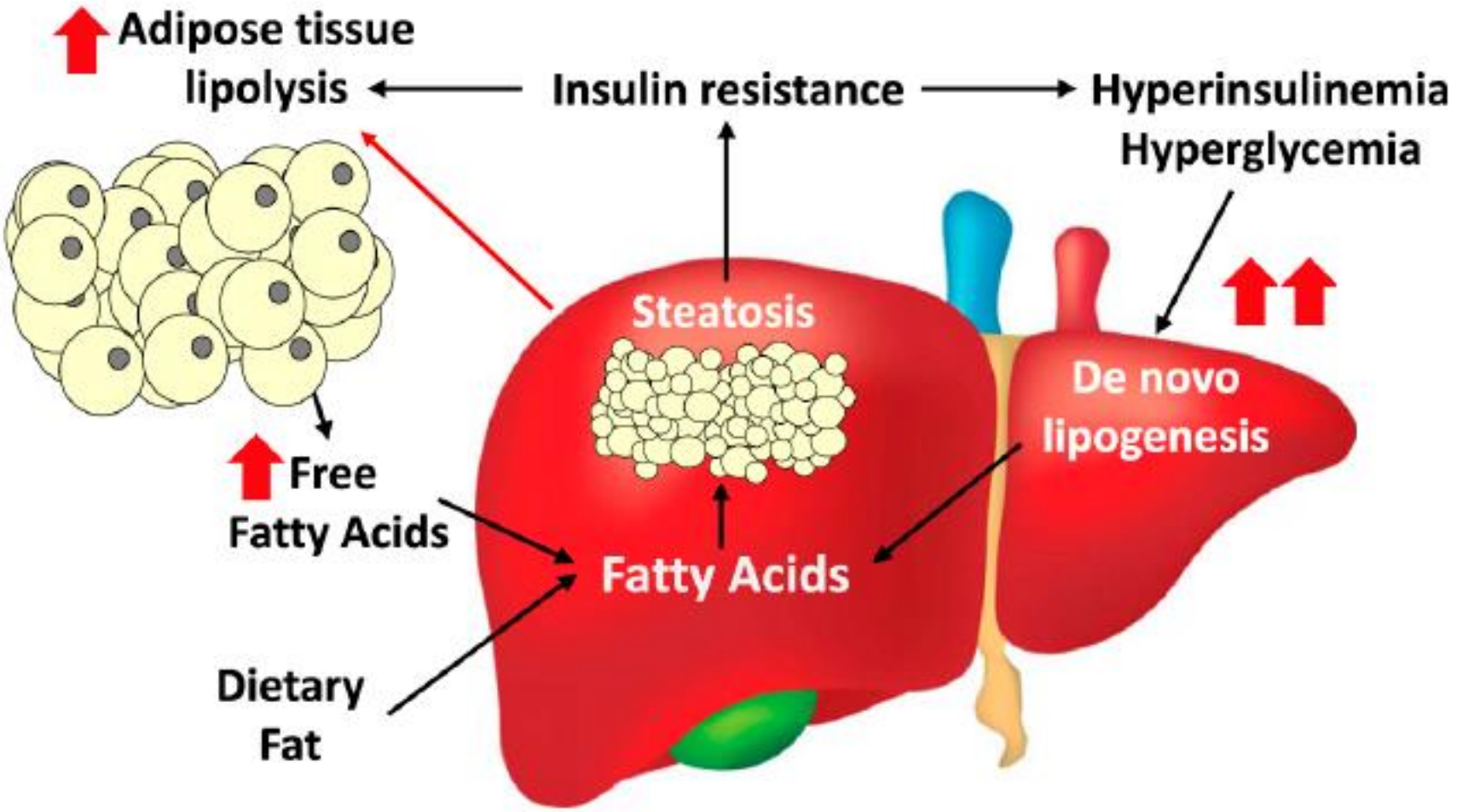
Parametro	Valore limite
Elevata circonferenza vita	102 cm (uomo)
	88 cm (donna)
Elevati trigliceridi	≥ 150 mg/dl
Ridotto colesterolo HDL	< 40 mg/dl (uomo)
	< 50 mg/dl (donna)
Pressione sanguigna elevata	sistolica ≥ 130 e/o diastolica ≥85 mm/Hg
Elevata glicemia a digiuno	≥ 100 mg/dl

M. Romero-Gomez et al.Journal of Hepatology 2017



SM Francque et al. JHEP Reports 2021

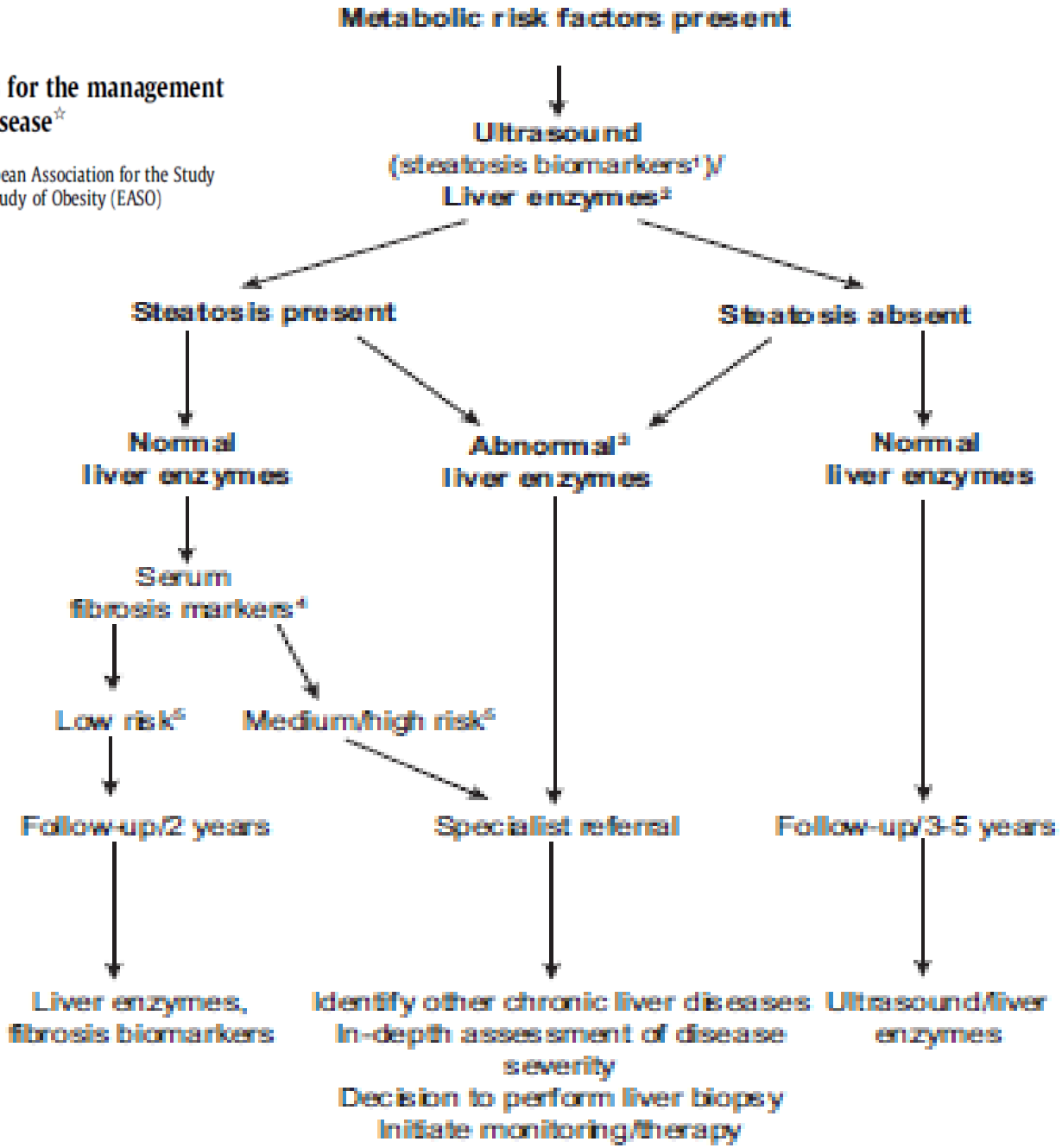
Interazione tra insulino-resistenza, diabete tipo 2 e NAFLD



JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)



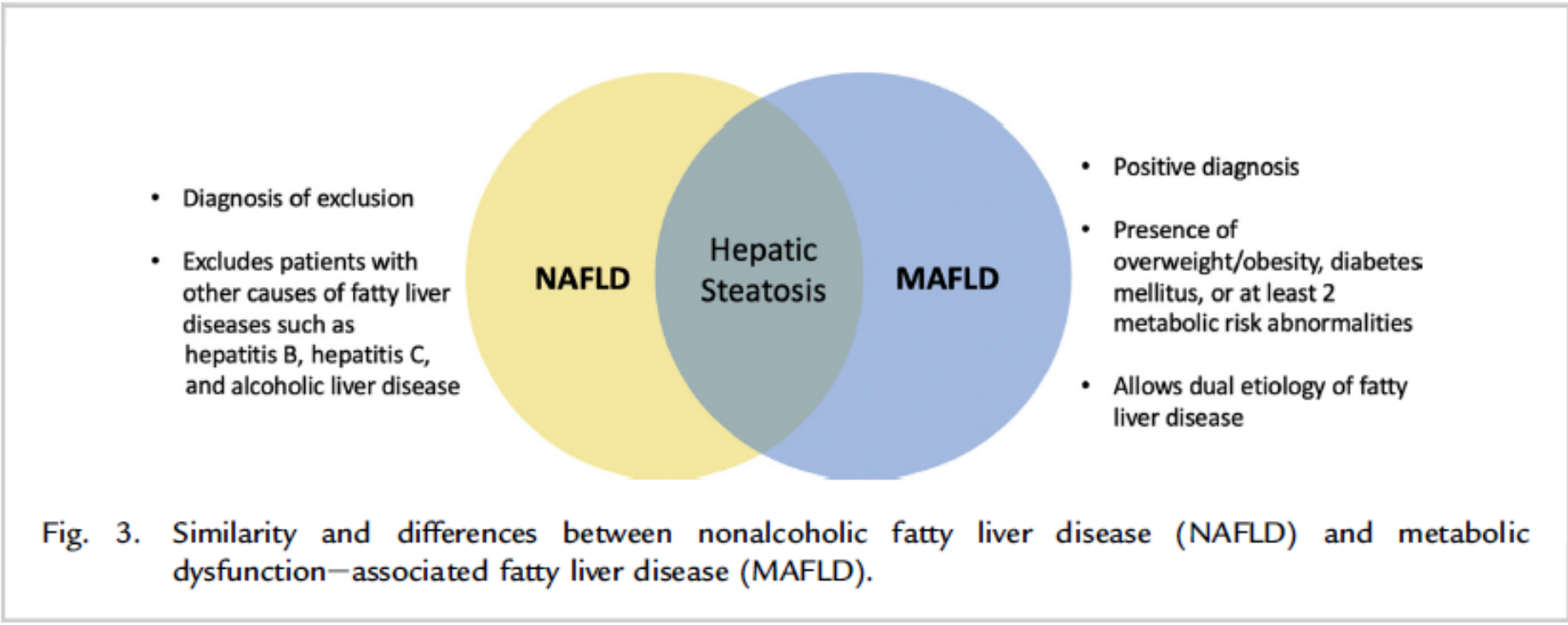


Fig. 3. Similarity and differences between nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction–associated fatty liver disease (MAFLD).

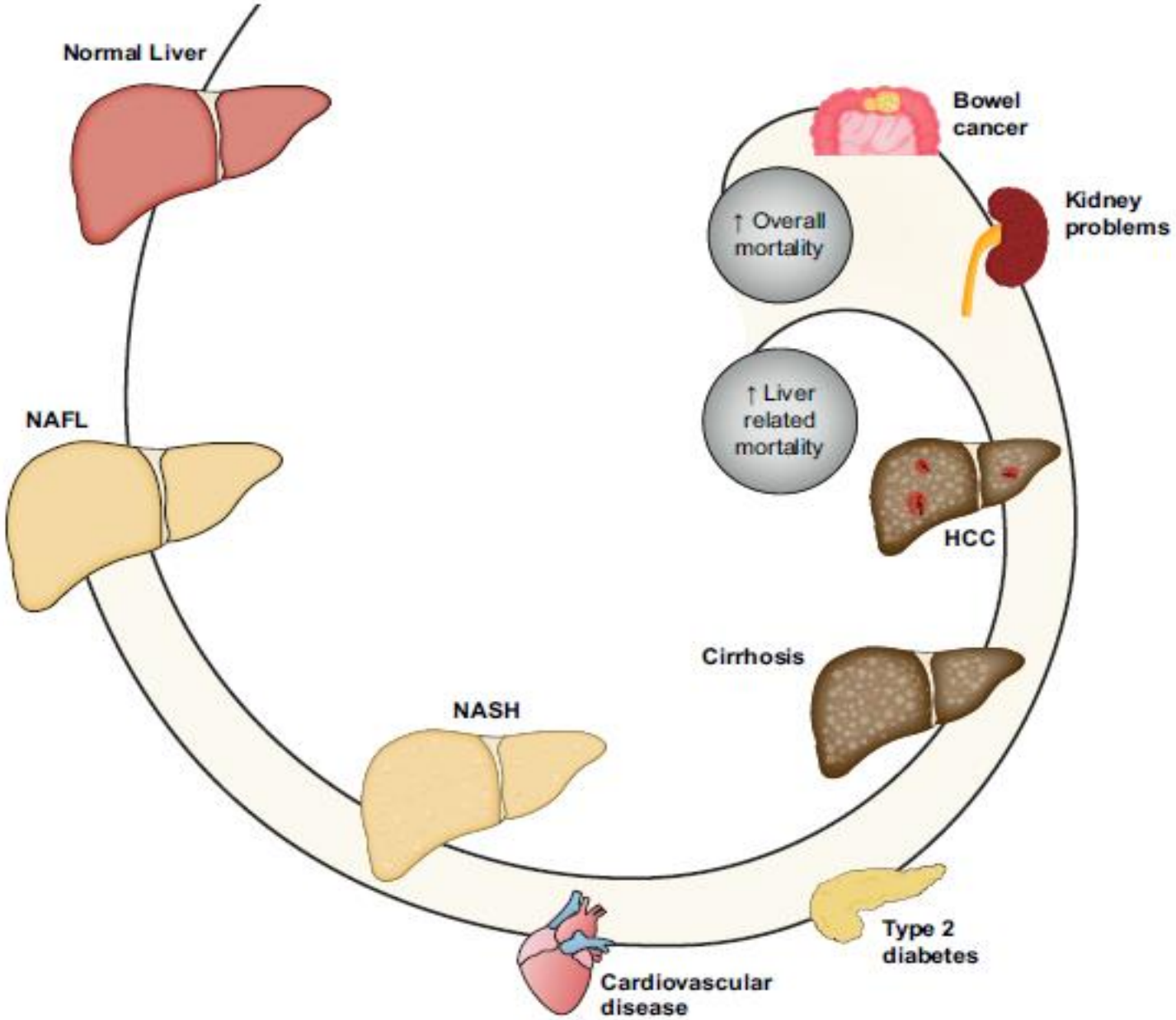
WK Wong et al. Clinical Therapeutics/Volume 43, Number 3, 2021

Editorial

JOURNAL OF HEPATOLOGY

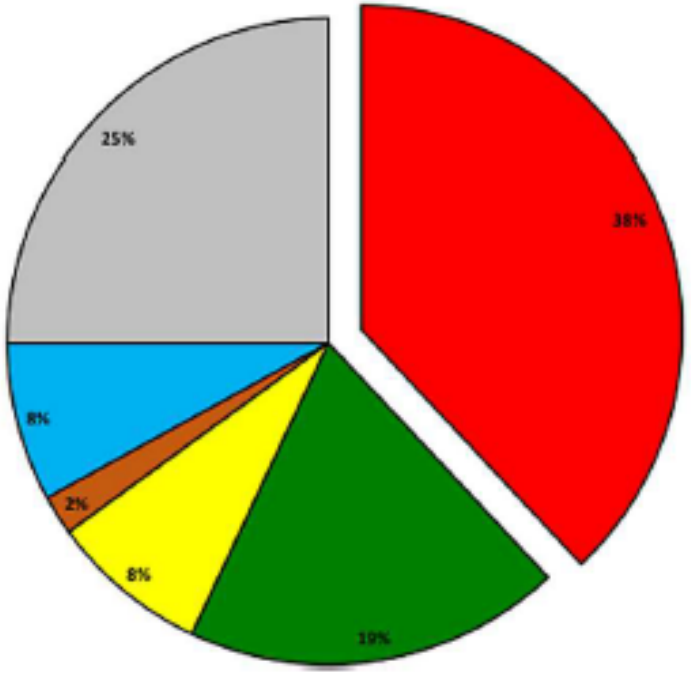
Prognosis of MAFLD *vs.* NAFLD and implications for a nomenclature change

Vincent Wai-Sun Wong[1,2,*], Jeffrey V. Lazarus[3,*]



Non-alcoholic fatty liver disease: A patient guideline – SM Francque et al. JHEP Reports

Principali cause di morte nei pazienti con NAFLD



Coorte di 619 pazienti con NAFLD (diagnosi mediante biopsia epatica) di cui 193 sono deceduti durante un periodo di follow-up (mediana) di 12.6 anni

- Malattia cardiovascolare
- Neoplasie extra-epatiche
- Complicanze epatiche (cirrosi)
- Epatocarcinoma
- Infezioni
- Altro

Mantovani A et al, L'Endocrinologo 2018

Cause of death	*N* (% of all deaths)
Coronary artery disease [ICD-9: 404 (hypertensive heart disease), 410–414 (ischemic heart disease), 427-429 (cardiac dysrhythmias, heart failure), 440 (atherosclerosis); ICD-10: I20–I25 (ischemic heart diseases), I46 (cardiac arrest), I50 (heart failure)]	32 (27.8 %)
Liver-related [ICD-9: 571–572 (chronic liver disease, cirrhosis, sequelae of CLD), 155.0 (primary liver cancer); ICD-10: K72–K74 (hepatic failure, chronic hepatitis, fibrosis and cirrhosis of liver), C22.0 (liver cell carcinoma)]	30 (26.1 %)
Malignancy [ICD-9: 151–153 (gastrointestinal), 157 (pancreas), 189 (kidney), 199 (other), 201 (Hodgkin's disease), 202 (other lymphoma); ICD-10: C18 (colon), C34 (lung), C64 (kidney), C81 (Hodgkin's disease), C97 (multiple)]	18 (15.7 %)
Other (diabetes, infection, pulmonary, accident, unknown)	35 (30.4 %)
Total (% of the studied cohort)	115 (39.8 %)

Terapia della NAFLD

Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFL	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

EASL

Drug treatment

Rationale. Drug therapy should be indicated for progressive NASH (bridging fibrosis and cirrhosis) but also for early-stage NASH with increased risk of fibrosis progression (age >50 years; diabetes, MetS, increased ALT [122]) or active NASH with high necroinflammatory activity [123]. No drug has currently been tested in phase III trials and is approved for NASH by regulatory agencies. Therefore, no specific therapy can be firmly recommended and any drug treatment would be off-label (for reviews see [124–126], Table 4). Safety and tolerability are essential prerequisites for drug treatment, because of NASH-associated comorbidities and polypharmacy, a potential source of drug-drug interactions.

Table 5. Elements of a comprehensive lifestyle approach to NAFLD treatment.

Area	Suggested intervention	Supportive literature
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week	Calorie restriction drives weight loss and the reduction of liver fat, independent of the macronutrient composition of the diet [107]
	• 7-10% total weight loss target	A 12-month intensive lifestyle intervention with an average 8% weight loss leads to significant reduction of hepatic steatosis [108]
	• Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment	Hepatic fat increases along with total body fat regain, but most of the beneficial metabolic effects are maintained and progression to T2DM is delayed [109].
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein	Adherence to the Mediterranean diet has been reported to reduce liver fat on ^{1}H-MRS, when compared with a low fat/ high carbohydrate diet in a cross-over comparison [110, 111]
Fructose intake	• Avoid fructose-containing beverages and foods	In the general population, an association has been reported between high fructose intake and NAFLD [9]
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)	In epidemiological surveys, moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis at histology [112-114]. Total abstinence is mandatory in NASH-cirrhosis to reduce the HCC risk [115]
Coffee drinking	• No liver-related limitations	Protective in NAFLD, as in liver disease of other aetiologies, reducing histological severity and liver-related outcomes [116]
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise	Physical activity follows a dose-effect relationship and vigorous (running) rather than moderate exercise (brisk walking) carries the full benefit, including for NASH and fibrosis [110, 117, 118] Any engagement in physical activity or increase over previous levels is however better than continuing inactivity

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease–JHEP 2016

Review

JOURNAL OF HEPATOLOGY

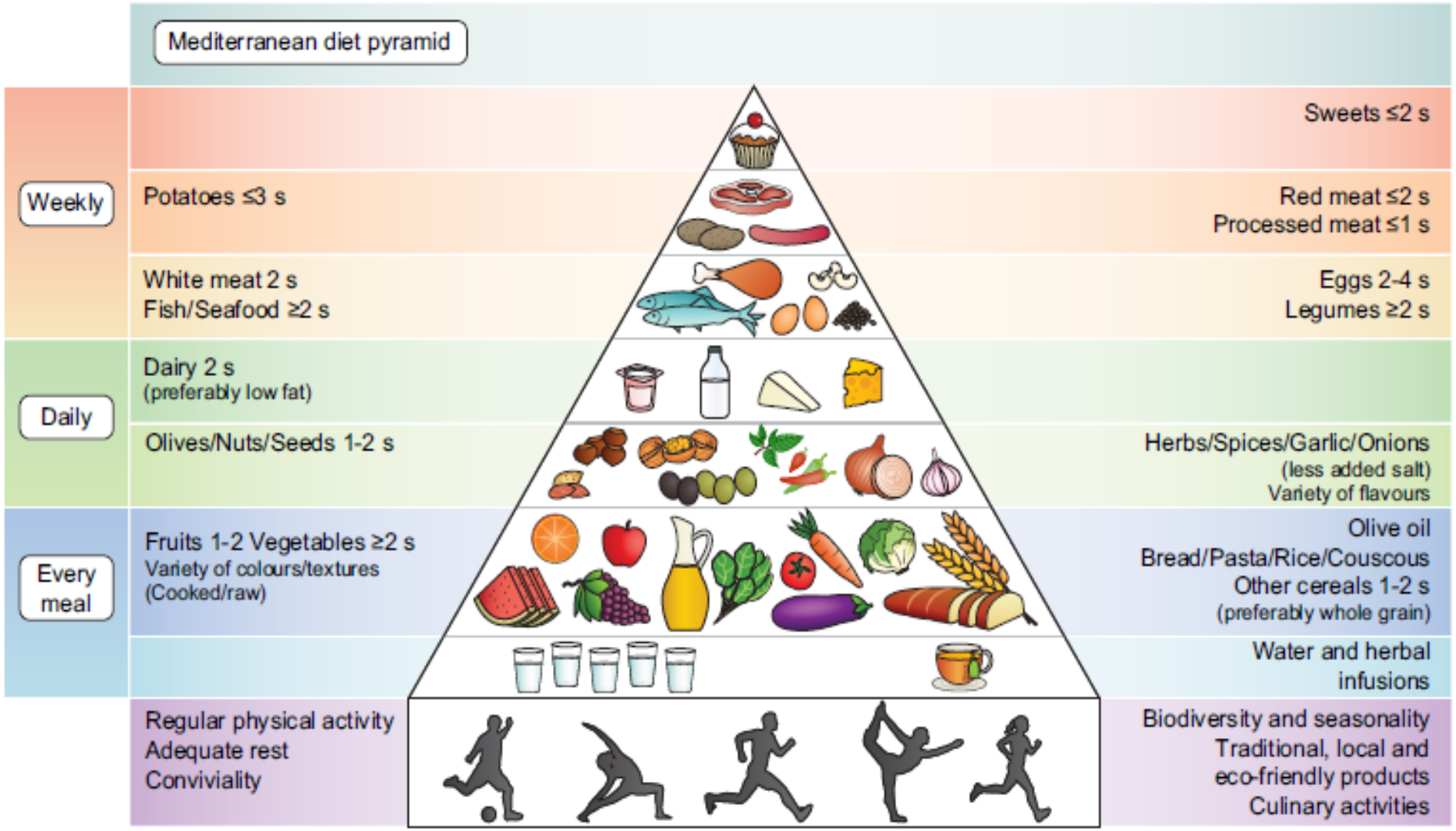
Treatment of NAFLD with diet, physical activity and exercise

Manuel Romero-Gómez[1,*], Shira Zelber-Sagi[2,3], Michael Trenell[4]

«Triple hit behavioural phenotype»:

- Dieta «errata».
- Vita sedentaria;
- Scarsa attività fisica;

Fattori indipendenti di rischio per NAFLD secondo pathways diversi!



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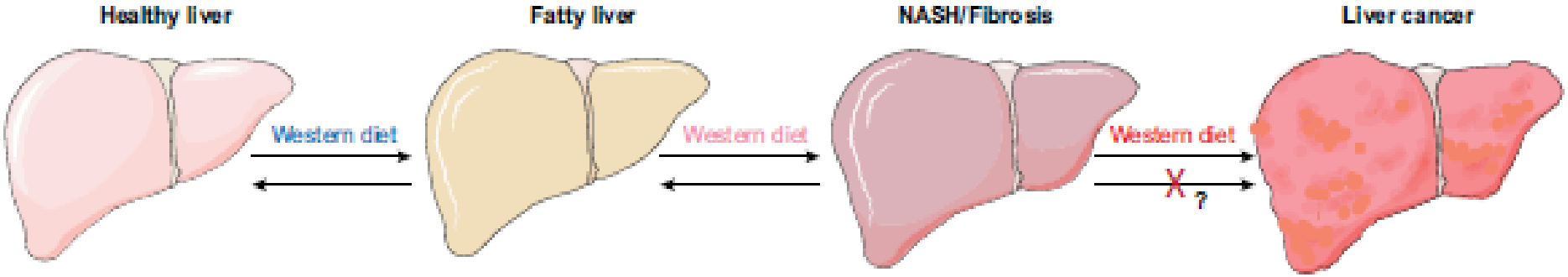
Terapia della NAFLD



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)

Fructose consumption is associated with alterations in gut microbiota, increased intestinal permeability, endotoxemia, increased hepatic TNF production and lipid peroxidation, promoting hepatic steatosis and NAFLD.

Drinking coffee reduces HCC risk. The hepatoprotective effects of coffee may be linked not only to caffeine but also to its polyphenolic fraction.

Review

JOURNAL OF HEPATOLOGY

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Fattori indipendenti di rischio per NAFLD secondo pathways diversi!

› Med Sci Sports Exerc. 2010 Aug;42(8):1511-8. doi: 10.1249/MSS.0b013e3181d322ac.

Increased cardiometabolic risk is associated with increased TV viewing time

Katrien Wijndaele [1], Genevieve N Healy, David W Dunstan, Adrian G Barnett, Jo Salmon, Jonathan E Shaw, Paul Z Zimmet, Neville Owen

Conclusions: These findings indicate that an increase in television viewing time is associated with adverse cardiometabolic biomarker changes. Further prospective studies using objective measures of several sedentary behaviors are required to confirm causality of the associations found.


SQUAT NATURALE
il segreto vitale
dell'uomo e del runner

Attività fisica:

- L'esercizio fisico senza perdita di peso riduce del 20-30% i lipidi intraepatici;
- Differenti tipologie di attività fisica (esercizi aerobici, esercizi di resistenza o attività ad alta intensità intermittente) hanno simili effetti sulla steatosi epatica;
- L'efficacia inizia dopo 8-12 settimane;
- Se il paziente smette l'esercizio fisico i benefici vengono persi;
- PNPLA3 influenza la risposta all'esercizio fisico;
- L'esercizio fisico ha poca efficacia sull'insulino-sensibilità epatica ma migliora quella dei tessuti periferici →
  ↓ lipogenesi epatica;
- Ancora pochi studi…

In diabete…:

ALLENAMENTO SETTIMANALE

150 minuti di esercizi a moderata intensità

SE Mahady et al. Metabolism 2016

In diabete…:

ALLENAMENTO SETTIMANALE

150 minuti di esercizi a moderata intensità

+

75 minuti di esercizi ad intensità vigorosa

Riduzione fibrosi epatica

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In diabete…:

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150 minuti di esercizi a moderata intensità

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75 minuti di esercizi ad intensità vigorosa

+

Riduzione fibrosi epatica

2 sedute di potenziamento

Riduzione enzimi epatici e insulino-resistenza dopo 3 mesi di allenamento

SE Mahady et al. Metabolism 2016

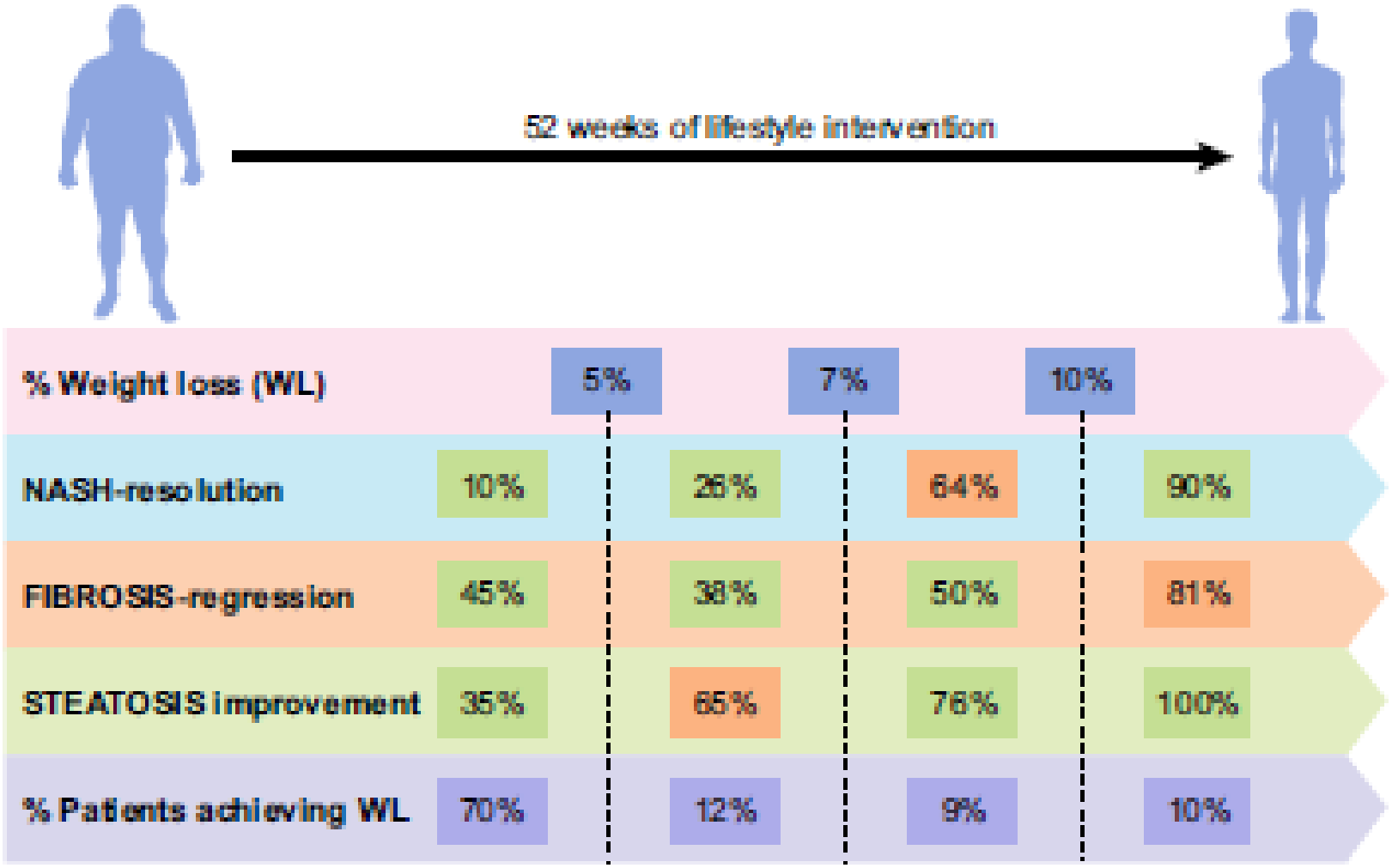


Fig. 3. Probability of reaching NASH resolution, fibrosis regression (at least one stage) and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss (modified from Vilar-Gomez *et al.*[12]).

M. Romero-Gomez et al.Journal of Hepatology 2017

Journal of Hepatology
Volume 58, Issue 4, April 2013, Pages 771-777

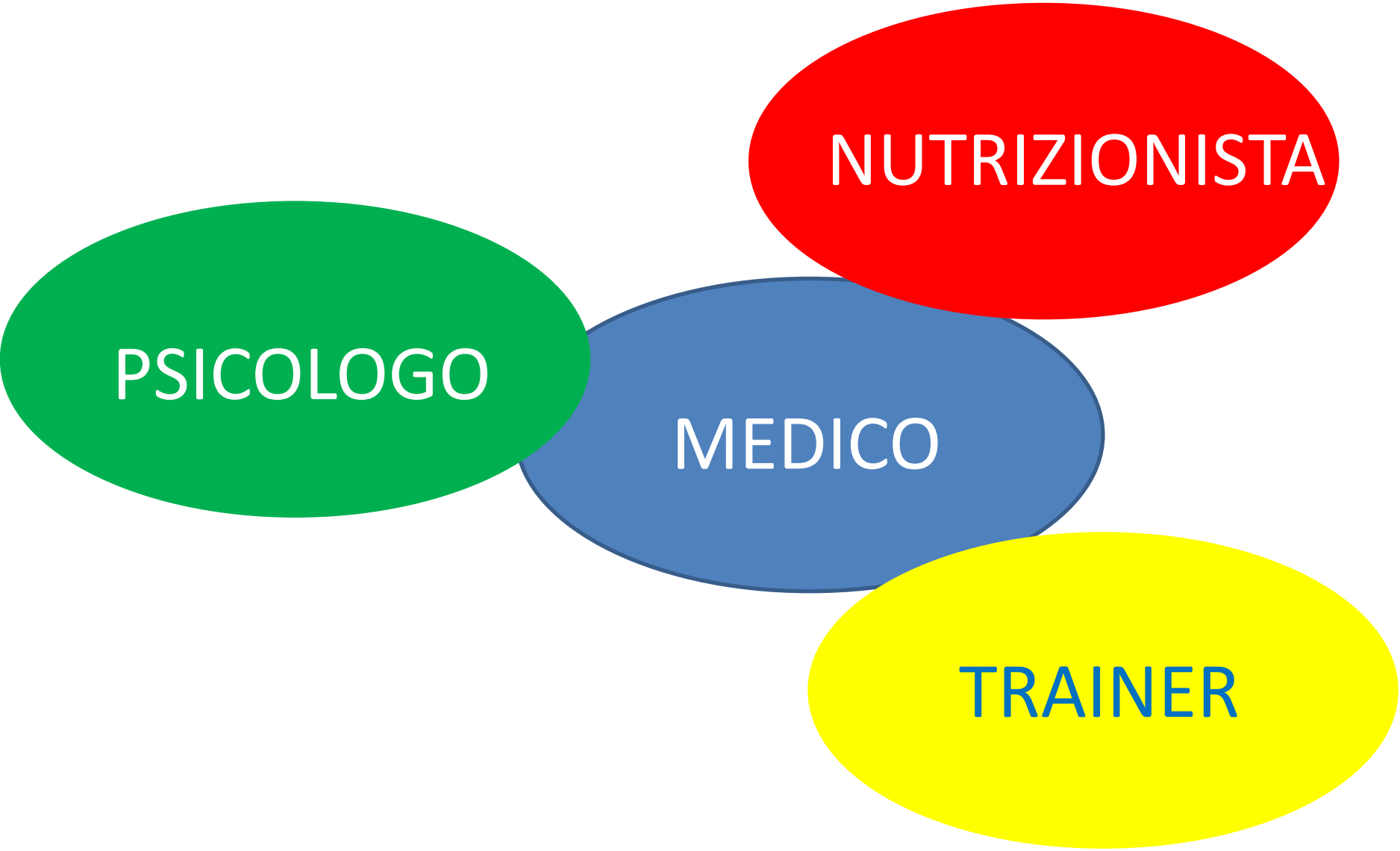
Research Article

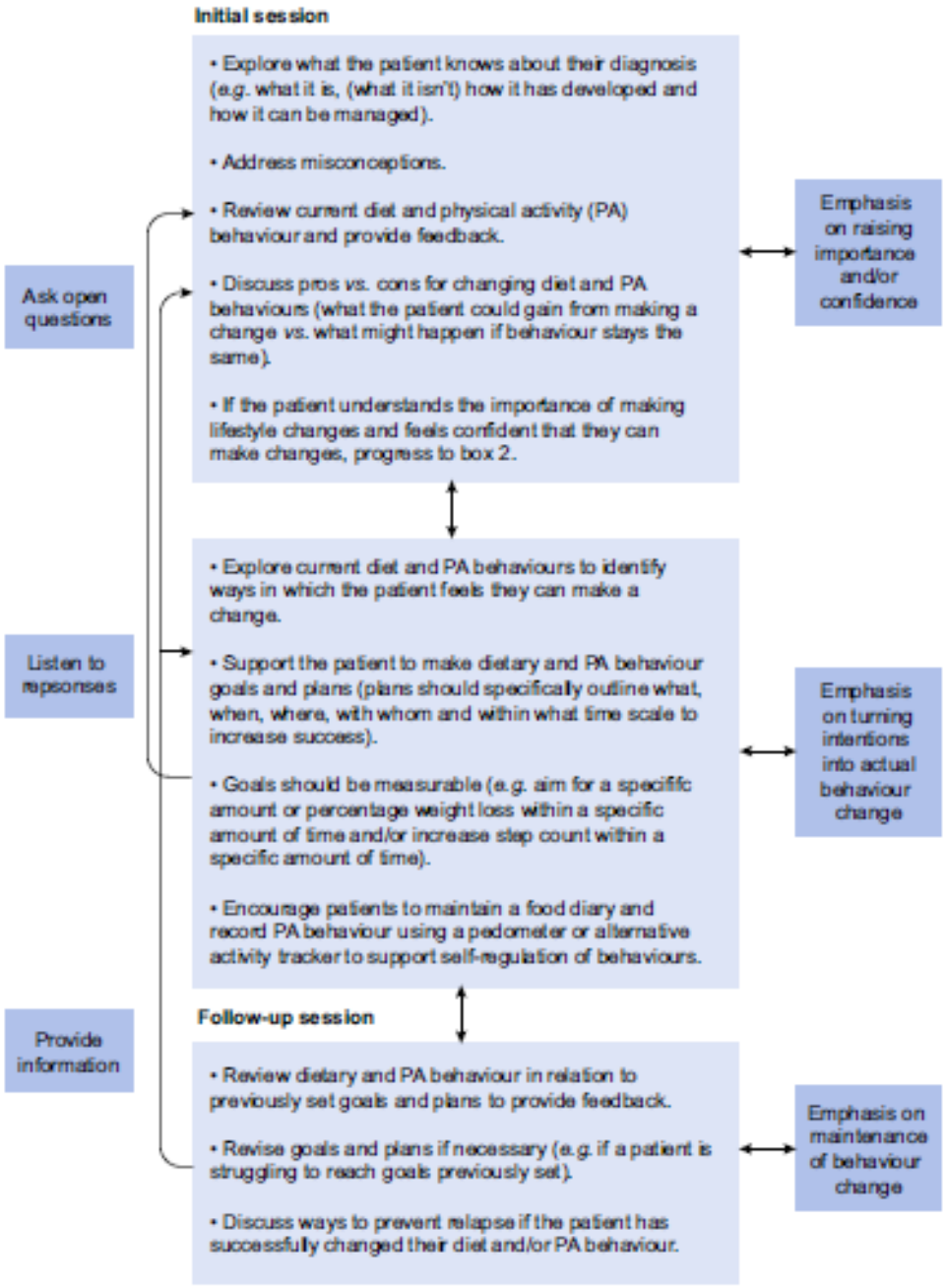
Stage of change and motivation to healthier lifestyle in non-alcoholic fatty liver disease

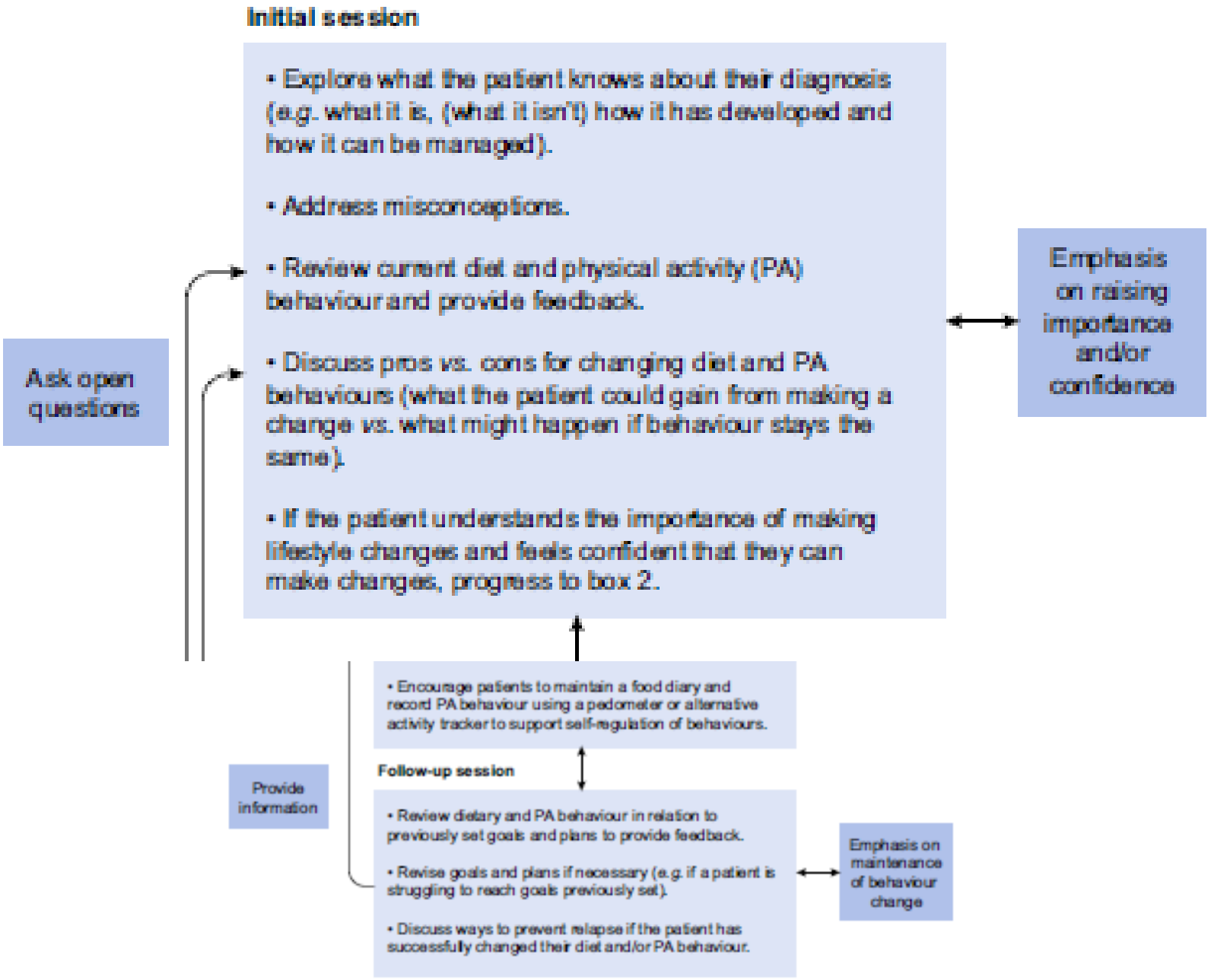
Elena Centis [1], Simona Moscatiello [1], Elisabetta Bugianesi [2], Stefano Bellentani [3], Anna Ludovica Fracanzani [4], Simona Calugi [5], Salvatore Petta [6], Riccardo Dalle Grave [5], Giulio Marchesini [1]

Conclusions

NAFLD cases have scarce readiness to lifestyle changes, particularly with regard to physical activity. Defining stages of change and motivation offers the opportunity to improve clinical care of NAFLD people through individual programs exploiting the powerful potential of behavioral counseling, an issue to be tested in longitudinal studies.


NUTRIZIONISTA
PSICOLOGO
MEDICO
TRAINER


Initial session
• Explore what the patient knows about their diagnosis (e.g. what it is, (what it isn't) how it has developed and how it can be managed).
• Address misconceptions.
• Review current diet and physical activity (PA) behaviour and provide feedback.
• Discuss pros vs. cons for changing diet and PA behaviours (what the patient could gain from making a change vs. what might happen if behaviour stays the same).
• If the patient understands the importance of making lifestyle changes and feels confident that they can make changes, progress to box 2.
Emphasis on raising importance and/or confidence
Ask open questions
• Explore current diet and PA behaviours to identify ways in which the patient feels they can make a change.
• Support the patient to make dietary and PA behaviour goals and plans (plans should specifically outline what, when, where, with whom and within what time scale to increase success).
• Goals should be measurable (e.g. aim for a specific amount or percentage weight loss within a specific amount of time and/or increase step count within a specific amount of time).
• Encourage patients to maintain a food diary and record PA behaviour using a pedometer or alternative activity tracker to support self-regulation of behaviours.
Emphasis on turning intentions into actual behaviour change
Listen to reponses
Follow-up session
• Review dietary and PA behaviour in relation to previously set goals and plans to provide feedback.
• Revise goals and plans if necessary (e.g. if a patient is struggling to reach goals previously set).
• Discuss ways to prevent relapse if the patient has successfully changed their diet and/or PA behaviour.
Emphasis on maintenance of behaviour change
Provide information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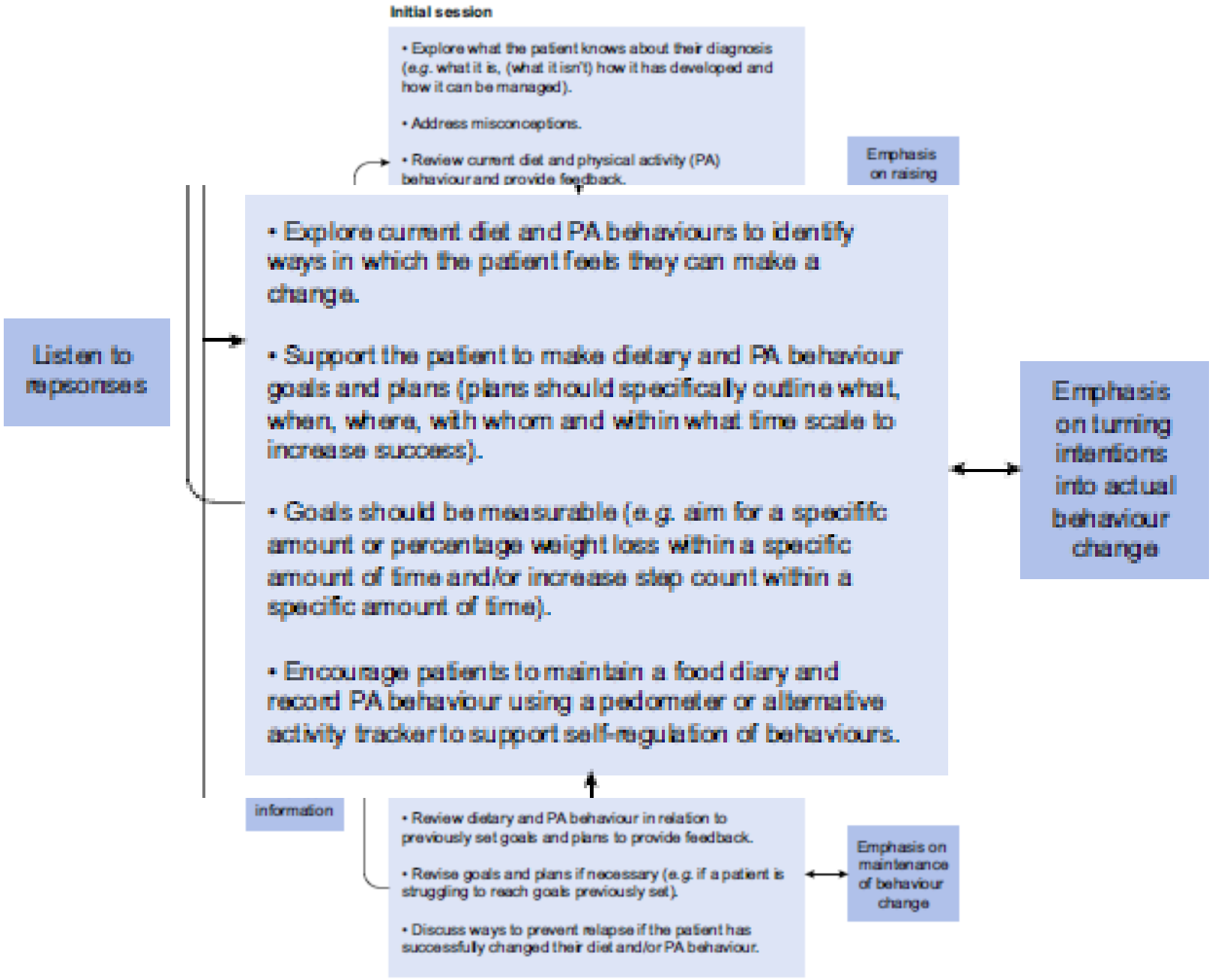
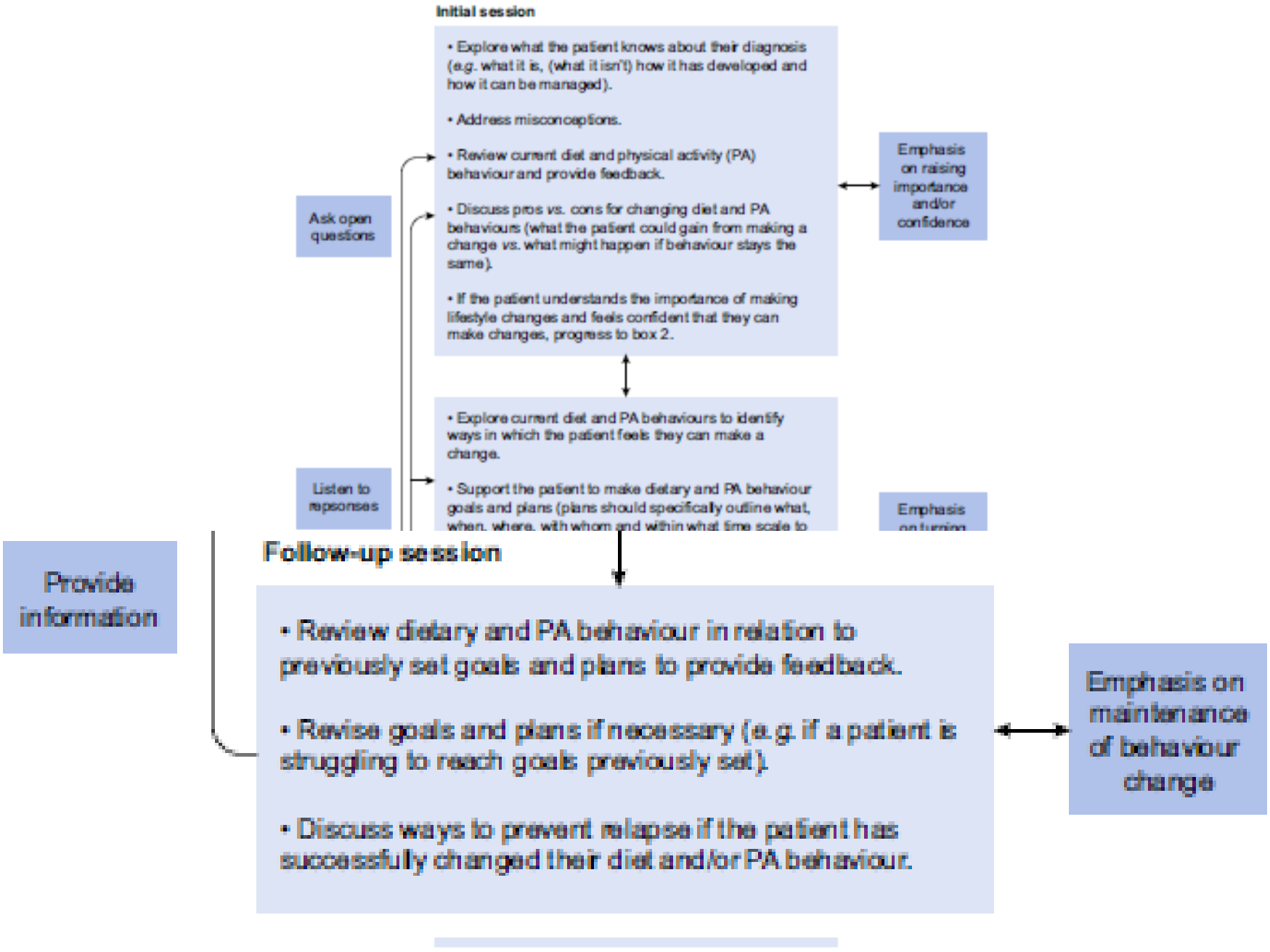
• Discuss ways to prevent relapse if the patient has successfully changed their diet and/or PA behaviour.
Emphasis on maintenance of behaviour change


Initial session
• Explore what the patient knows about their diagnosis (e.g. what it is, (what it isn't) how it has developed and how it can be managed).
• Address misconceptions.
• Review current diet and physical activity (PA) behaviour and provide feedback.
Emphasis on raising
Listen to reponses
• Explore current diet and PA behaviours to identify ways in which the patient feels they can make a change.
• Support the patient to make dietary and PA behaviour goals and plans (plans should specifically outline what, when, where, with whom and within what time scale to increase success).
• Goals should be measurable (e.g. aim for a specific amount or percentage weight loss within a specific amount of time and/or increase step count within a specific amount of time).
• Encourage patients to maintain a food diary and record PA behaviour using a pedometer or alternative activity tracker to support self-regulation of behaviours.
Emphasis on turning intentions into actual behaviour change
information
• Review dietary and PA behaviour in relation to previously set goals and plans to provide feedback.
• Revise goals and plans if necessary (e.g. if a patient is struggling to reach goals previously set).
• Discuss ways to prevent relapse if the patient has successfully changed their diet and/or PA behaviour.
Emphasis on maintenance of behaviour change


Initial session
• Explore what the patient knows about their diagnosis (e.g. what it is, (what it isn't) how it has developed and how it can be managed).
• Address misconceptions.
• Review current diet and physical activity (PA) behaviour and provide feedback.
• Discuss pros vs. cons for changing diet and PA behaviours (what the patient could gain from making a change vs. what might happen if behaviour stays the same).
• If the patient understands the importance of making lifestyle changes and feels confident that they can make changes, progress to box 2.
Emphasis on raising importance and/or confidence
Ask open questions
• Explore current diet and PA behaviours to identify ways in which the patient feels they can make a change.
• Support the patient to make dietary and PA behaviour goals and plans (plans should specifically outline what, when, where, with whom and within what time scale to
Listen to reponses
Emphasis
Follow-up session
Provide information
• Review dietary and PA behaviour in relation to previously set goals and plans to provide feedback.
• Revise goals and plans if necessary (e.g. if a patient is struggling to reach goals previously set).
• Discuss ways to prevent relapse if the patient has successfully changed their diet and/or PA behaviour.
Emphasis on maintenance of behaviour change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Grazie per l'attenzione!