

Metabolic Dysfunction-Associated Fatty Liver Disease: a 24-h Integrated Behaviour Perspective

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Overview

01

MASLD

Prevalence and burden

02

Evidence and current management

Diet, sociocultural adaptations

Exercise

Sleep

03

Future Direction

Access and application

Recommendations

MASLD: Prevalence

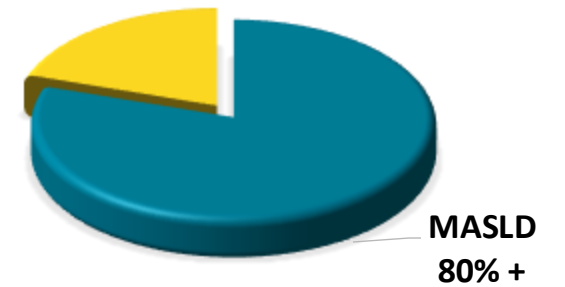
DEVELOPED POPULATION



DIABETES



OBESITY



MASLD: Definition

*Cardiometabolic criteria

<u>Adult Criteria</u>	<u>Pediatric Criteria</u>
At least 1 out of 5:	At least 1 out of 5:
☐ BMI $\geq 25 \text{ kg/m}^2$ [23 Asia] OR WC $> 94 \text{ cm}$ (M) 80 cm (F) OR ethnicity adjusted equivalent	☐ BMI $\geq 85^{\text{th}}$ percentile for age/sex [BMI z score $\geq +1$] OR WC $> 95^{\text{th}}$ percentile OR ethnicity adjusted equivalent
☐ Fasting serum glucose $\geq 5.6 \text{ mmol/L}$ [100 mg/dL] OR 2-hour post-load glucose levels $\geq 7.8 \text{ mmol/L}$ [$\geq 140 \text{ mg/dL}$] OR HbA1c $\geq 5.7\%$ [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes	☐ Fasting serum glucose $\geq 5.6 \text{ mmol/L}$ [$\geq 100 \text{ mg/dL}$] OR serum glucose $\geq 11.1 \text{ mmol/L}$ [$\geq 200 \text{ mg/dL}$] OR 2-hour post-load glucose levels $\geq 7.8 \text{ mmol/L}$ [$\geq 140 \text{ mg/dL}$] OR HbA1c $\geq 5.7\%$ [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
☐ Blood pressure $\geq 130/85 \text{ mmHg}$ OR specific antihypertensive drug treatment	☐ Blood pressure age $< 13\text{y}$, BP $\geq 95^{\text{th}}$ percentile OR $\geq 130/80 \text{ mmHg}$ (whichever is lower); age $\geq 13\text{y}$, $130/85 \text{ mmHg}$ OR specific antihypertensive drug treatment
☐ Plasma triglycerides $\geq 1.70 \text{ mmol/L}$ [150 mg/dL] OR lipid lowering treatment	☐ Plasma triglycerides $< 10\text{y}$, $\geq 1.15 \text{ mmol/L}$ [$\geq 100 \text{ mg/dL}$]; age $\geq 10\text{y}$, $\geq 1.70 \text{ mmol/L}$ [$\geq 150 \text{ mg/dL}$] OR lipid lowering treatment
☐ Plasma HDL-cholesterol $\leq 1.0 \text{ mmol/L}$ [40 mg/dL] (M) and $\leq 1.3 \text{ mmol/L}$ [50 mg/dL] (F) OR lipid lowering treatment	☐ Plasma HDL-cholesterol $\leq 1.0 \text{ mmol/L}$ [$\leq 40 \text{ mg/dL}$] OR lipid lowering treatment

Health Burden

- Metabolic dysfunction associated fatty liver disease affects >1 in 3 adults and compared with healthy populations results in **69% greater mortality**.
- No country has a national strategy for MASLD
- Of the prevalent MASH (more advanced liver disease) population in the UK in 2018, an estimated 79.8% were not diagnosed.

Economic Implications



Liver disease was estimated to cost Australia **\$5.4 billion annually in 2013**



Liver cancer is the fastest growing cause of cancer-related deaths in Australia, costing Australians a staggering **\$4.8 billion in 2019-20 alone.**

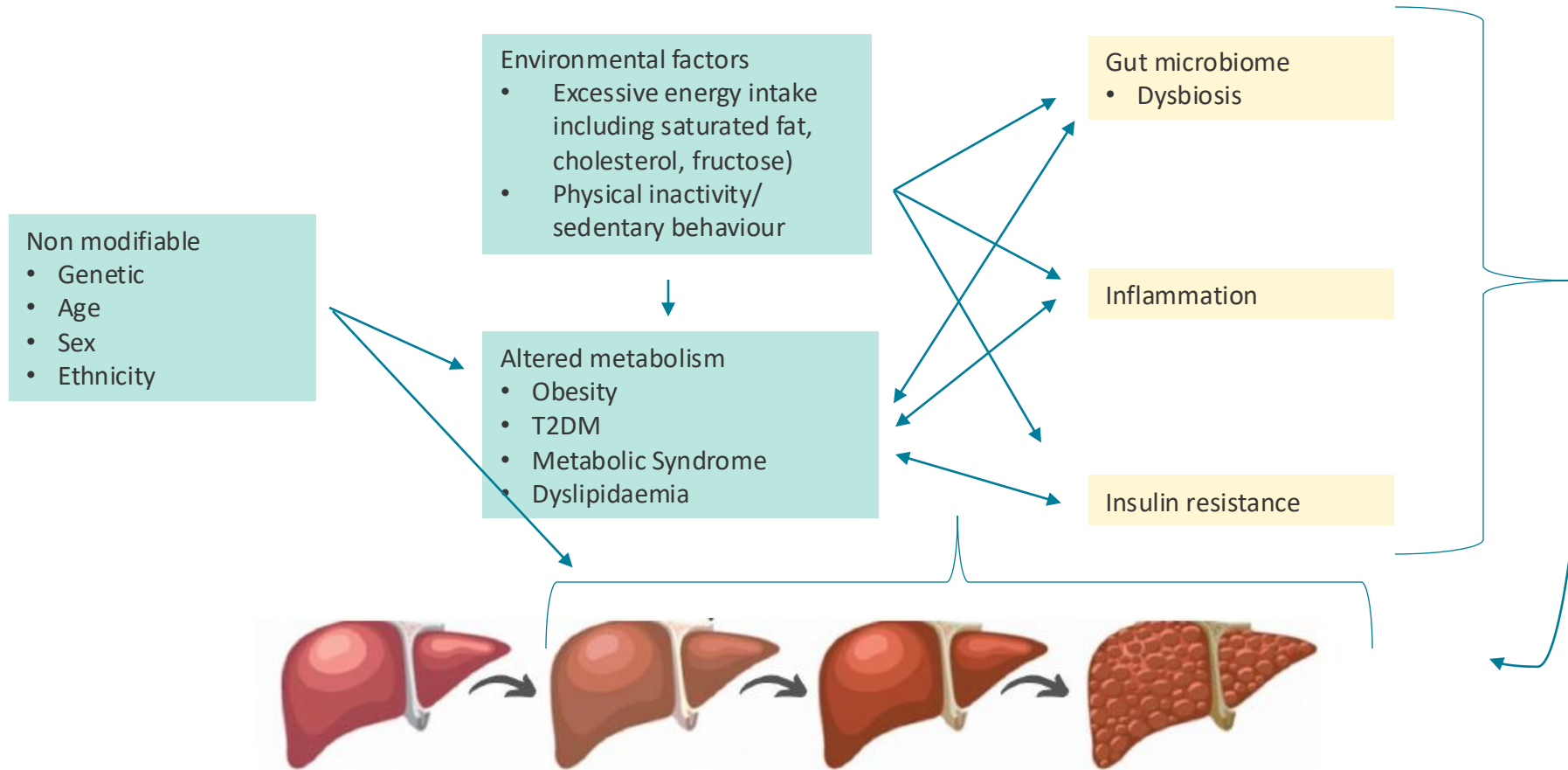


In the UK ranged from £2.3 billion to £4.2 billion annually in 2018. Total wellbeing costs were estimated to range between £5.6 to £10.5 billion.



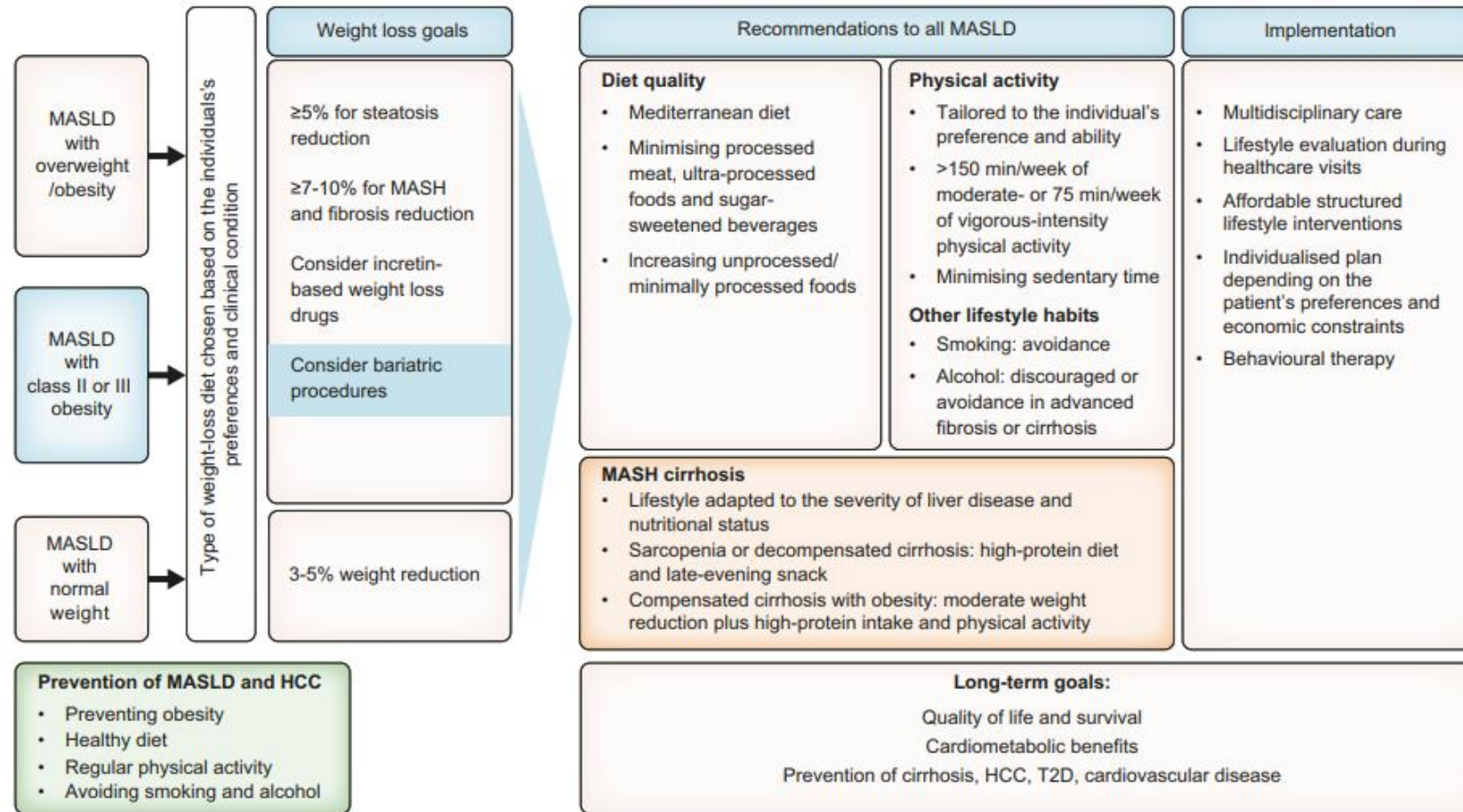
In 2018 in the UK people with MASH were estimated to experience 94,094 to 174,564 disability-adjusted life years (DALYs) overall.

MASLD: Risk Factors



MASLD Clinical Practice Guidelines

Lifestyle Management Algorithm



Weight loss

$\geq 5\%$
reductions in liver fat
 $\geq 7\%$
resolution of fatty liver
 $\geq 10\%$
regress fibrosis

$< 1/3$ MASLD patients
achieve $\geq 5\%$ weight
loss with lifestyle
intervention in 1 year

5–10% of patients
with MASLD have
normal BMI*

Highest rates
observed among
middle-aged people in
Asian countries

* $< 25 \text{ kg/m}^2$ in Western populations,
 $< 23 \text{ kg/m}^2$ in Asian populations

24-h Integrated lifestyle behavior for MASLD management

Sedentary Behaviour

- Limit sitting to **< 8 hours/day** to reduce risk of MAFLD.
- **Break up** prolonged periods of sitting/sedentary behaviour every 30 min with standing and/or activity.

Physical Activity & Exercise

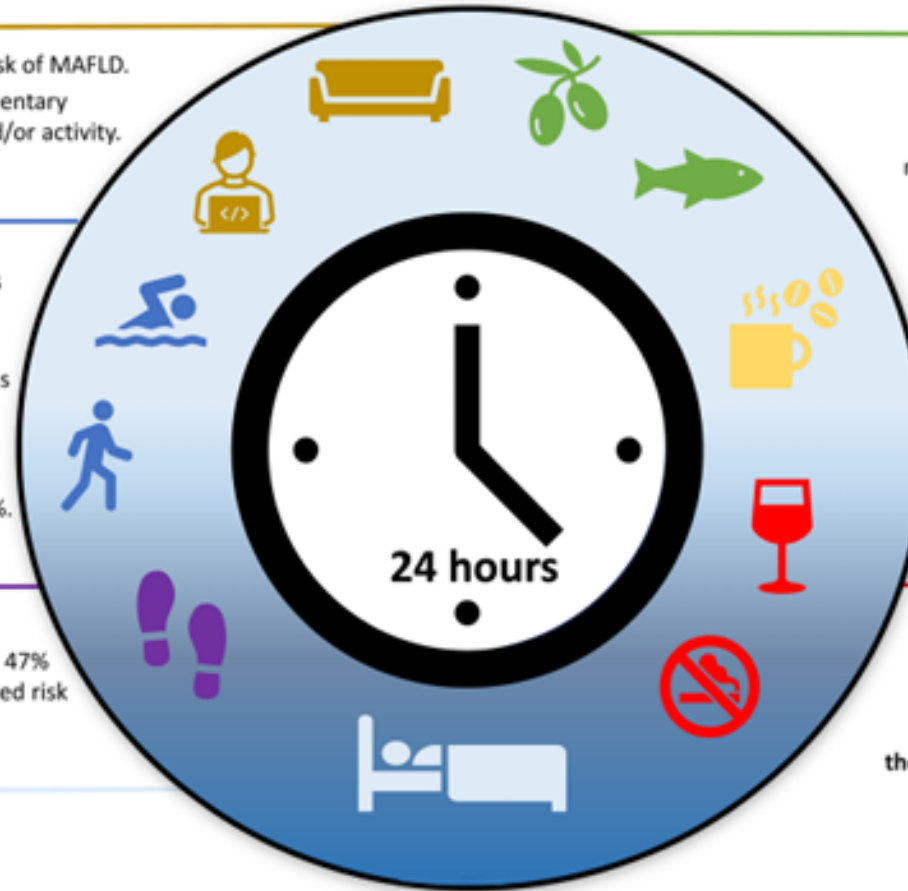
- 150-240 min/week of moderate-vigorous **aerobic exercise** (e.g., walking, cycling). As little as 135 min/week can reduce hepatic steatosis.
- *In addition* to aerobic exercise, 2-3 sessions of **resistance/muscle strengthening exercise** /week.
- 500-1000 MET-mins/week of physical activity to reduce MAFLD risk by up to 40%.

Daily Steps

- 8,000-10,000 steps/day
- Adding 2,500 steps/day is associated with 47% decreased risk of MAFLD and 44% decreased risk of liver disease progression.

Sleep

- Consistent, **7-8 hours** sleep.
- A bedtime before 10pm
- Reduce daytime napping to **< 30min**



Healthy Diet

- Diet-induced weight loss ($\geq$ -7-10% body weight) via hypocaloric diet (**500 to 1000 kcal deficit**) in a dose dependent manner improves hepatic steatosis, MASH and hepatic fibrosis.
- Improving diet quality through **healthy dietary patterns** (e.g., Mediterranean diet).
- **Mediterranean diet** improves hepatic steatosis and insulin resistance

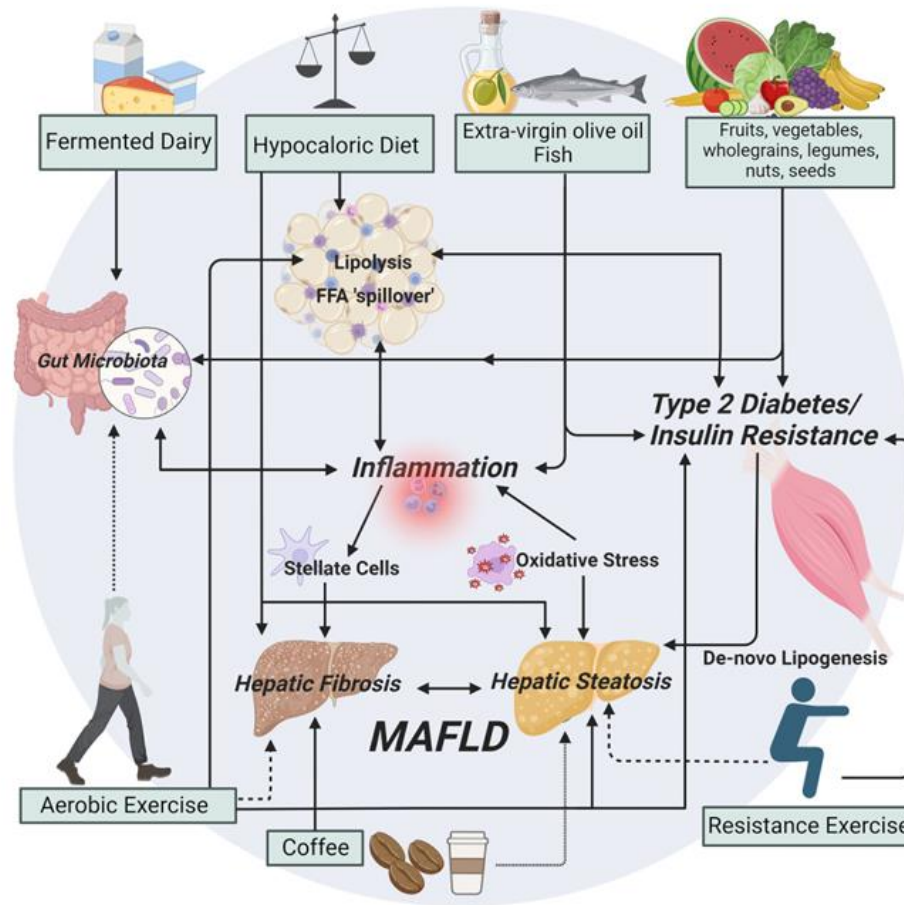
Coffee

- Drinking **3 cups or more** of coffee/day (no sugar), can reduce the risk of MAFLD and liver fibrosis.

Smoking & Alcohol

- Smoking **cessation**
- Abstinence of alcohol.
- Those without significant fibrosis (<F2) who choose to drink should adhere to levels **below the risk threshold** (20g and 30g/day) for females and males, respectively.

The evidence and current management



Beyond Weight Loss

Lifestyle interventions with an average weight loss of $\leq 5\%$ relative reduction $\geq 30\%$ liver fat observed

Every point increase in Mediterranean Diet score (0-55) reduces MASLD risk by 36%

Weight management should be advised and supported however, **health targets beyond weight loss should be highlighted** with goals individually tailored depending on patient presentation, capabilities and preferences.

Basic Principles: Health Benefits

Function	Food Sources
High in antioxidants	Fruit, vegetables
Potential protective effect from B-group vitamins (e.g. folate and vitamin B12). Gut-microbiome diversity from resistant starch, pre- and probiotics.	Whole grain cereals, legumes, nuts, olives and seeds, fermented dairy
Vascular and anti-inflammatory properties. Involved in enhancement of cell membrane fluidity .	Long chain omega-3 fatty acids from marine sources e.g. oily fish.
Antioxidant actions, bioactive polyphenols with important anti-inflammatory properties.	Extra virgin olive oil

Physical Activity and Sedentary Behavior

- Increased PA is associated with a reduced risk of MASLD in a dose dependent manner.
- Benefits are irrespective of weight loss
- Aerobic exercise with the addition of resistance exercise is optimal

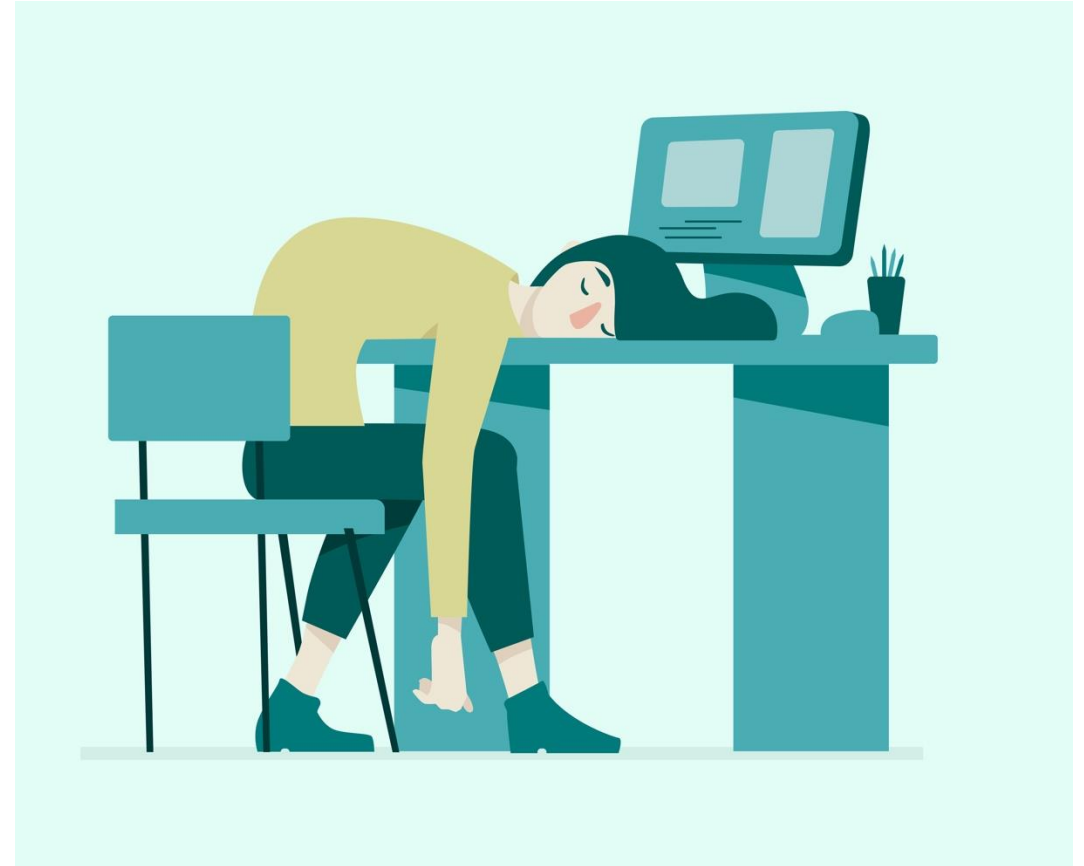
Increasing moderate intensity physical activity to ~150-300 min/wk can reduce the risk by $\geq 40\%$



Sleep

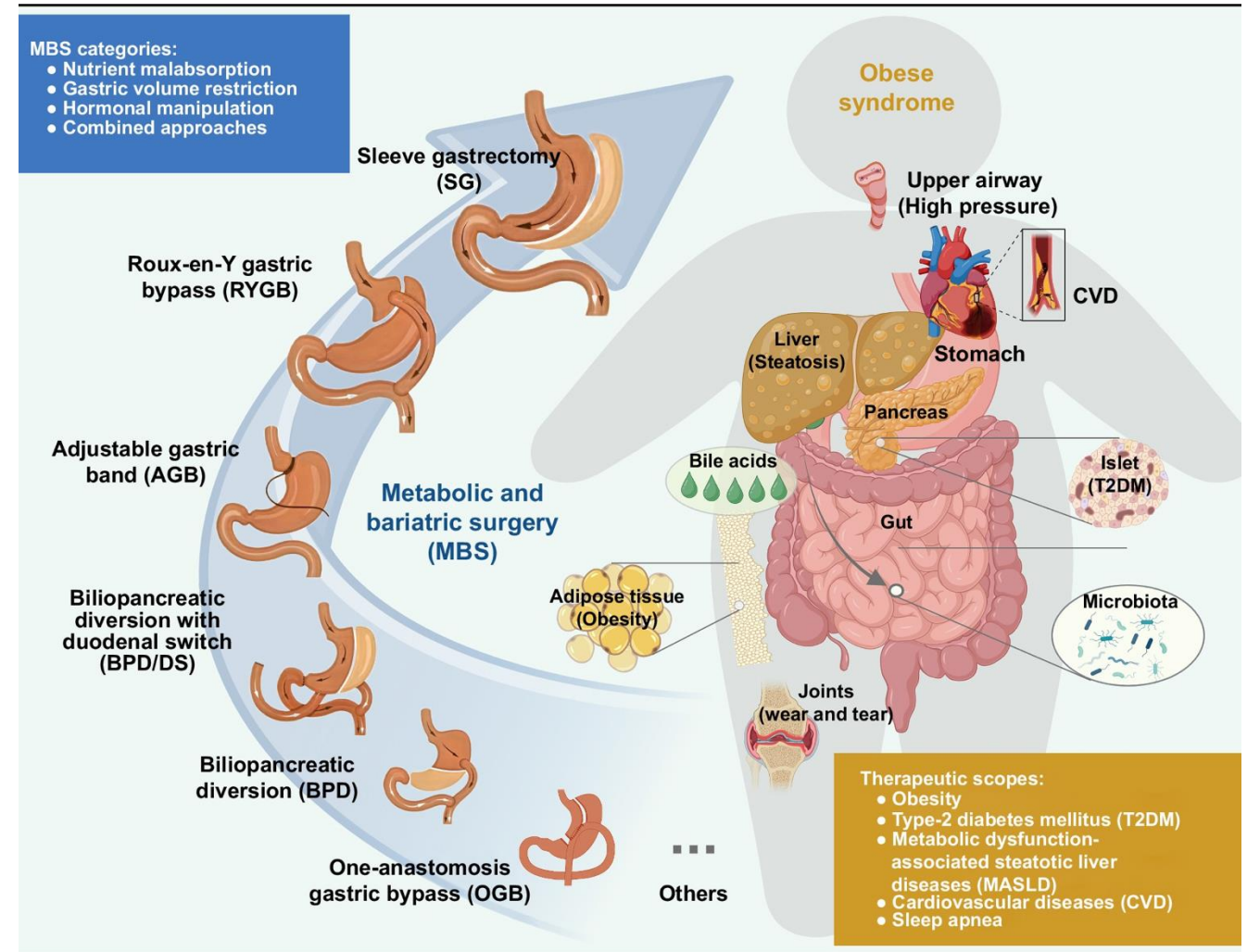
- Very few studies, evidence is observational.
- People with MASLD have poorer sleep efficiency, more frequent daytime napping (> 30 min), higher use of sleeping pills and later wake-up and bedtimes than those without MASLD

Short sleep duration (<5-6 hours) can increase MASLD risk by ~20%

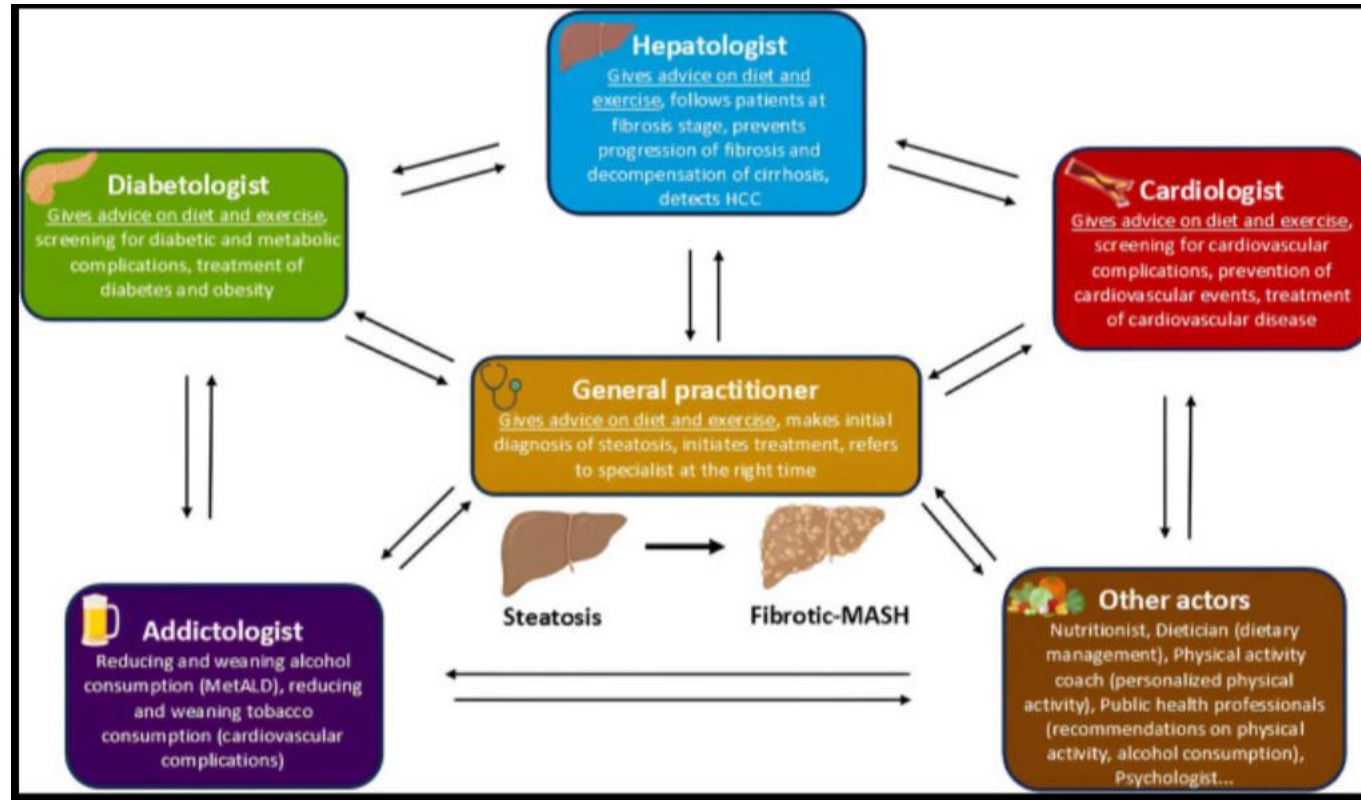


Bariatric Surgery

- Improves MASLD via improvements in hepatic steatosis, inflammation, fibrosis and reduced cancer risk.
- Benefits include reduced caloric intake – not improved diet quality



Incretins and MASLD: at the Crossroads of Endocrine and Hepatic Disorders



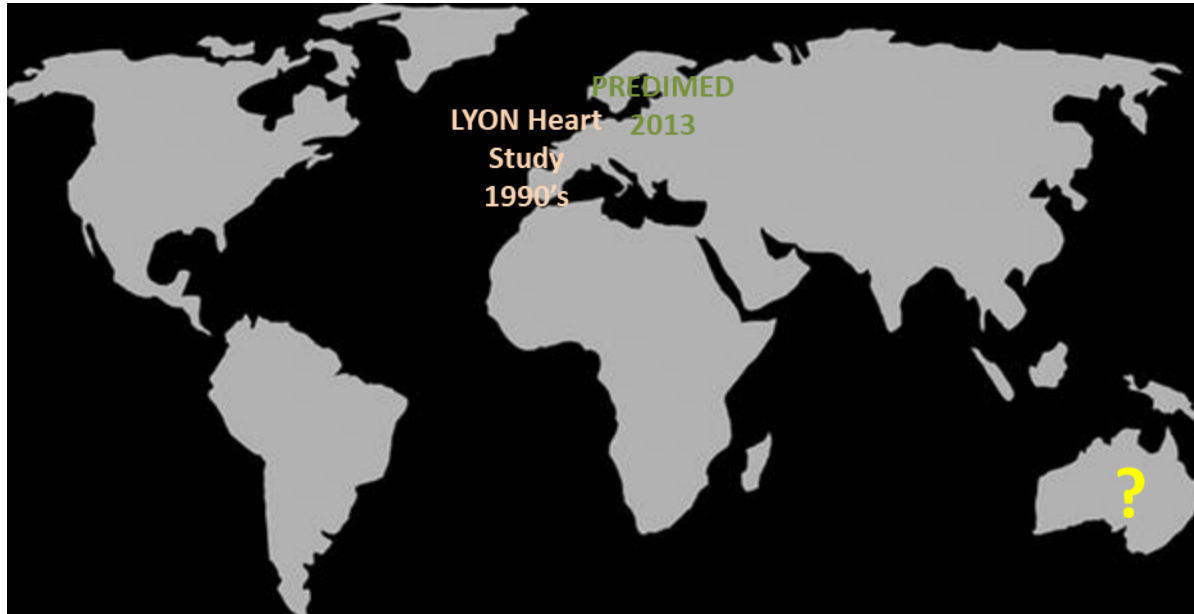
- Incretins therapeutic target for diabetes management – improve IR T2DM
- Demonstrated benefits in CVD
- Weight loss leads to improved hepatic steatosis and fibrosis* (Phase III trials are ongoing)
- Diet quality poorly assessed – appears to be low quality
- Lifestyle management poorly co-prescribed

* Not as well elucidated

Lifestyle management serves as a standalone solution but should also be provided alongside weight loss drugs / surgery.

Mediterranean Diet in the West and the *Australian context*

- Not as well researched
- Lower adherence overall – not habitual
- Can it be translated?



Diet: Sociocultural adaptations

Culturally and linguistically diverse (CALD) communities are disproportionately affected by MASLD and have poorer access to healthcare services



Mediterranean diet albeit optimal is not habitual in Western / multiethnic communities



MedDiet can be adapted, and we have demonstrated this

Fatty liver disease

- 6-week RCT of Greek-style Med diet “ad libitum” vs LF/HCD in NAFLD
- Significant reduction in liver fat after the MD compared with the LF/HCD: $39 \pm 4\%$ versus $7 \pm 3\%$ ($p < 0.001$)
- MD HOMA- β and fasting insulin concentrations significantly
- No significant change in insulin sensitivity with

• Trials were successful indicating efficacy of the diet in non-Mediterranean populations

- **IMPROVED INSULIN SENSITIVITY**
- But - full provision of meals!
- So, what about in free living individuals?

Diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease

Georgios Ntzani^{2,6}, Tania Thodis^{2,6}, Glenn Ward², Nicholas Trost³, V. Desmond¹, Nathan A. Johnson^{4,5}, Andrew M. Wilson²

¹Department of Medicine, St Vincent's Hospital, Melbourne, Australia; ²Department of Medicine, St Vincent's Hospital, Melbourne, Australia; ³Discipline of Exercise and Sport Science, St Vincent's Hospital, Melbourne, Australia; ⁴Discipline of Exercise and Sport Science, St Vincent's Hospital, Melbourne, Australia; ⁵Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Australia; ⁶Discipline of Human Nutrition, Faculty of Health Sciences, La Trobe University, Melbourne, Australia; ⁷Sansom Institute for Health Research, University of South Australia, Australia

Mediterranean Diet, Liver and Metabolic Outcomes

- 12-week RCT Med Diet vs. low fat diet
- HOMA-IR reduced in the LFD group
(6.5 ± 5.6 to 5.5 ± 5.5 , $p < .01$) with
weight loss (almost 5%)
- Not in the M group
 3.9 ± 2.3 , $p =$
- Visceral fat reduced in
both groups;

LFD (−76%)
MedDiet (−

- Weight loss remains important for improving insulin sensitivity and liver fat
- Mediterranean diet meaningful improvement in insulin sensitivity without weight loss
- Mediterranean diet achievable in multiethnic Australians

LIVER INTERNATIONAL WILEY

low fat diet on hepatic and metabolic
fatty liver disease: The MEDINA

manda J. Nicoll³ | Marno C. Ryan⁴ |
Nathan A. Johnson⁶ | Siddharth Sood⁷ |

and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia

Participant feedback

Mediterranean diet is novel- participants likes trying something new

Participants liked convenient options provided in the Mediterranean diet intervention

Participants thought the food tasted good

Participants were more likely to adopt and maintain changes if the food tasted good; **flavour**, and this in turn predicted whether they **enjoyed** it.

↑ **enjoyment** of food = ↑ **likelihood** that participants reported that they would **maintain dietary changes**.

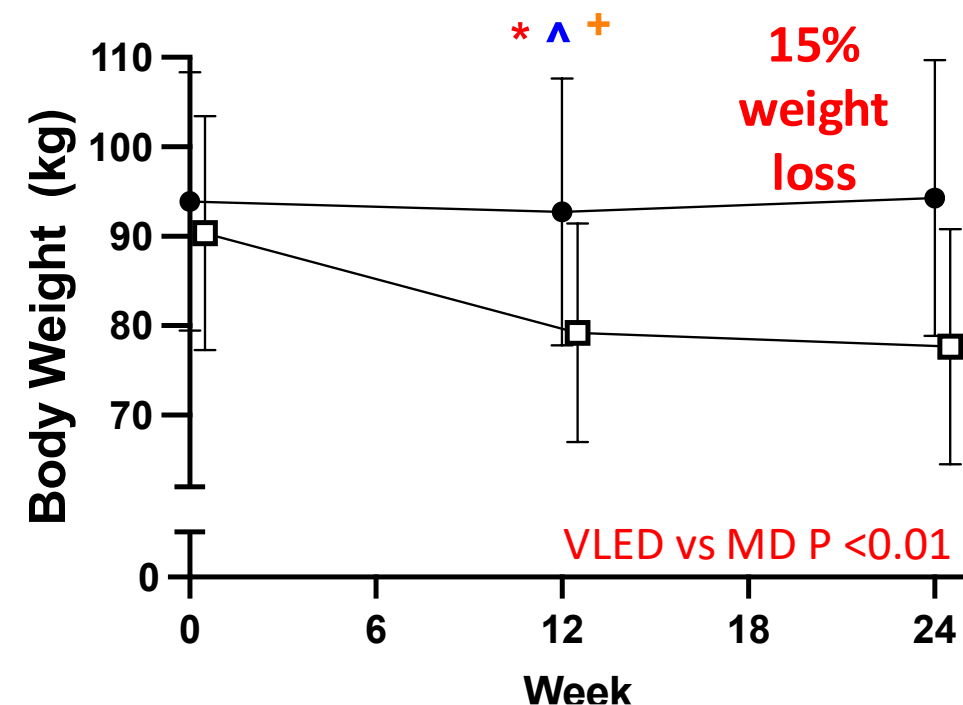
↑ **overall enjoyment** was associated with reporting ↑ **strategies surrounding implementation and maintenance of the dietary changes**.

**Mediterranean Diet is
beneficial *ad libitum*, weight
loss remains important**

How do they compare?

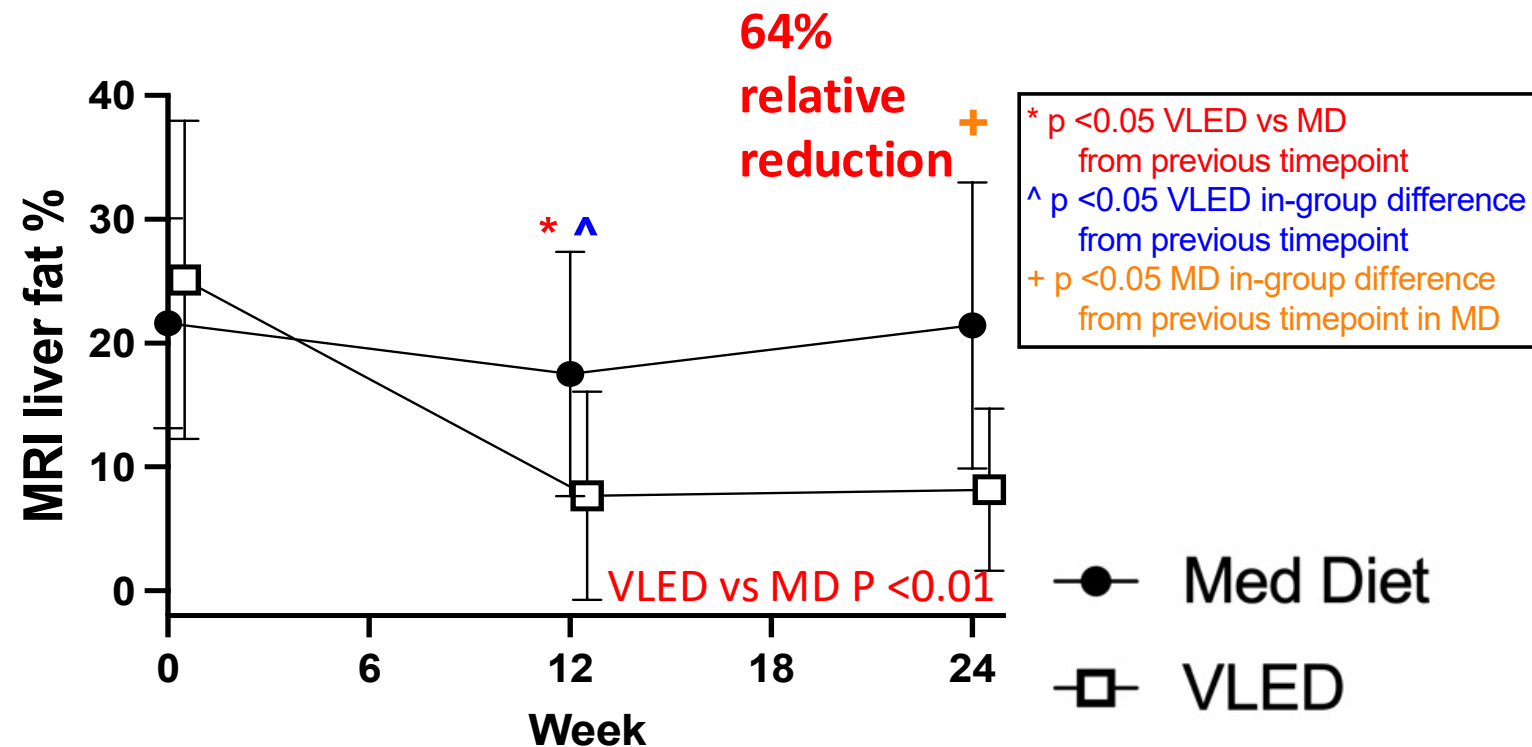
The VLED approach resulted in greater weight loss and reduction in MRI liver fat %

Farrell *et al.* under review



Clinically significant weight loss (>10% TBWL)

71% (n=10)

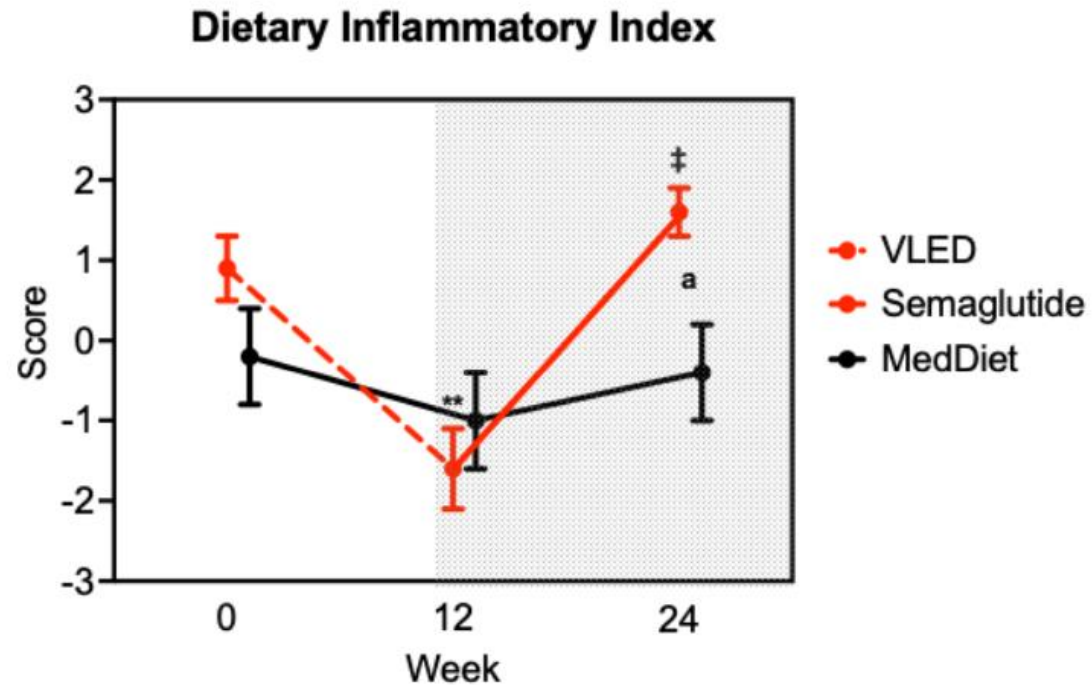


Normalization of liver fat ($\leq 5\%$ steatosis)

46% (n=6)

Quality matters

Paris *et al.* under review



Eat less ≠ diet quality

Results analysis underway...

- Inflammatory outcomes mixed
- Diet quality deteriorates

**Independent clinical benefits
associated with weight loss
and diet quality.
Can we combine and amplify
the effects?**

Designing a dietary intervention

- Diet is effective and we can make successful sociocultural adaptations
 - How can we reach marginalised communities (CALD)?
 - Workforce limitations- a minority of people receive lifestyle management (diet, physical activity), inadequate dose



One step further...

Co-designing a MULTIMODAL intervention



People with MASLD and HCPs



**Addressing healthy habits – multimodal
is more effective and it's what people
want!**

**Physical Activity
Sleep**

LiverERAS: Eat Move and Rest

- Co-designed (people with lived experience, HCPs)
- Evidence based resources needed
- Holistic management
- Multidisciplinary team of leading experts
- Socio-culturally adapted- longer term plans to translate
- Accessible website – addressing workforce limitations and regional/ rural/ remote communities can access



Summary - *Using the challenges to drive the solution*



MASLD is an enormous global problem with no strategy in place in any country



Lifestyle provides profound benefits

MedDiet or personalised diet, Move and Sleep



Workforce limitations are the heart of the problem – this is not going away



We can achieve sociocultural adaptations and more accessible digital interventions to support those who need it most



Co-design with people who have lived experience and healthcare professionals, and subject matter experts is key

Thank you

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