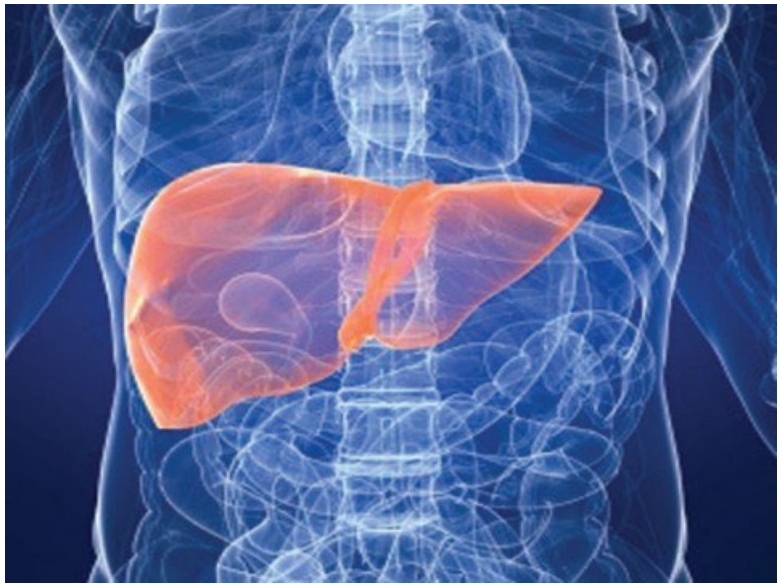
Mastering MASLD
Steatotic liver disease in Primary Care



Dr Sarah Davies
GP, Cardiff

Disclosures

- I have received honorarium for speaking or support for attending meetings from:
  - Abbott
  - Astra Zeneca
  - Bayer
  - Boehringer Ingelheim
  - Daiichi Sankyo
  - Dexcom
  - Lilly
  - Menarini
  - Novo Nordisk
  - Roche

Learning Objectives

- What is MASLD and why does it matter?
- Making the diagnosis of MASLD in primary care
  - Case based, step by step
- Treatment approaches for MASLD

MASLD
Metabolic dysfunction associated steatotic liver disease

”Steatotic (fatty) liver disease in the presence of one or more cardiometabolic risk factors and the absence of harmful alcohol intake”

- New name for NAFLD!

Journal of Hepatology
Volume 79, Issue 6, December 2023, Pages 1542-1556

A multisociety Delphi consensus statement on new fatty liver disease nomenclature

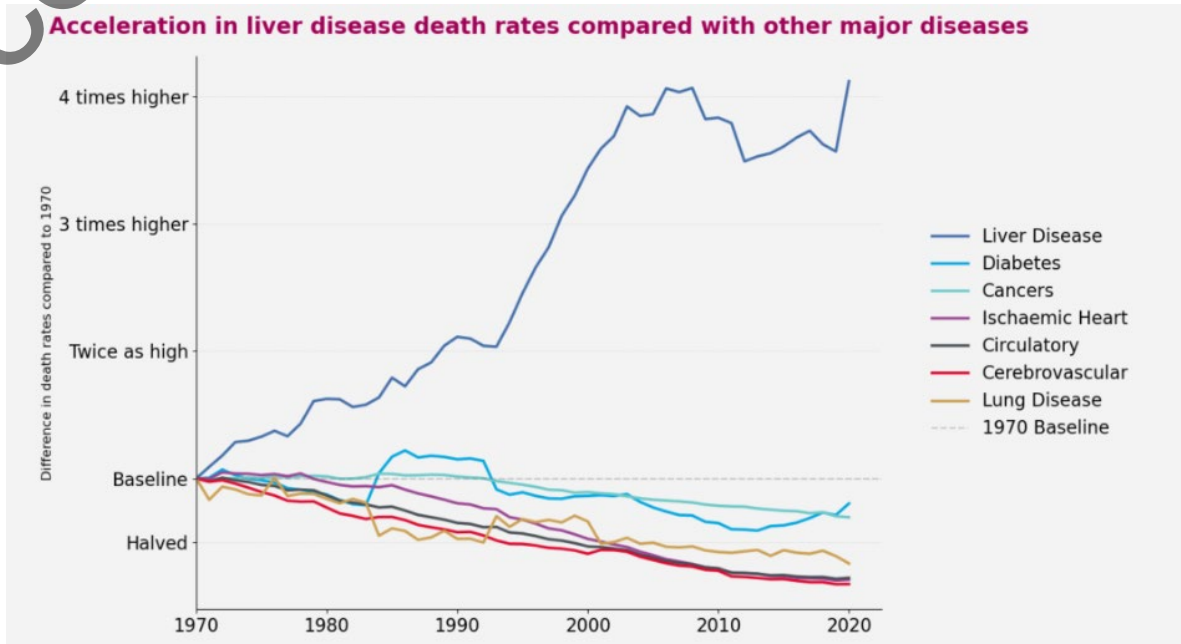
- Why?
  - Better reflects the pathophysiology and cardiometabolic implications
    - NAFLD did not portray the key **metabolic dysfunction** aspect of the disease
    - New clear set of cardiometabolic diagnostic criteria
  - NAFLD felt to be stigmatising “non alcoholic”, “fatty”

Prevalence and spectrum of MASLD

- Rising rates of MASLD across the world
- Rising rate of liver related deaths
- Currently estimated to affect **38%** of the global population

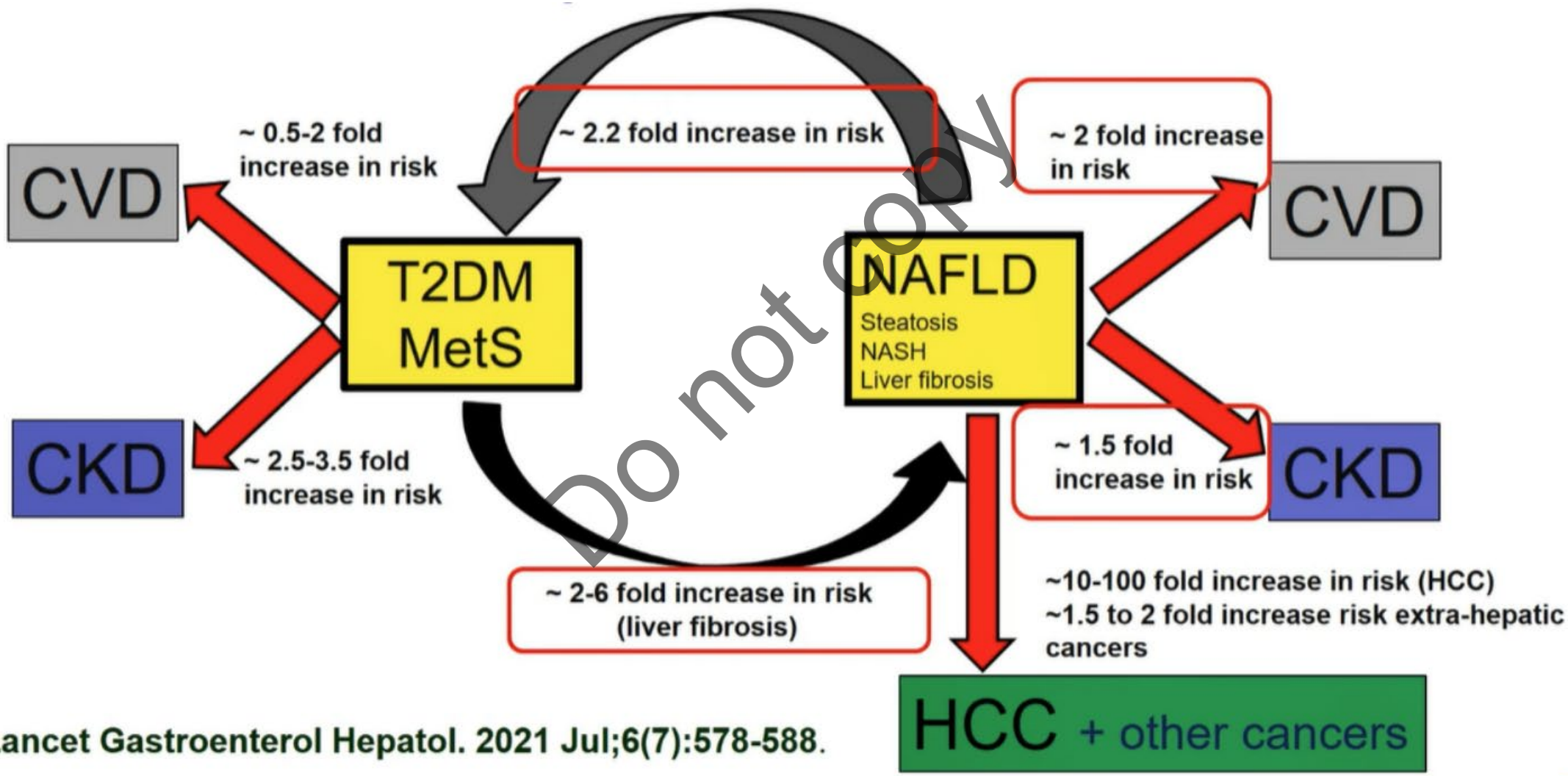
- **70%** of those with overweight
- **75%** of those with obesity
- Up to **65%** of those with Type 2 Diabetes

- Complications: Cirrhosis, HCC, CVD, CKD



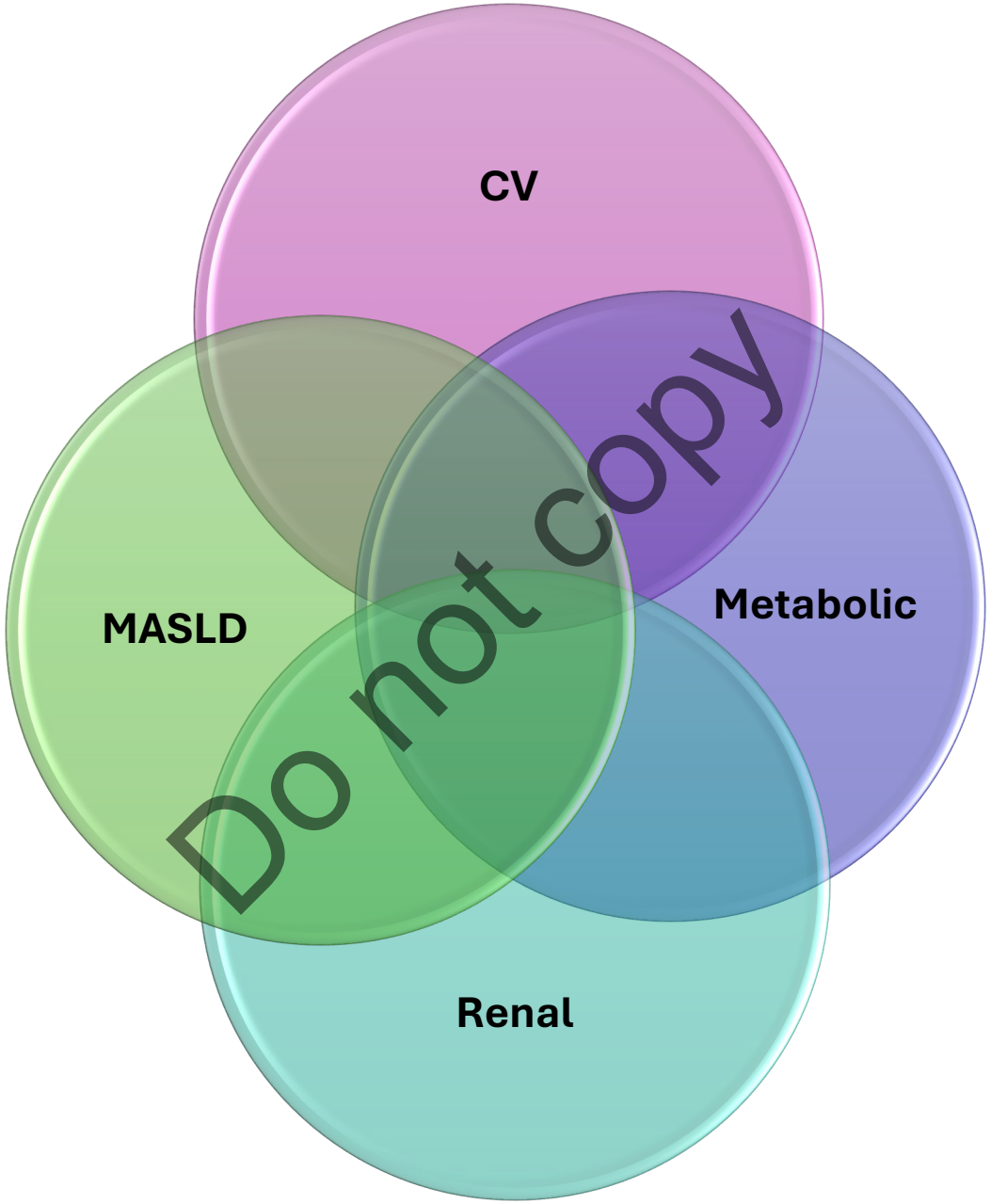
Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis - The Lancet Gastroenterology & Hepatology
Wong V-S , Ekstedt M , Wong G-H , *et al*. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;**79**:842–52. doi:10.1016/j.jhep.2023.04.036
MASLD: a systemic metabolic disorder with cardiovascular and malignant complications | Gut
Liver disease in numbers – key facts and statistics - British Liver Trust

Links between MASLD, T2DM, CVD and CKD

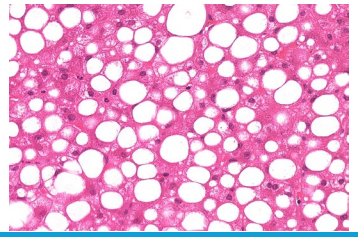


Lancet Gastroenterol Hepatol. 2021 Jul;6(7):578-588.

CVRML?



Spectrum of disease

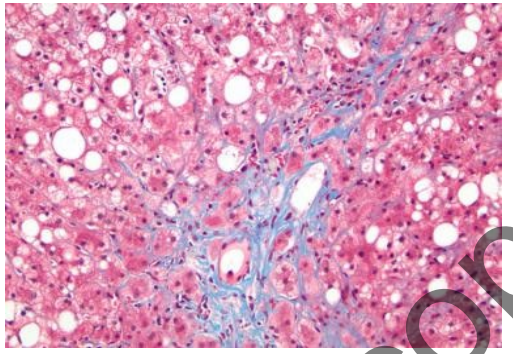


MASLD

Fatty infiltration

38% of population

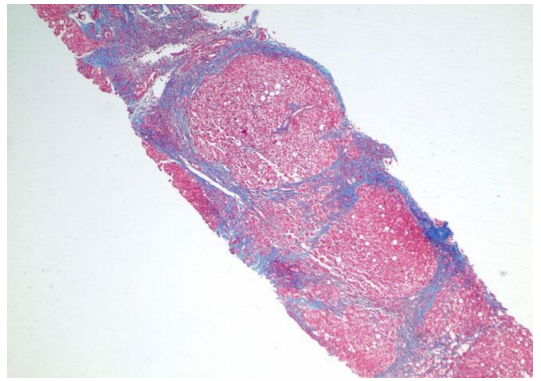
10-33%



MASH

Inflammation +/- fibrosis

Approx 20%



Cirrhosis / HCC

Increasing cardiovascular risk

More cardiometabolic risk factors = higher chance of progression, especially T2D and obesity

Targher G, Byrne CD, Tilg H MASLD: a systemic metabolic disorder with cardiovascular and malignant complications *Gut* 2024;**73:**691-702.
EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 – 542

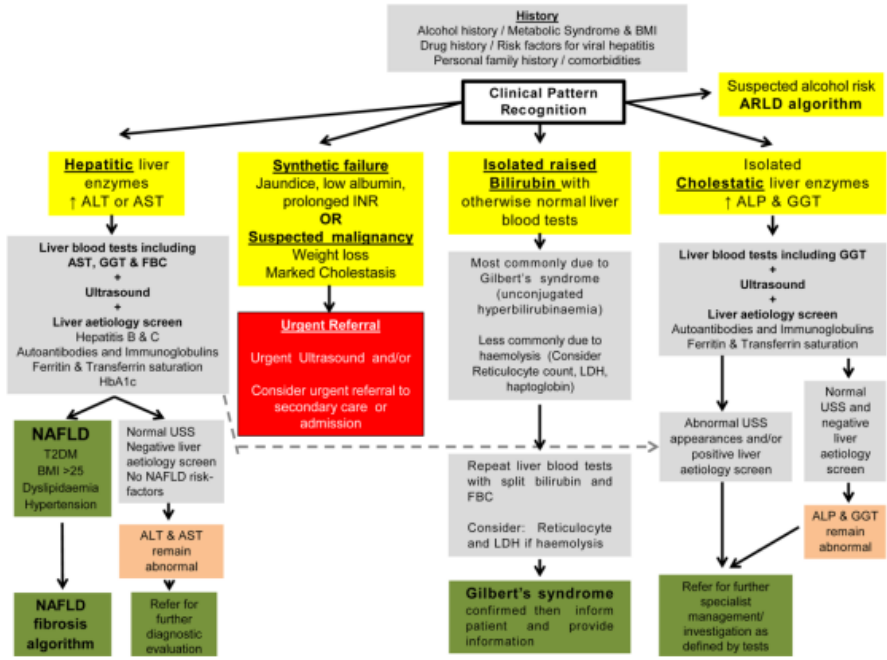
Guidelines

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

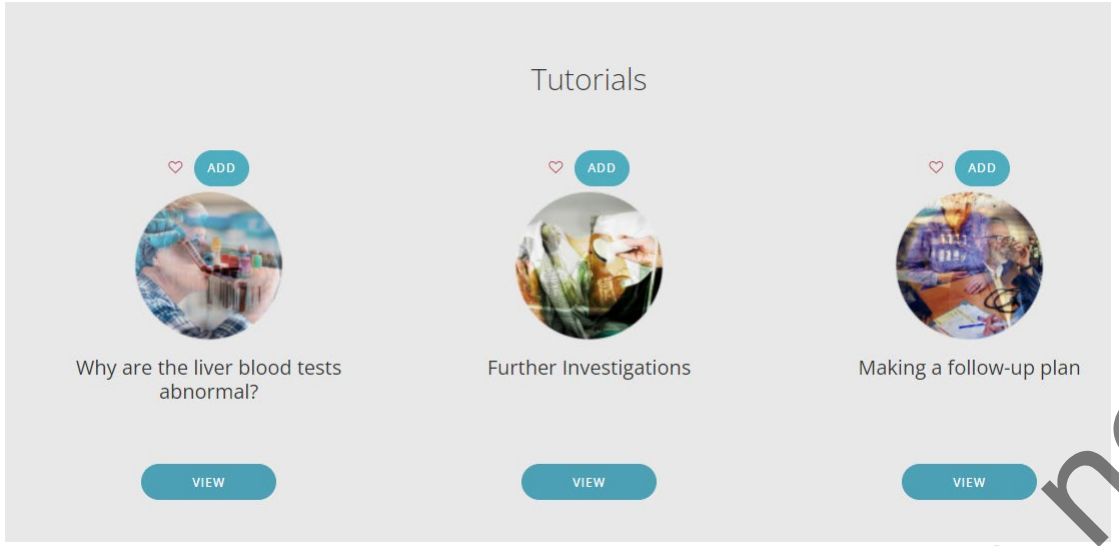
In development [GID-NG10434] Expected publication date: TBC Register as a stakeholder

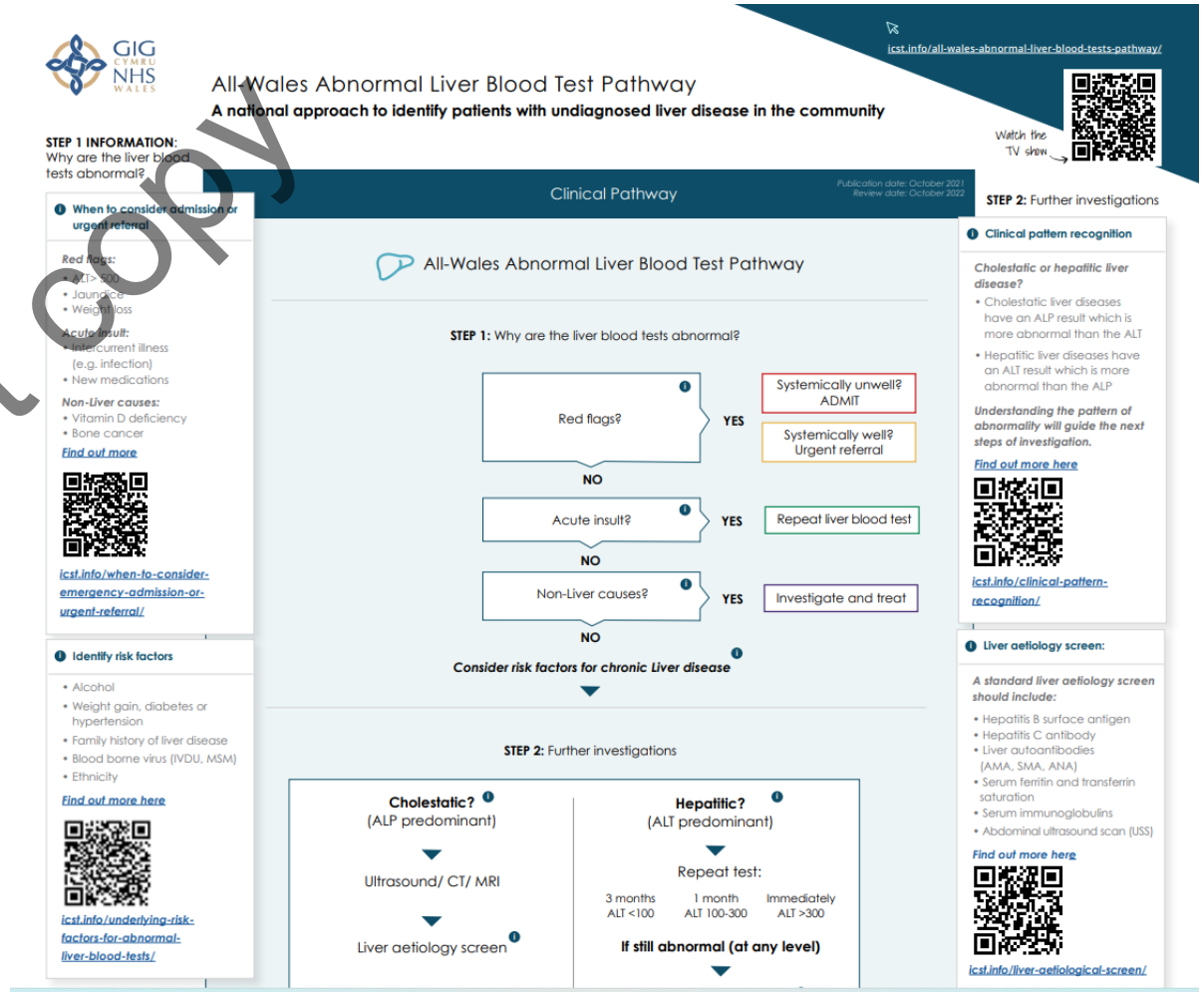
BSG Guidelines on the management of abnormal liver blood tests



EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 – 542
Guidelines-on-the-management-of-abnormal-liver-blood-tests.pdf Newsome PN, Cramb R, Davison SM, et al. Gut doi:10.1136/ gutjnl-2017-314924

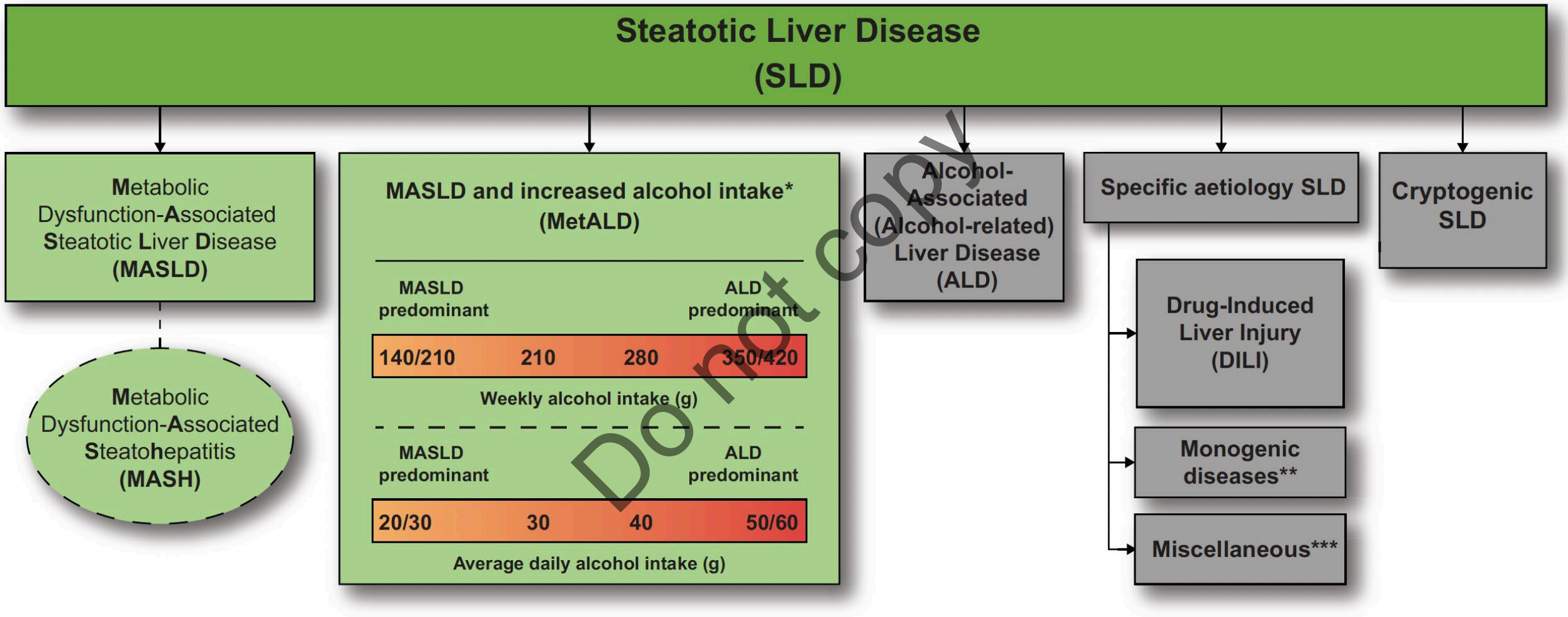
All Wales Abnormal Liver blood test pathway





https://allwales.icst.org.uk/programmes/all-wales-abnormal-liver-blood-tests-pathway/

New Nomenclature



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

A multisociety Delphi consensus statement on new fatty liver disease nomenclature - ScienceDirect

Cardiometabolic Diagnostic criteria

Need at least one of:

BMI ≥ 25 (23 in Asian ethnicity)

Waist circumference > 94cm (M) or 80cm (F)

Fasting glucose ≥ 5.6mmol/l, HBA1c ≥ 39mmol/mol, Type 2 diabetes

BP ≥ 130/85 or on anti hypertensives

Triglycerides ≥ 1.7 mmol/l

HDL ≤ 1.0 mmol/l (M), ≤ 1.3 mmol/l (F) or on lipid lowering medications

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 – 542

Screening for MASLD?

- **MASLD is common but on a population level,** the absolute risk of liver-related events from MASLD in the general population is very low
- **Not** currently recommended due to lack of evidence indicating benefit/cost effectiveness – this may change in future esp as better testing and treatments emerge.
- European guideline *does* advise active case finding in at risk groups
  - Healthcare providers should look for MASLD in individuals with
    - Type 2 diabetes or
    - Abdominal obesity and ≥1 additional metabolic risk factor
    - Abnormal liver function tests

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 – 542

Steven, 48 yo man

- Hypertension, pre-diabetes
- Ramipril 10mg
- BMI 30, waist circumference 103cm
- BP 142/86

- HBA1c 47 (45 last year)
- AST 50 (<30), 52 last year
- ALT 90 (<35), 80 last year
- ALP and Bilirubin normal
- TC 6.0 LDL 3.8 HDL 1.2

- Drinks 3-4 pints on Fridays and Saturdays, rare during the week

Poll Q: What do you do next?

- Ignore, busy enough already, reassure
- Repeat LFTs 1 month
- Repeat LFTs 3 months
- Arrange a “liver screen” +/- USS
- Diagnose likely MASLD on basis of current results and advise accordingly

Spotting MASLD

- Beware LFTs alone – neither sensitive nor specific for diagnosing MASLD/MASH
  - However, in people with T2D, NAFLD is the commonest cause of a raised ALT
- Little correlation between degree of LFT abnormality and severity of disease
- Risk factors: Obesity, metabolic syndrome, Type 2 Diabetes
  - Don’t forget also PCOS and OSA
- Bidirectional relationship between MASLD and type 2 diabetes
  - MASLD in type 2 diabetes associated with increased severity of MASLD and risk of progression to fibrosis
  - Resolution of liver steatosis strongly linked with *remission* of type 2 diabetes

Approach for MASLD diagnosis in primary care

- History and examination
  - Good alcohol history, risk factors, cardiometabolic co-morbidities
  - Signs of liver disease

- Bloods
  - Liver enzymes (include an **AST**), HBA1c, lipids, FBC
  - **Limited liver aetiology screen**: Hep virology, iron studies, autoantibodies (*consider* copper studies / alpha 1 antitrypsin)

- USS abdomen – "echogenic liver"
  - Does everyone need an USS?
    - NICE "consider", BSG 2021 "USS or liver screen"
    - In individual with raised ALT, neg liver screen and cardiometabolic risk factors - not always needed

- Next step to assess the likelihood of any ***significant fibrosis***
  - Majority are low risk and can be managed in primary care, but need to identify the significant minority who require further intervention

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- Liver screen
  - Viral hepatitis screen, iron studies, autoantibodies – all normal
- USS liver - echogenic liver in keeping with fatty deposition
- Cardiometabolic criteria for MASLD?
  - Yes, multiple criteria
    - HbA1c, BP, HDL, BMI

Assessing risk of significant fibrosis

- Following likely diagnosis of MASLD we need to assess risk of significant fibrosis using **non invasive scores** - several available
  - NICE (2016) - consider an ELF score. Accurate test but not widely available.
  - BSG (2021), European (2024) – do a **FIB-4** or **NFS (NAFLD fibrosis)** score
  - AST:ALT ratio (>1 = higher risk fibrosis) Note: ratio still relevant when LFTs in normal range.
- Note – need AST – not always automatically included in LFTs
- Non invasive scores - high NPP – good rule out tests for significant fibrosis, if low can safely manage in primary care

Fibrosis-4 (FIB-4) Index for Liver Fibrosis ☆

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients	48	years
AST Aspartate aminotransferase	50	U/L
Platelet count	300	× 10⁹/L ⇋
ALT Alanine aminotransferase	90	U/L

0.84 points

Advanced fibrosis excluded

Approximate fibrosis stage: Ishak 0-1 (Sterling et al 2006)

Copy Results | Next Steps »»

NAFLD (Non-Alcoholic Fatty Liver Disease) Fibrosis Score ☆

Estimates amount of scarring in the liver based on several laboratory tests.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Age	48	years
BMI	30	kg/m²
Impaired fasting glucose/diabetes	No 0 / Yes +1	
AST	50	U/L
ALT	90	U/L
Platelet count	300	× 10⁹/L ⇋
Albumin	37	g/L ⇋

-1.74 points

Correlated Fibrosis Severity: F0-F2

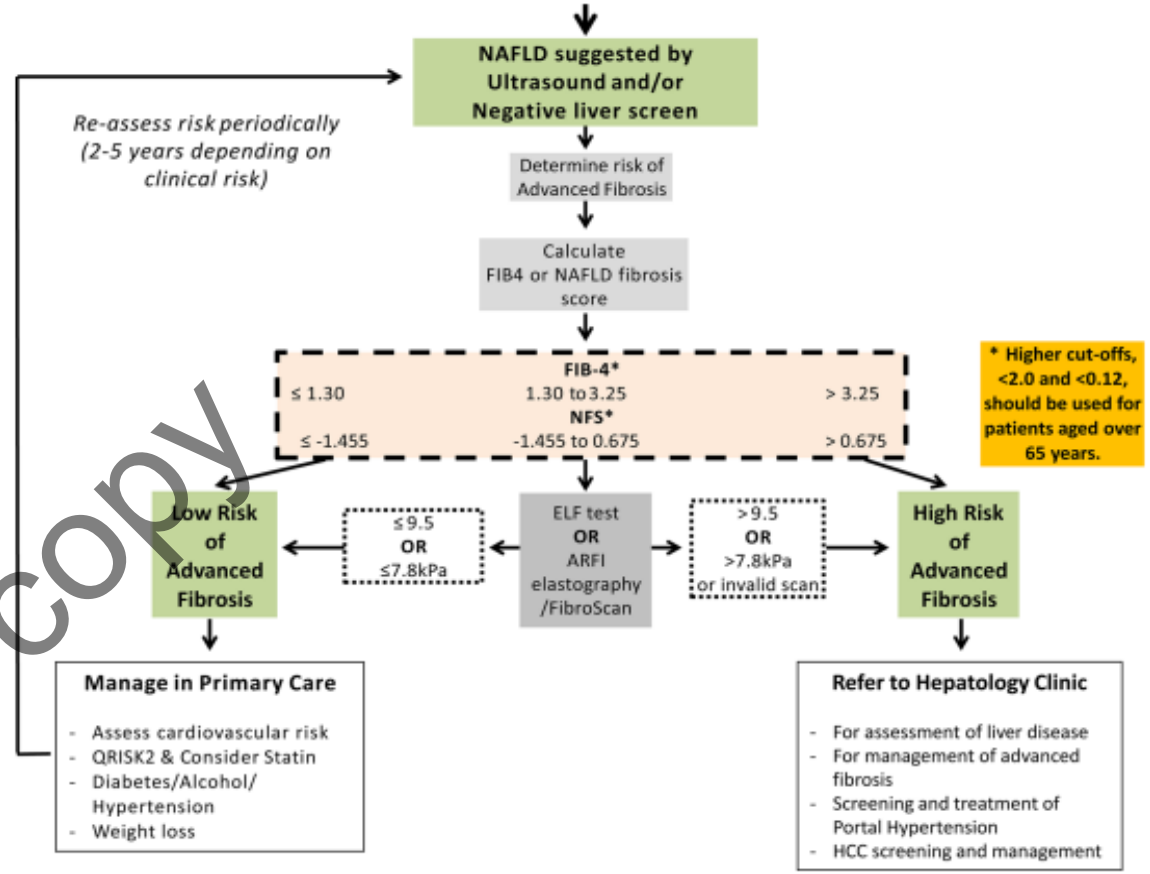
Copy Results | Next Steps »»

MDCalc - Medical calculators, equations, scores, and guidelines

Next steps

- If low risk (majority) FIB4 ≤ 1.3
  - Primary care management
  - Reassess periodically by repeating the score every 2-5 years (Wales = 4)
  - Set recall reminder

- If intermediate or high risk, FibroScan *if available*, or referral.
  - FibroScan is a USS with elastography
    - Asses fat and stiffness with is a proxy measure for fibrosis
    - Regional variation in availability



Dr P Horn, Prof P. Newsome British Society of Gastroenterology "NAFLD – diagnosis, assessment and management" Feb 2020, updated Nov2021

Low risk, manage in primary care

- Make an active diagnosis, **read coding**
- **Tell Steve** about MASLD and how he can make lifestyle modifications
- What can we do next?

MASLD, NAFLD and fatty liver disease

MASLD, NAFLD and fatty liver disease are different names for the same condition. You can read more about the different names and what they mean below.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a long-lasting liver condition caused by having too much fat in the liver. It is closely linked with being overweight as well as conditions such as type 2 diabetes and heart and circulatory disease.

Metabolic dysfunction-associated steatohepatitis (MASH, previously called NASH) is a more serious stage of MASLD. In a small number of people it can lead to liver cancer or liver failure.

The main treatment is eating a well-balanced diet, being physically active and (if needed) losing weight. Research shows these can reduce liver fat and in some cases reverse MASLD.

https://britishlivertrust.org.uk/

Interventions for MASLD

- Reduce alcohol consumption to at least normal limits, or zero

- Support for weight loss
  - ≥5% reduces liver fat
  - 7-10% can be effective to reduce liver inflammation
  - Consider referral for wt management support, tailored interventions, Tier 3 if available and appropriate
  - Bariatric surgery
    - Prospective study
      - 109 pts with MASH and severe obesity,
      - 85% had resolution of MASH 12 months after surgery

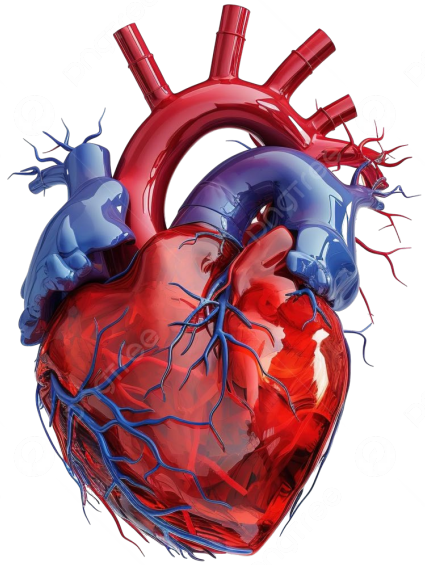
Lassailly G, Caiazzo R, Buob D*, et al.* Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. Gastroenterology 2015;**149**:379-88; quiz e15-6

MASLD and CV risk

- Cardiovascular events are the leading cause of mortality in adults with MASLD, more common than liver related deaths

- Increase risk partly due to close association with other cardiometabolic risk factors, but studies show risk is also increased **independently** of those common risk factors

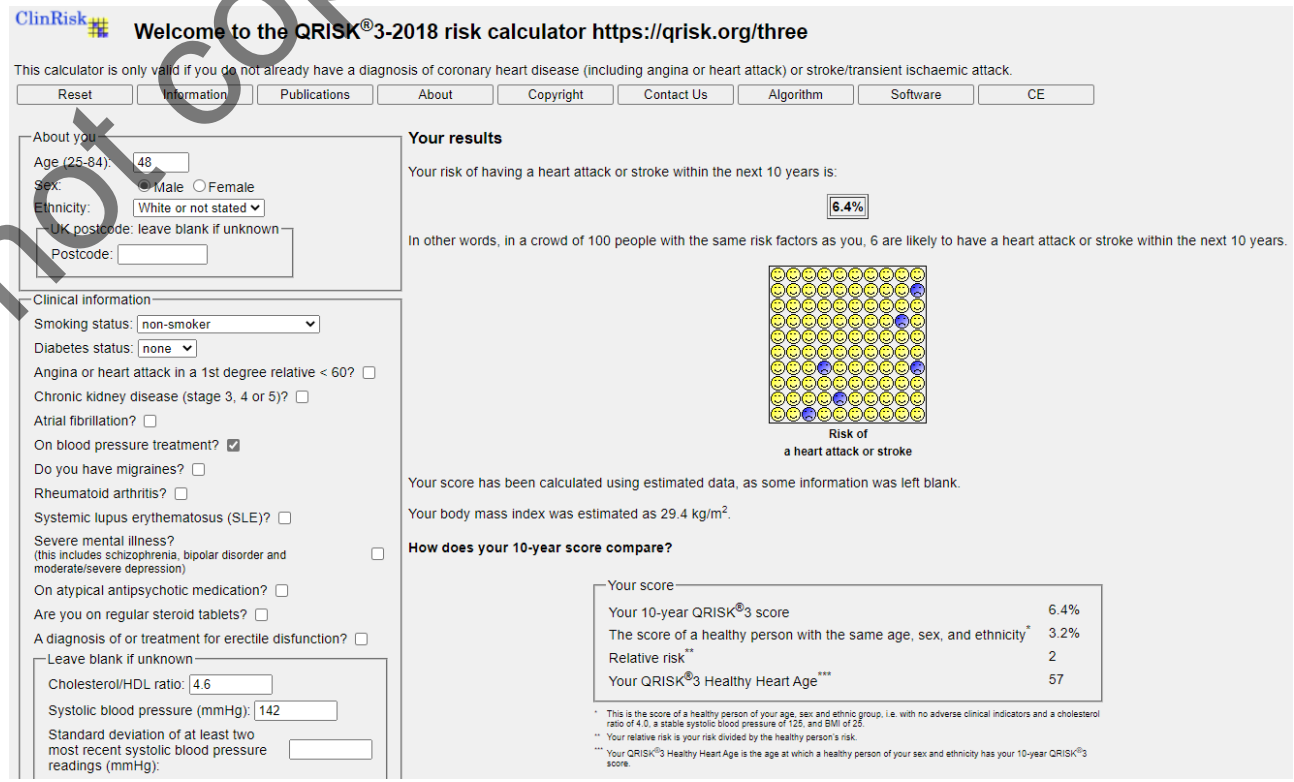
- Individuals with MASLD have a higher risk of:
  - Atherosclerotic CV disease – incl MI, stroke, CV death
  - Heart failure
  - AF



Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach - The Lancet Gastroenterology & Hepatology 2021 Jul;6(7):578-588
Targher G, Byrne CD, Tilg H MASLD: a systemic metabolic disorder with cardiovascular and malignant complications *Gut* 2024;**73:**691-702.

Assess CV risk

- NICE: Offer statin treatment for the primary prevention of CVD to people with a 10-year QRISK3 score of 10% or more, including those with type 2 diabetes.
  - If the 10-year QRISK3 score is less than 10%, do not rule out statin treatment if the person has an informed preference for taking it or if there is concern that CVD risk may be underestimated
- Consider lifetime risk esp in < 40s
- Steven – 10 year risk Qrisk 3: 6.4%
- Discuss
  - Lifestyle modifications
  - Optimise BP
    - < 140/90 or lower esp if younger



Recommendations | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE

Statins and MASLD

- Considered safe but underused
- Improve CV risk, *probably* not liver histology

NICE G/L

- Check LFTs before initiating statins
- Do not withhold statin if LFTs are elevated, providing ALT/AST < 3x upper limit
- Recheck LFTs within 3 months of starting treatment, 3 months after any titration and again at 12 months
- Continue statin unless ALT/AST become >3x upper limit of normal
- Further monitoring is not necessary unless clinically indicated

Recommendations | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE

Medications for MASLD

- Currently **no *specific licenced drug treatment***

- Pioglitazone
  - Directly tackles insulin resistance, favorable impact on lipid profile
  - Histological improvements in steatohepatitis in small studies, no improvement in fibrosis
  - Can be an option in patients with lots of features of metabolic syndrome, consider in primary care in ppl with T2DM and MASLD, beware SEs / contra indications
    - Heart failure, Fractures, Undiagnosed haematuria, Weight gain

- Vitamin E
    - Concerns re long term safety
    - Not advised in most recent European G/L

Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis.*N Engl J Med.* 2010; **362**: 1675-1685

Emerging evidence

- SGLT2i's
  - Reduce liver fat content and ALT in people with T2D

- GLP1/GIP agonists
  - Increasingly convincing evidence of improvements in liver histology

N Engl J Med 2021; 384:1113-1124 A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis Philip N. Newsome et al
LEAN The Lancet 2016 VOLUME 387, ISSUE 10019, P679-690, FEBRUARY 13, 2016
Diabetes Care Feb 2022 Glucagon-Like Peptide 1 Receptor Agonists and Sodium–Glucose Cotransporter 2 Inhibitors and Risk of Nonalcoholic Fatty Liver Disease Among Patients With Type 2 Diabetes
Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. *Lancet Gastroenterol Hepatol*. Published online January 11, 2022. doi: 10.1016/S2468-1253(21)00261-2

ORIGINAL ARTICLE

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

The NEW ENGLAND JOURNAL of MEDICINE

- ESSENCE trial – April 2025
- Semaglutide 2.4mg OW vs placebo
- 1197 pts with MASH and fibrossi stages 2 or 3
- Significant improvement in both MASH and also fibrosis stage

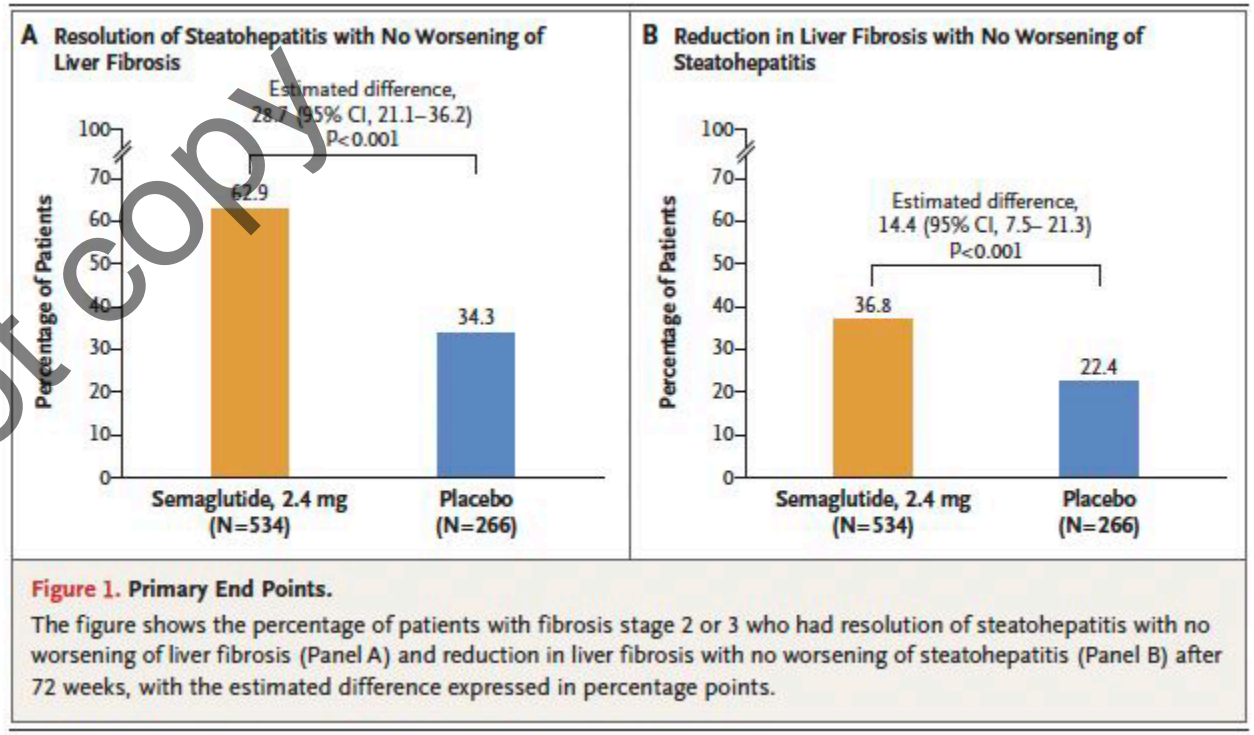


Figure 1. Primary End Points.
The figure shows the percentage of patients with fibrosis stage 2 or 3 who had resolution of steatohepatitis with no worsening of liver fibrosis (Panel A) and reduction in liver fibrosis with no worsening of steatohepatitis (Panel B) after 72 weeks, with the estimated difference expressed in percentage points.

- Next phase will look at progression to cirrhosis

Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis | New England Journal of Medicine

Can early use reduce incidence of MASLD in T2D?

- UK Cohort study using CPRD comparing new users of GLP1, SGLT2i or DPP4i with **no known** MASLD
- Both GLP1's and SGLT2i's associated with a lower incidence of MASLD and a decreased risk of abnml LFTS vs DPP4i's
- Supports earlier use of these medications in T2D
  - Already doing so with SGLT2i's
  - Position of GLP/GIP agonists under review by NICE

Diabetes Care Feb 2022 Glucagon-Like Peptide 1 Receptor Agonists and Sodium–Glucose Cotransporter 2 Inhibitors and Risk of Nonalcoholic Fatty Liver Disease Among Patients With Type 2 Diabetes

The future?

- Survodutide
  - Dual GLP / glucagon agonist
  - Phase 2 clinical trial 2024 NEJM
    - Up to 83% resolution in MASH, 65% improved fibrosis score
- Tri agonists in the way as well!
    - GIP / GLP1 / glucagon receptor agonist
- Likely to develop specific licensed indications for MASH in the future

.Sanyal AJ, et al. N Engl J Med 2024;391:311-319

Steven

- Fibrosis risk low
  - Reassess in 4 years – flag on notes / set recall
- Education and support for weight loss
  - Reduce MASLD and risk of progression
  - Reduce risk of progressing to type 2 diabetes
  - Consider suitability for incretin meds for weight management as eligibility criteria widens over the next few years
- Active CV risk management
  - Qrisk 6.4%
- Annual HBA1c
  - If he develops Type 2 Diabetes, prioritise SGLT2i / GLP1/GIP.

Conclusions

- MASLD is very common, especially in people with T2D or obesity
- Can progress to steatohepatitis and fibrosis
- Our role in primary care
  - Identify and make active diagnosis (bloods, liver screen +/- USS)
  - Assess the likelihood of significant fibrosis and refer if required
  - Support for weight loss
  - Active CV risk management
    - Statins are generally safe
  - Potential for benefit from newer diabetes medications

- **MASLD is not a benign condition, that raised ALT needs actioning!**
- **Consider actively looking for MASLD in at risk populations**
  - **Consider adding FIB4 into diabetes annual review**

QI idea: Have your patients with known MASLD had a Fib4?

Thank you

Any questions?