GWENT LIVER UNIT
REGISTERED CHARITY NO: 1098728

NAFLD

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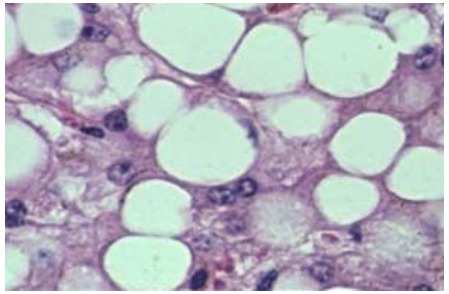
WEQAS
Dec 6th 2017

Non alcoholic fatty liver disease

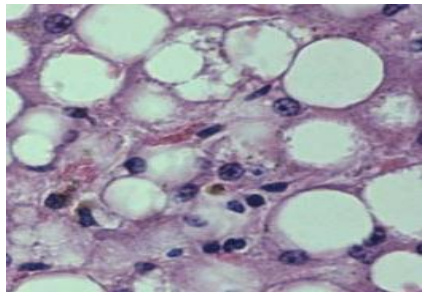
- Does not have the recognition that alcohol has
- Commonest case of abnormal LFTs in the population
- Increasingly common cause of end stage liver disease
- NAFLD leads to an increase risk of HCC even without cirrhosis
  - 43% in one cohort of HCC patients with NAFLD were not cirrhotic

Spectrum of NAFLD

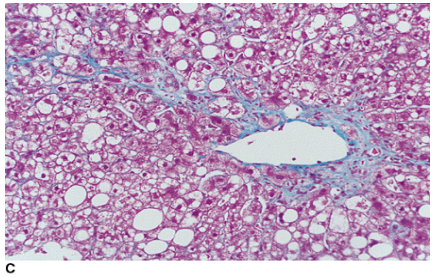
Steatosis



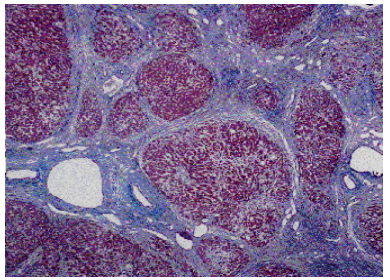
Steatohepatitis (NASH)



Fibrosis



Cirrhosis



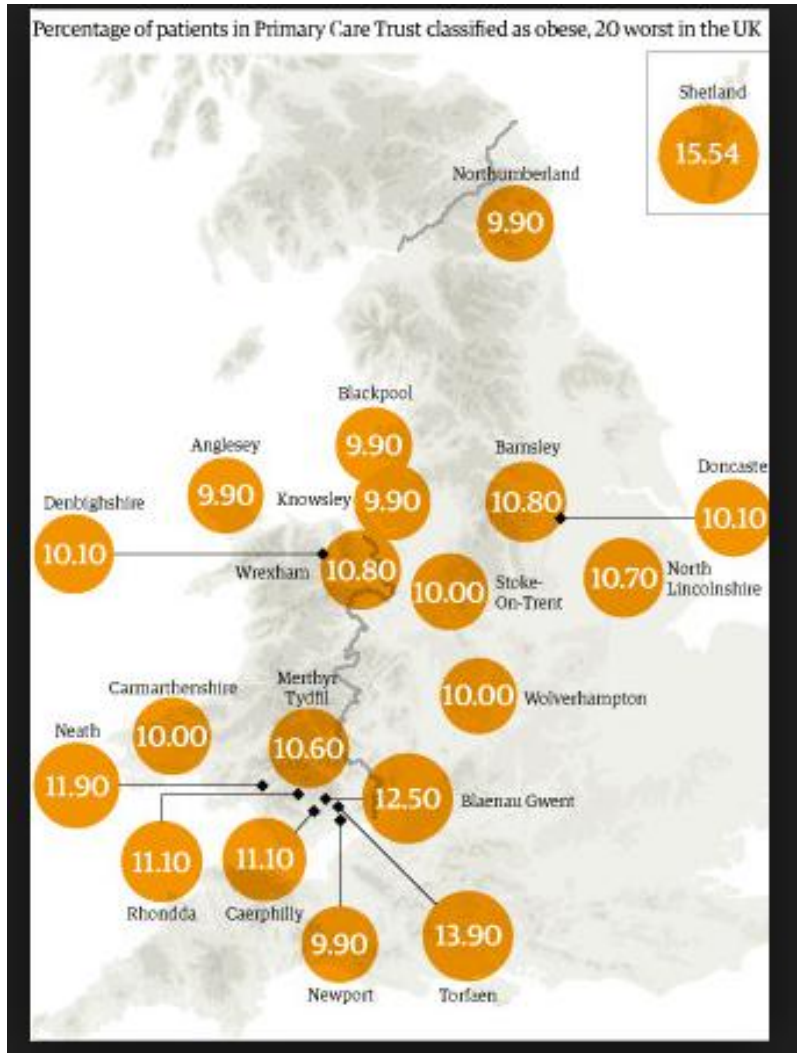
Natural History of NAFLD

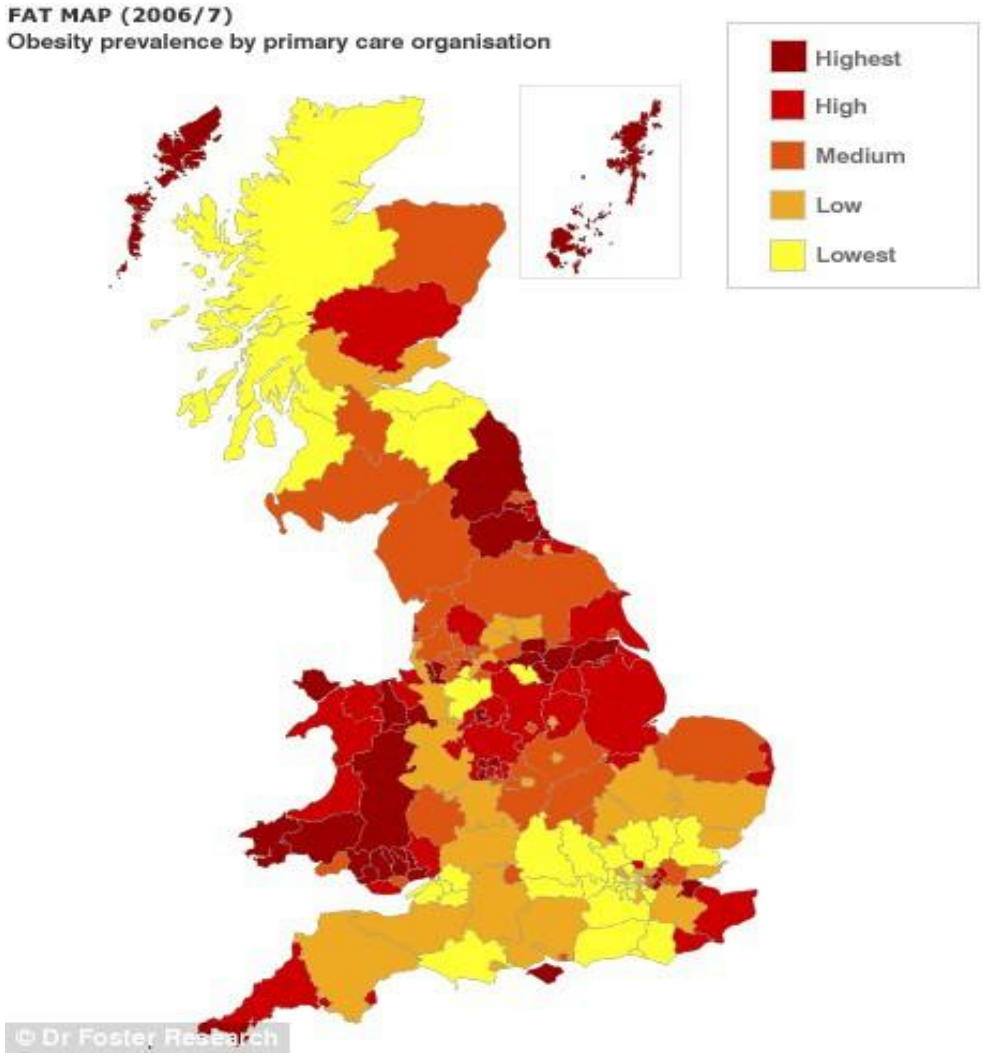
- Simple Steatosis more benign than NASH
- 1-2% with simple steatosis - significant liver disease
- Overall 10% with NAFLD have NASH
- 25% of NASH will develop cirrhosis
  - ¾ of these die a liver related death
- Liver disease is 3rd commonest cause death in NAFLD (13th in gen population)

Incidence & Prevalence of NAFLD/NASH

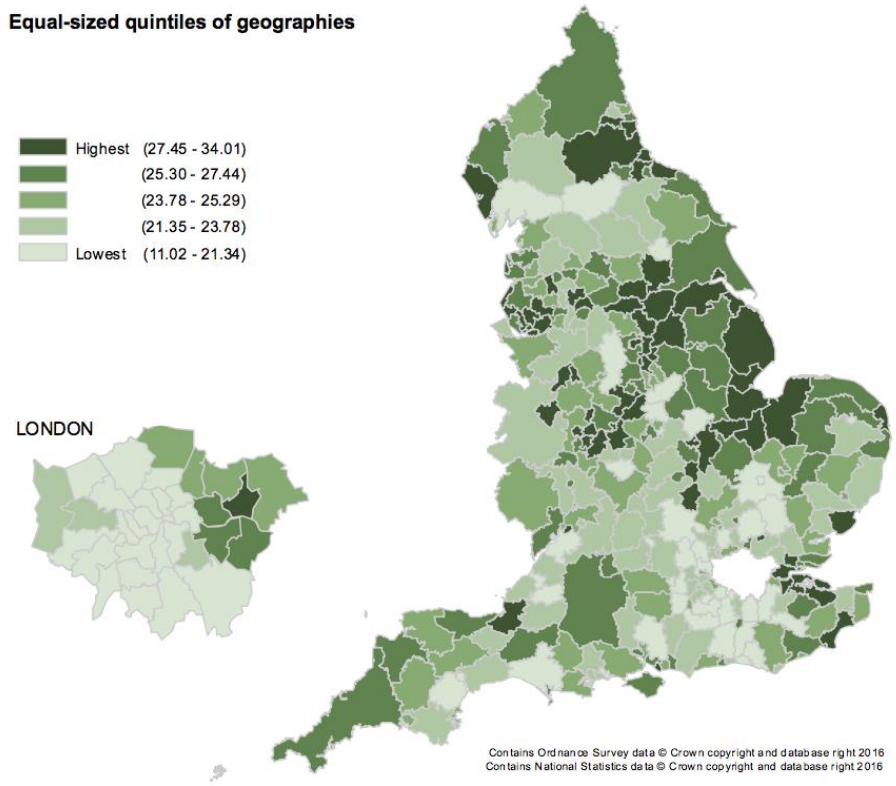
- Healthy potential live liver donors in US:
  - NAFLD found in 20%
- Autopsy study of US trauma victims:
  - NASH in 2.7% of lean non alcohol abusers vs 18.5% in obese non abusers
- Large European study:
  - NAFLD in 25% with normal body weight, 67% of those overweight and 94% of obese individuals
- UK data (BSG)
  - NAFLD 30%, NASH 2-5%

UK Obesity

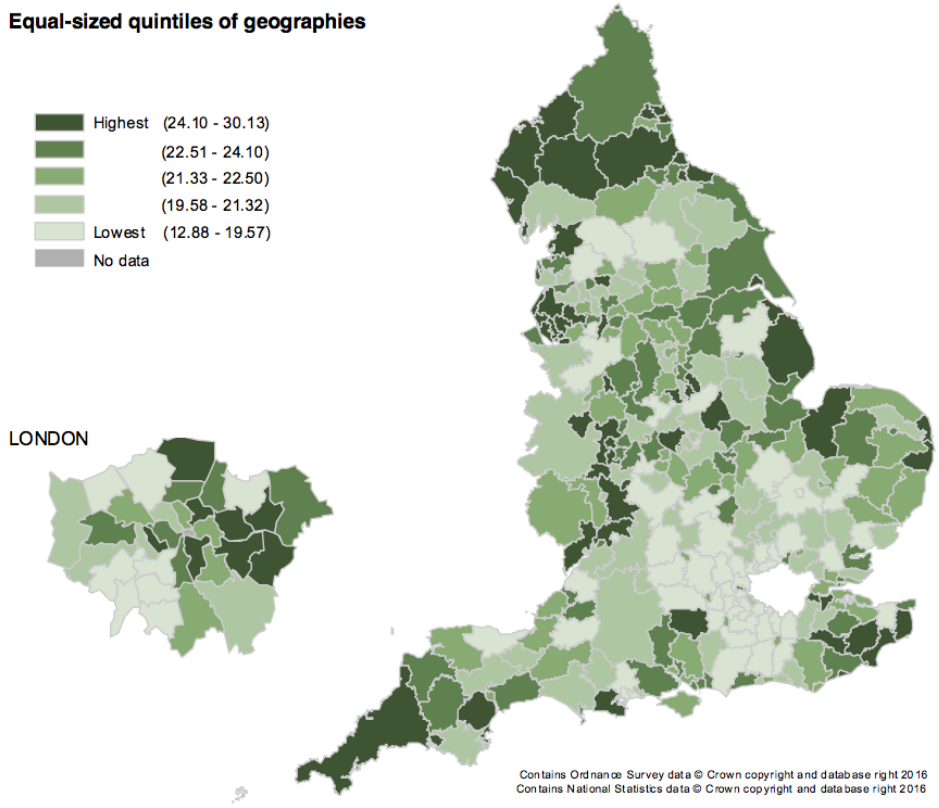

Percentage of patients in Primary Care Trust classified as obese, 20 worst in the UK
Shetland
15.54
Northumberland
9.90
Blackpool
9.90
Anglesey
9.90
Knowsley
9.90
Barnsley
10.80
Doncaste
10.10
Denbighshire
10.10
Wrexham
10.80
10.00
Stoke-On-Trent
10.70
North Lincolnshire
Carmarthenshire
10.00
Merthyr Tydfil
10.60
10.00
Wolverhampton
Neath
11.90
12.50
Blaenau Gwent
11.10
Rhondda
11.10
Caerphilly
9.90
Newport
13.90
Torfaen


FAT MAP (2006/7)
Obesity prevalence by primary care organisation
Highest
High
Medium
Low
Lowest
© Dr Foster Research

Proportion of those Obese: >16 yrs old



Proportion children obese at reception



Burden in England

- Health Survey Data
  - 37% normal BMI = 19,610,000
  - 36% overweight = 19,080,000
  - 27 % obese = 14,310,000
- Based on BSG data
  - 15 million people with NAFLD
  - 1.5 million NASH
  - 375,000 will develop cirrhosis = 0.7% of population
  - 281,250 will die from liver disease

It may be worse….

- One study from western Europe defined the incidence of NAFLD as
  - 25% in those with normal body weight,
  - 64% in those overweight and
  - 94% in obese patients
- Equates to 31,155,500 people in England
  - = 61% of population
- Subsequently
  - 3 million with NASH
  - 778,000 will develop cirrhosis (1.5% of population)
  - 584,000 liver deaths solely due to NAFLD

Diagnosis of NAFLD

- Definition: >5% liver volume by fat in absence of significant alcohol intake (<2u/day)
- Usually incidental finding
  - Abnormal LFT or on US
- Severity:
  - Mild 5-33%
  - Moderate 33-50%
  - Severe >50%
- Note USS not highly sensitive at picking up if <33%
  - MRI is best

Abnormal LFTs in NAFLD

- Raised GGT almost universal
- Usually isolated rise in ALT
- Ferritin elevated in 50%
- In NAFLD ALT typically greater than AST in a ratio of 2:1
  - However that ratio reverses with advancing fibrosis

Guidelines on the management of abnormal liver blood tests

Philip N Newsome,[1,2] Rob Cramb,[1] Suzanne M Davison,[3] John F Dillon,[4] Mark Foulerton,[5] Edmund M Godfrey,[6] Richard Hall,[7] Ulrike Harrower,[8] Mark Hudson,[9,10] Andrew Langford,[11] Anne Mackie,[8] Robert Mitchell-Thain,[12] Karen Sennett,[13,14] Nicholas C Sheron,[15] Julia Verne,[8] Martine Walmsley,[16] Andrew Yeoman[17]

Newsome PN, *et al*. *Gut* 2017;**0**:1–14.

Utility of ALT in diagnosis of NAFLD

- ALT references ranges are inherently insensitive
- ALT classically fluctuates in NAFLD
  - 2/3rds of patients have a normal ALT at some time
- In morbidly obese pts with raised ALT (>40)
  - sensitivity for NAFLD 45% specificity 100% for NASH 45% and 64%
- ALT may be normal in cirrhosis

True “Normal” ALTs

Table 3. ALT and AST levels and liver related mortality

Author /year	Proposed ALT/AST cutoff level	ALT/AST level for increased mortality	Comments
Arndt *et al.* (27)	AST 18	AST>18	3X increase in all cause mortality
Kim *et al.* (28)	ALT<20	ALT 30–39	RR of liver mortality 2.9 (2.4–3.5) and 9.5 (7.9–11.5) in men, 3.8 (1.9–7.7) and 6.6 (1.5–25.6) in women
Lee *et al.* (29)	ALT (ULN 45 IU/l for M, 29 for F	ALT 45–90 M 29–58 for F	SMR risk 1.32 for 1–2X ULN, and 1.78 for >2X ULN
Ruhl and Everhart (30)	ALT 30 IU/l M, 19 IUL for F	ALT>30 for M ALT >19 for F	Increased liver related mortality

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; RR, relative risk; M, male; ULN, upper limit of normal.

A true healthy normal ALT level ranges from:
29 to 33 IU/l for males
19 to 25IU/l for females
Levels above this should be assessed.

Assessment of the patient with NAFLD

- NAFLD is so common should not preclude search for other causes

- If just NAFLD the most important question is:

1) Is this just simple steatosis?
2) Is there inflammation?
3) Is there fibrosis/cirrhosis?

Risk assessment of NAFLD

- Gold standard is liver biopsy
- But cant biopsy 1/3rd of the population!
- Non invasive methods needed

NICE Guideline on NAFLD

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Overview

This guideline covers how to identify the adults, young people and children with non-alcoholic fatty liver disease (NAFLD) who have advanced liver fibrosis and are most at risk of further complications. It outlines the lifestyle changes and pharmacological treatments that can manage NAFLD and advanced liver fibrosis.

The language of NICE CG's

- Offer = you must
- Consider = you may wish to

NAFLD Assessment

1.1 Assessment for NAFLD

Identifying NAFLD in higher-risk groups

1.1.1 Be aware that non-alcoholic fatty liver disease (NAFLD) is more common in people who have:

- type 2 diabetes or
- metabolic syndrome.

1.1.2 Take an alcohol history to rule out alcohol-related liver disease. See also NICE's cirrhosis guideline.

1.1.3 Do not use routine liver blood tests to rule out NAFLD.

Liver fibrosis assessment in NAFLD

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1.2 *Assessment for advanced liver fibrosis in people with NAFLD*

Identifying people with advanced liver fibrosis

1.2.1 Offer testing for advanced liver fibrosis to people with NAFLD.

1.2.2 Consider using the enhanced liver fibrosis (ELF) test in people who have been diagnosed with NAFLD to test for advanced liver fibrosis.

1.2.3 Do not use routine liver blood tests to assess for advanced liver fibrosis in people with NAFLD.

1.2.4 Diagnose people with advanced liver fibrosis if they have:

- an ELF score of 10.51 or above and
- NAFLD.

1.2.5 Refer adults and young people diagnosed with advanced liver fibrosis to a relevant specialist in hepatology.

1.2.6 Explain to people with an ELF score below 10.51 that:

- they are unlikely to have advanced liver fibrosis and
- reassessment for advanced liver fibrosis every 3 years for adults and every 2 years for children and young people is sufficient for regular monitoring and
- no interim tests are needed.

Give the person advice about lifestyle modifications they may be able to make (see section 1.2).

1.2.7 Offer retesting for advanced liver fibrosis for people with an ELF score below 10.51:

- every 3 years to adults
- every 2 years to children and young people.

1.2.8 Consider using ELF for retesting people with advanced liver fibrosis.

Risk assessment in NAFLD

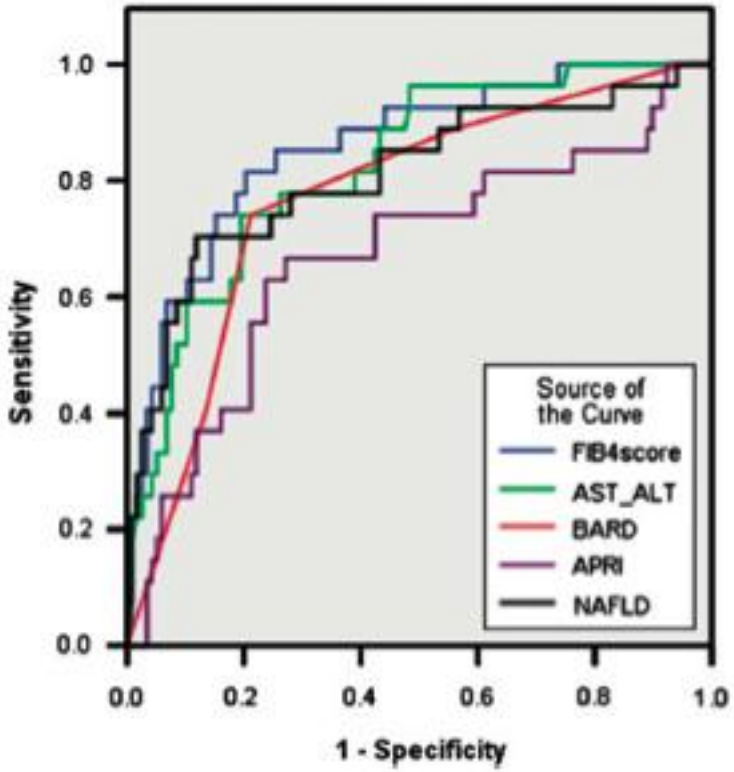
- Need a tool that can be used without additional skills that is cheap and reproducible on a population basis
- AST/ALT ratio and NAFLD fibrosis score fit the bill
- These tests have a high negative predictive value – ie good at excluding significant fibrosis
- If high need corroboration

Non Invasive Assessment of Fibrosis

Table 3 A comparison of the performance of each test for the diagnosis of advanced fibrosis in 145 patients with non-alcoholic fatty liver disease (NAFLD)

Test	AUROC (95% CI)	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)
AST/ALT ratio	0.83 (0.74 to 0.91)	0.8	74	78	44	93
		1	52	90	55	89
APRI	0.67 (0.54 to 0.8)	1	27	89	37	84
BARD score	0.77 (0.68 to 0.87)	2	89	44	27	95
FIB-4 score	0.86 (0.78 to 0.94)	1.30	85	65	36	95
		3.25	26	98	75	85
NAFLD fibrosis score	0.81 (0.71 to 0.91)	−1.455	78	58	30	92
		0.676	33	98	79	86

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; Sens, sensitivity; Spec, specificity.



Fibroscan

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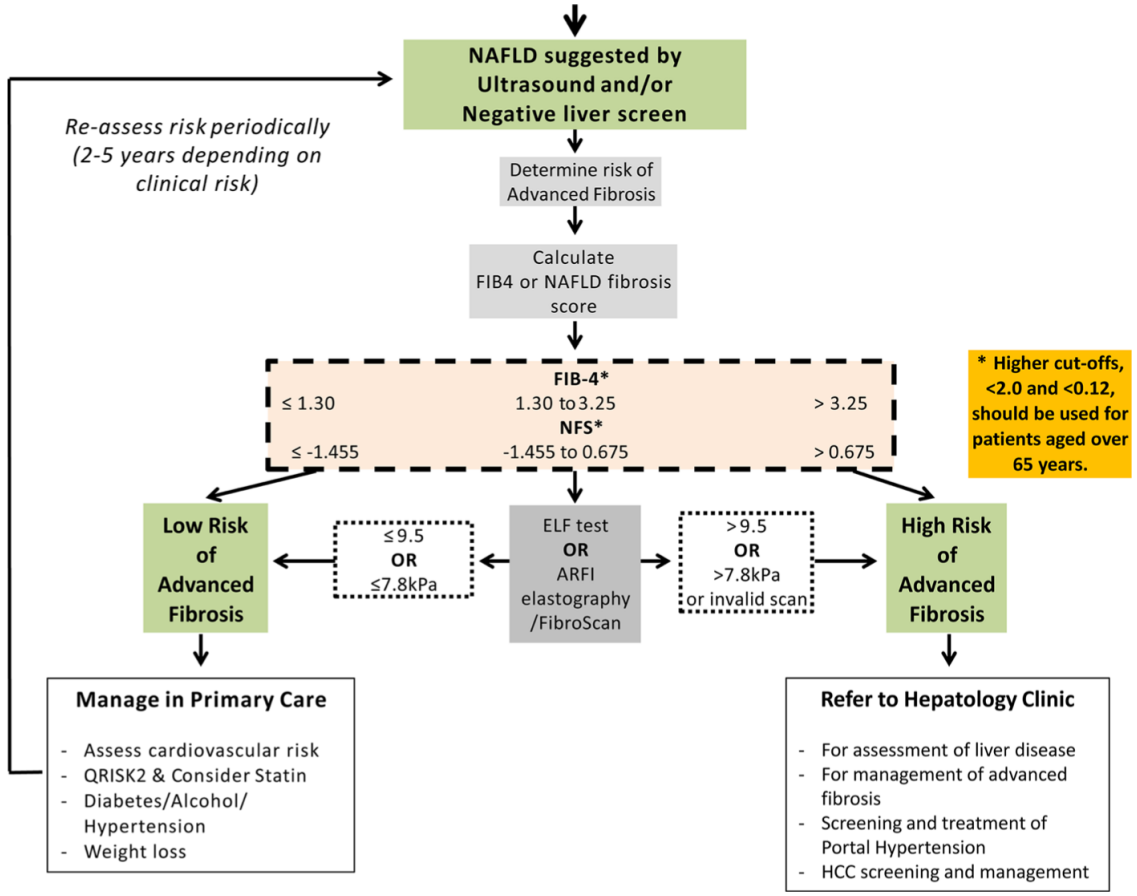
Stick to the spirit rather than the letter..



Management of NAFLD

- Manage features of the metabolic syndrome
- Weight reduction is key
  - 5% TBW if simple steatosis, 10% if NASH
- Increased exercise key
- Pharmacological agents:
  - Glitazones, Metformin
  - Vitamin E
  - Losartan
  - Liraglutide

Therapy in NASH with fibrosis

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1.4 *Pharmacological treatment*

1.4.1 In secondary or tertiary care settings only, consider pioglitazone[1] or vitamin E[2] for adults with advanced liver fibrosis, whether they have diabetes or not.

1.4.2 Before prescribing pioglitazoneor vitamin E to adults, take into account any comorbidities that they have and the risk of adverse events associated with these conditions.

1.4.3 In tertiary care settings only, consider vitamin E for children with advanced liver fibrosis, whether they have diabetes or not.

1.4.4 In secondary or tertiary care settings only, consider vitamin E for young people with advanced liver fibrosis, whether they have diabetes or not.

1.4.5 Offer to retest people with advanced liver fibrosis 2 years after they start a new pharmacological therapy to assess whether treatment is effective.

1.4.6 Consider using the ELF test to assess whether pharmacological therapy is effective.

Its not just about the liver

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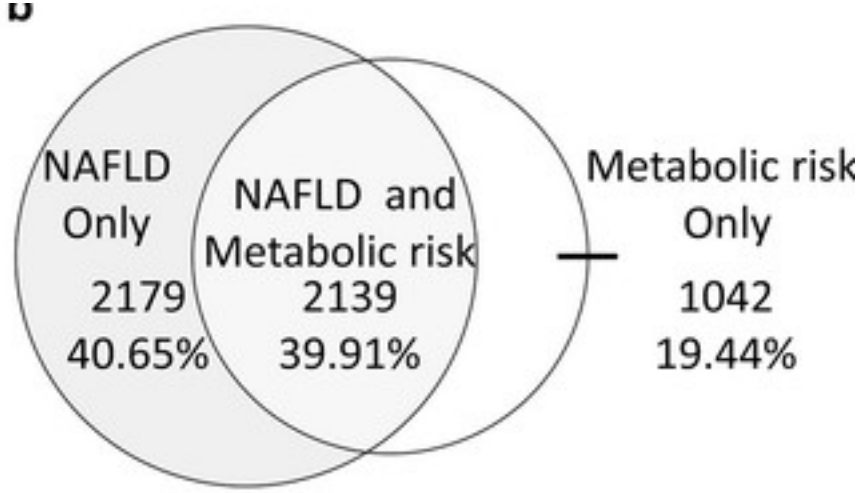
Extra-hepatic conditions

1.2.10 Be aware that NAFLD is a risk factor for type 2 diabetes, hypertension and chronic kidney disease.

1.2.11 Be aware that in people with type 2 diabetes, NAFLD is a risk factor for atrial fibrillation, myocardial infarction, ischaemic stroke and death from cardiovascular causes.

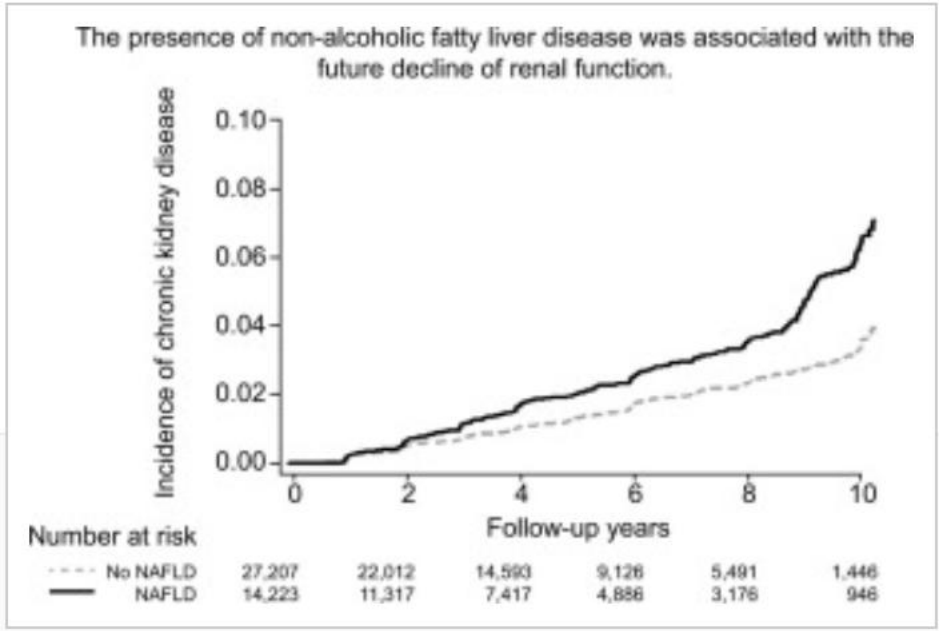


NAFLD and CKD

The hazard ratio for CKD with and without NAFLD was 1.22 (95% [CI] 1.04–1.43).

The risk of CKD increased progressively with increased NAFLD severity.

HR for CKD with NFS <−1.455 and NFS ≥−1.455 to participants without NAFLD:
1.09 (95% CI 0.91–1.32) and
1.58 (95% CI 1.30–1.92)



NAFLD associations:

- Increased risk of CVD
- Increased rate of CKD
- DM risk : 5 fold
  - Majority of Morbidly Obese Type II DM have NAFLD
- Single study in T2DM pts with normal LFTs
  - 4% cirrhotic
- Liver cancer

Challenge of Obesity

- Not a disease but risk factor for many others
- Need to be aware of ”high risk associations”
  - NAFLD is one
  - So is abnormal liver blood tests
- Major progress will only be made via multi-specialty collaboration
- Interventions likely to be same
  - Targeted to management of obesity

Take home messages

- NAFLD and NASH are very common
  - Assessment of risk of fibrosis essential
- Think about associations – don't silo it to liver disease
- Weight reduction remains mainstay of Rx
- Statins are safe!