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PRACTICE

UNCERTAINTIES PAGE

How big a problem is non-alcoholic fatty liver disease?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease encompassing simple fatty infiltration (steatosis), fat and inflammation (non-alcoholic steatohepatitis (NASH)), and cirrhosis, in the absence of excessive alcohol consumption (typically a threshold of <20 g a day for women and <30 g a day for men is adopted). Simple steatosis has not been associated with liver related morbidity, but NASH may lead to progressive liver fibrosis, cirrhosis, and liver cancer, as well as increase cardiovascular risk. NAFLD is strongly associated with obesity, insulin resistance or type 2 diabetes mellitus, and dyslipidaemia and may be considered the hepatic manifestation of the metabolic syndrome.^{1,2} Estimates vary between populations, but one large European study found NAFLD in 94% of obese patients (body mass index (kg/m²) >30), 67% of overweight patients (>25), and 25% of normal weight patients.³ The overall prevalence of NAFLD in people with type 2 diabetes ranges from 40% to 70%.³ With the advent of increasingly sedentary lifestyles and changing dietary patterns, the prevalence of obesity and insulin resistance have increased and NAFLD has rapidly become the most common cause of abnormal liver biochemistry in many developed countries.⁴ Despite substantial clinical and basic research in this field, the true prevalence of NAFLD and NASH in the community and the likely future disease burden remain unclear. Furthermore, clinical uncertainties persist from diagnosis and risk stratification through to treatment and long term follow-up.

Diagnosis and risk stratification—Much of the population is at risk of NAFLD through being overweight or insulin resistant, or both, but how best to identify patients with NAFLD remains unclear, especially in patients with NASH, who are at greatest risk of liver related complications. Many patients remain undiagnosed and so it is not known what the true prevalences of steatosis and steatohepatitis are and how many people will

actually develop liver related morbidity. These uncertainties have made it difficult to establish strategies for service delivery in routine clinical practice.

Prognosis—Although most patients with NAFLD have steatosis, only a minority progress to more advanced disease, characterised by inflammation and subsequent fibrosis, cirrhosis, and hepatocellular carcinoma. Studies indicate that about 5.4% of patients with NASH develop complications of end stage liver disease during long term follow-up.^{3,5} Such progression is probably influenced by genetic and environmental factors, only some of which have been identified.^{4,6} Recognised independent risk factors for progression are age >45 years, presence of diabetes (or severity of insulin resistance), obesity (body mass index >30), and hypertension.⁴ The patients who do progress often present late in the natural course of the disease and have substantial liver related morbidity.

Treatment—Although current treatment is aimed at weight loss and amelioration of the metabolic syndrome through lifestyle interventions such as diet and exercise, insufficient evidence exists to formulate authoritative and balanced clinical guidelines for specific therapies.⁴

What is the evidence of the uncertainty?

The need for better evidence is apparent from the start of a patient's journey with NAFLD when we consider how best to identify affected individuals in the population, how to stratify individual risk of disease progression so that care may be tailored to individual need, and how to establish strategies for service delivery in routine clinical practice (box 1). We searched PubMed, Medline, Embase, the Cochrane Library, the metaRegister of Controlled Trials (mRCT), and clinicaltrials.gov databases for relevant literature and information on clinical trials (and other registered studies). No internationally accepted evidence based consensus guidelines have been published on this subject.

Box 1 Main uncertainties in non-alcoholic fatty liver disease (NAFLD)

- The prevalence of NAFLD and non-alcoholic steatohepatitis (NASH) in an unselected general population
- The risk of liver related morbidity in a general community population of individuals with NAFLD or NASH
- The optimum method of identifying subjects with NASH in the community
- Clinically relevant, economic, and patient acceptable non-invasive techniques for differentiating steatosis from NASH to identify those at greatest risk of liver related complications
- Strategies to facilitate sustainable modification of lifestyle to achieve weight loss and control the metabolic syndrome
- Effective drug treatments directed at the liver to control steatohepatitis and prevent fibrosis progression

How to diagnose NAFLD and NASH

NAFLD is often asymptomatic and commonly first discovered as an incidental biochemical abnormality (often mildly raised alanine aminotransferase levels) identified during routine blood tests.⁷ The characteristic biochemical changes (a relatively greater rise in alanine aminotransferase than in aspartate aminotransferase) tend to reverse, and alanine aminotransferase levels fall as hepatic fibrosis progresses. This means that steatohepatitis with advanced disease may be present even in those with relatively normal alanine aminotransferase levels. Furthermore, hepatic fat content tends to diminish as cirrhosis develops, and so NASH is probably underdiagnosed in the setting of advanced liver disease, where it is thought to be the underlying cause of 30-75% of cases where no specific cause is readily identified (“cryptogenic cirrhosis”).⁴

Routine ultrasound imaging of the liver provides a qualitative assessment of hepatic fat content; sensitivity is limited, however, particularly when <33% of hepatocytes are steatotic.⁸ Several methods (both proprietary and non-proprietary) have been proposed for non-invasive quantification of hepatic fat and inflammation, including magnetic resonance imaging or spectroscopy and biomarker panels. However, evidence supporting their use in wider clinical practice is still limited.⁴ Although magnetic resonance techniques for lipid quantification offer greater sensitivity for detecting milder degrees of steatosis, they are often resource intensive and are not yet widely available for routine clinical use.⁴ No widely accepted, reliable methods are available yet for differentiating simple steatosis from steatohepatitis in routine practice, other than liver biopsy.⁴

How to distinguish patients with progressive disease

As hepatic fibrogenesis takes many years to progress, high quality data from prospective trials on disease progression are limited, particularly for the primary care setting. Currently, liver biopsy is considered by many to be the optimum investigation for assessing degree of inflammation and extent of liver fibrosis as markers for risk of liver related morbidity. Accepting the limitations, studies indicate that 25-33% of patients with NASH have advanced fibrosis, including cirrhosis, at the time of diagnosis, and that after adjustment for confounders NASH has a similar fibrotic potential to that of chronic hepatitis C.^{3,4} Pooled data suggest that about 38% of patients with NASH will exhibit progressive fibrosis and 21% will have some regression during a mean 5.3 years' follow-up.³ A cohort study found that whereas lone steatosis was not associated with increased risk of morbidity, NASH was associated with a >10-fold increased risk of liver related death (2.8% v 0.2%) and a doubling of cardiovascular risk (15% v 7.5%) over a mean follow-up of 13.7 years.⁵

Invasive tests are generally not appropriate or practical outside specialist hepatology practice. There is a clear need to develop

non-invasive screening tests, ideally based on clinical history and readily available anthropometric and biochemical indices, to differentiate the patients at low risk of progression from those with more aggressive disease. The identification of appropriate biomarkers is an area of ongoing study, and the relative merits of currently published clinical scores and elastography techniques that identify patients with advanced fibrosis remain controversial.^{7,9,10} These clinical scores and elastography techniques indicate, however, only the current degree of fibrosis and do not necessarily predict subsequent disease progression.

How best to advise and treat patients with NAFLD and NASH

As recently highlighted in a position statement on NAFLD from the European Association for the Study of the Liver, evidence based clinical guidelines for this condition are badly needed but insufficient evidence is currently available to formulate authoritative and balanced guidance.⁴ No drugs are currently licensed specifically for treating NASH, although evidence from randomised control trials may support the use of specific insulin sensitising agents in selected patient groups.⁴ The mainstay of current treatment comprises lifestyle interventions to promote weight loss, with trial evidence showing that weight reduction of ≥7% maintained over 48 weeks is associated with significant reduction in histological severity of NASH.¹¹

Is ongoing research likely to provide relevant evidence?

Box 2 summarises the main clinically relevant research themes. From a public health perspective, the magnitude of disease burden in the general population needs to be determined so that consequent consumption of healthcare resources attributable to NAFLD alone or as a cofactor in disease progression may be predicted.

A search of ClinicalTrials.gov (www.clinicaltrials.gov) identifies more than 250 ongoing studies examining diagnostic modalities, physiology, and treatment of NAFLD. Several international collaborative research programmes are under way. The FLIP: Fatty Liver Inhibition of Progression consortium (www.flipfp7.eu/), sponsored by the European Union, has established large prospective and retrospective patient cohorts to identify genetic factors and pathophysiological mechanisms underlying NASH and also to enable development of innovative diagnostic methods for large scale screening and prognostic evaluation. Similarly, the United States' National Institute of Diabetes and Digestive and Kidney Diseases has sponsored the Nonalcoholic Steatohepatitis Clinical Research Network to coordinate clinical research on aetiology, contributing factors, natural course, and treatment (www.jhucct.com/nash/Default.asp).

Box 2 Recommendations for further research*Population studies*

- Development of appropriate methods for accurate determination of the prevalence of NAFLD and NASH in the community
- Large community based studies to accurately determine the prevalence of NAFLD and NASH and the rate of disease progression

Service development

- Studies to develop robust diagnostic strategies adapted for large scale screening
- Studies to develop strategies for effective triage of patients with NAFLD or NASH so that care can be tailored to the individual's risk of progression
- Biomarker discovery and clinical score development to help in discrimination of steatosis from NASH and/or predict risk of fibrosis progression

Basic science and therapeutics development

- Research into genetic and environmental factors that influence risk and rate of disease progression as targets for treatment
- Research into optimum lifestyle interventions to effect sustainable reduction in risk
- Studies of new therapeutic strategies to ameliorate NASH related liver damage and slow fibrosis

What should we do in the light of the uncertainty?

Beyond prognostication, identification of patients with NAFLD will change patient management by (a) providing a greater impetus for modification of diet and lifestyle; (b) guiding drug selection in patients with insulin resistance or diabetes (trial evidence indicates that glitazone oral antidiabetic agents may ameliorate steatohepatitis, although this has not translated into reduced fibrosis^{4 12}); and (c) allowing specific monitoring strategies to be instituted if cirrhosis is present. As a marker of the metabolic syndrome, identification of NAFLD should also prompt aggressive modification of cardiovascular risk factors.

Until further evidence becomes available, management will be dictated partly by the clinical situation. There is insufficient evidence to support routine screening of the general population outside epidemiological studies.⁴ As NASH is strongly associated with insulin resistance, it may be appropriate to assess patients with this condition for advanced liver disease, using biochemical liver function tests and ultrasound imaging of the liver.⁴ No imaging modality is ideal, and serum aminotransferase levels are not highly sensitive for NAFLD. However, until better methods are available, such pragmatic case identification is probably warranted, on the basis of evidence that patients with insulin resistance and increased aminotransferase levels are much more likely to have advanced liver fibrosis.^{4 13}

Where abnormalities are identified—either after targeted investigation or as an incidental finding—investigations need to exclude alternative causes (including viral, autoimmune, and metabolic).^{7 14} Although liver biopsy currently remains the optimum investigation for assessing degree of inflammation and extent of liver fibrosis as markers for risk of liver related morbidity, invasive tests are not generally appropriate or practical outside specialist hepatology practice. A first line, non-invasive assessment based on clinical history, readily available anthropometric and biochemical indices, and radiological investigation may be used to help exclude alternative causes and differentiate the patients with mild disease at low risk of progression from those with more aggressive disease or advanced fibrosis that require additional assessment, targeted intervention, and/or specialist referral.^{7 9 10} As an example, the figure shows the algorithm that we use in our region for investigating and assessing disease severity in patients

with NAFLD. Where this cannot be effectively implemented or if clinical suspicion remains high, onward referral is advised. The ultimate goal should be a multidisciplinary care pathway that delivers case identification and risk stratification through robust screening of those at greatest risk in the primary care setting (and in cardiology and diabetology clinics), and staged interventions first in the community and then through secondary and tertiary care as clinical need dictates.

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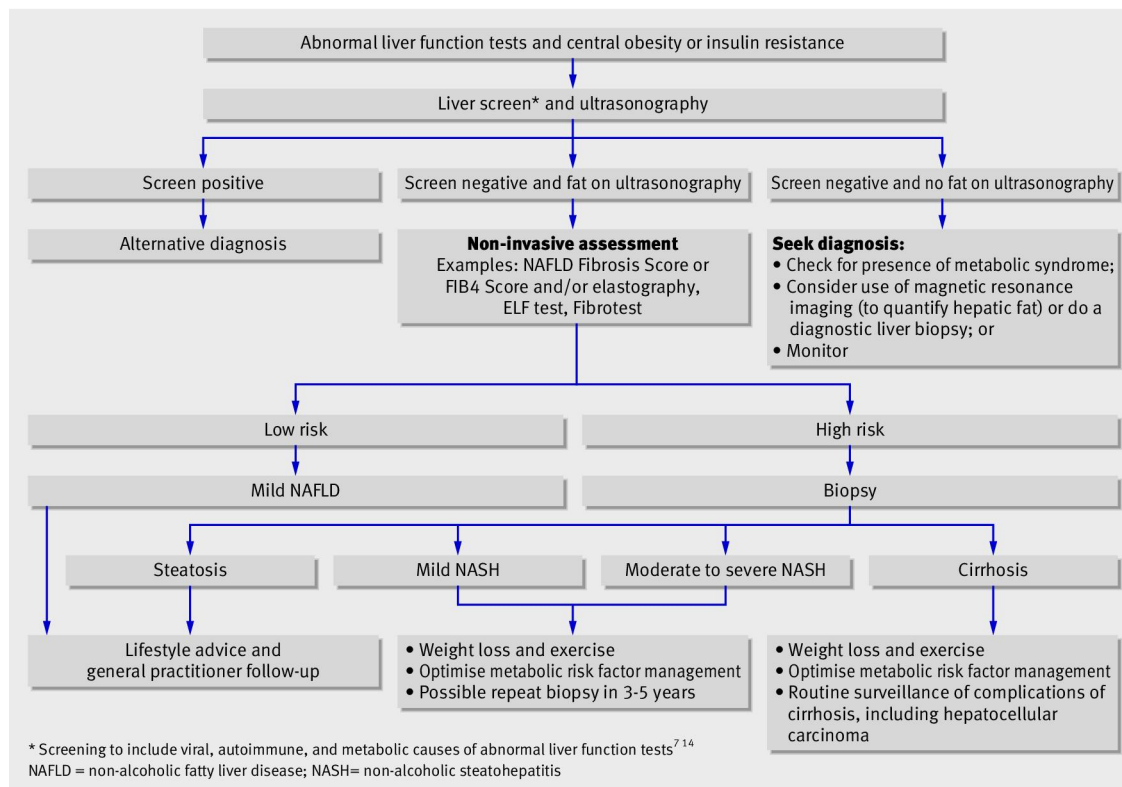
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Figure



Example algorithm for clinical assessment of patients at risk of non-alcoholic fatty liver disease (NAFLD), accepting the many uncertainties that currently exist in this field. The NAFLD Fibrosis Score and FIB4 Score are examples of validated non-proprietary clinical scores for estimating severity of liver fibrosis. Transient elastography (Fibroscan) uses ultrasound to measure the propagation of an induced elastic shear wave through liver tissue, measuring degree of liver stiffness as a surrogate for severity of hepatic fibrosis. The ELF (Enhanced Liver Fibrosis) test and Fibrotest are examples of proprietary techniques that have also been proposed for the non-invasive assessment of liver fibrosis based on clinical biochemical indices and/or panels of specific serum markers