FIGHTING THE FATTY LIVER



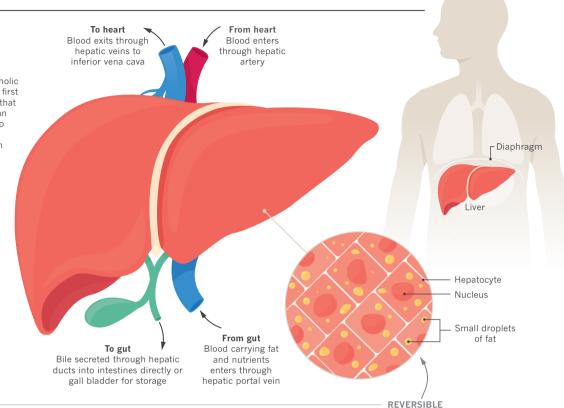
Increased levels of obesity are driving an epidemic of non-alcoholic fatty liver disease. Understanding, diagnosing and treating this progressive condition are now priorities. By **Liam Drew**; illustration by **Lucy Reading-Ikkanda**

CALORIES NOT ALCOHOL

An advanced stage of non-alcoholic fatty liver disease (NAFLD) was first described in 1980, confirming that liver disease characterized by an accumulation of fat can develop in people who do not consume excess alcohol¹. Associated with obesity and type 2 diabetes, NAFLD is set to become the most common cause of serious liver disease in many nations.

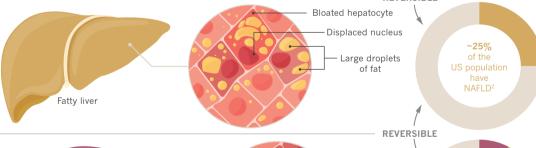
1 HEALTHY LIVER

The liver carries out many tasks, including processing nutrients absorbed from the gut, and controlling the levels of glucose, fat and protein in the blood. It stores carbohydrates and a limited amount of fat. Most liver cells are hepatocytes, which can metabolize almost all types of nutrient. A healthy hepatocyte contains a nucleus at its centre and evenly distributed droplets of fat.



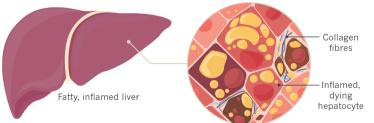
2 NAFLD

In NAFLD, hepatocytes accumulate excess fat, a process known as steatosis. Such fat can come from the diet, be made in the liver or be released by insulin-resistant fatty (adipose) tissue.



3 NASH

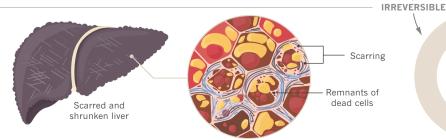
If accumulated fat causes stress and injury to hepatocytes, non-alcoholic steatohepatitis (NASH) develops. Already-bloated hepatocytes swell further and start to die, causing inflammation. Scarring (fibrosis) occurs as collagen fibres replace dead cells.



Up to 30% of people with NAFLD will develop NASH²

4 cirrhosis

Over the years or decades, dead hepatocytes are broken down and scar tissue accumulates, which stiffens the liver and impairs its function. Known as cirrhosis, this can lead to liver failure and an increased risk of liver cancer.



Up to 20% of people with NASH may go on to develop cirrhosis³

RISK FACTORS

Age, gender and genetics all contribute to a person's risk of developing NAFLD and NASH. But the main risk factors are obesity and diabetes, as well as other features of metabolic syndrome, including high blood pressure and insulin resistance.

OBESITY

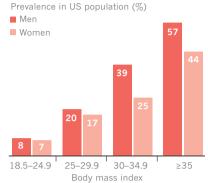
The link between obesity, its complications and NAFLD is strong.

so too has the prevalence of NAFLD⁴. US population with obesity (%) Chronic liver disease in US caused by NAFLD (%) 63 47 30 33

1999-2004

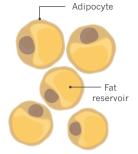
As levels of obesity have increased.

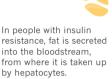
NAFLD increases in prevalence with body mass index, and is more common in men⁵.



DIABETES AND INSULIN RESISTANCE

In healthy people, insulin inhibits the breakdown and release of fat by fat cells (adipocytes).







DIAGNOSIS

1988-1994

To determine the extent of NAFLD and associated fibrosis, and to monitor patients' responses to treatment — without using an invasive liver biopsy — biomarker discovery and advances in imaging technology are needed.

2005-2008



IN THE BLOOD

Although current blood tests for liver disease can help to assess the severity of NAFLD, researchers are seeking new biomarkers with concentrations that reliably correlate with disease activity.

GUIT

ULTRASOUND

Diagnostic tools that use ultrasound technology can help to assess the health of the liver, but the fine resolution and sensitivity of such techniques needs improvement.

Ultrasound

probe

Fatty liver

Absorbs a large proportion of ultrasound waves

Scarred and stiffened liver

Shear waves travel more rapidly through damaged tissue

MORE THAN 75 MILLION

people in the Inited States ma have NAFLD²

HALTING NAFLD

The cornerstones of NAFLD treatment are weight loss and increased amounts of exercise, but maintaining these lifestyle changes can be hard. NASH is now considered to be a serious condition that requires the development of targeted drugs. As a result, hundreds of trials of potential treatment strategies are under way.

Fat

Inhibiting enzymes in the gut that break down fats (lipases) to limit the absorption of fat by blood, as well as bariatric surgery, may aid weight loss to help resolve NAFLD.

Gut-liver interactions

Modifying the gut microbiome with probiotic bacteria may promote intestinal-wall integrity, preventing inflammation-causing bacterial products from reaching the liver.

Metabolic stress

Many drugs aim to reverse the accumulation of fat or its damaging effects. Some mimic hormones; others block pathogenic signalling pathways or alter fat processing directly.

LIVER -Inflammation

Drugs that block receptors for chemokines released by white blood cells in the liver (Kupffer cells), inhibit pro-inflammatory enzymes, or reduce oxidative stress, are being tested.

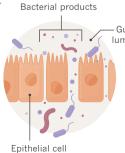
Fibrosis

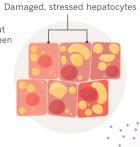
Hepatic stellate cells in the liver mediate fibrosis. Drugs that block receptors on the surfaces of these cells and antibodies that inactivate key fibrotic molecules are in development.

Henatic stellate cell

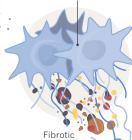
Lipase

Absorbable fat droplets









matrix

Sources: 1. Ludwig, J., Viggiano, T. R., McGill, D. B. & Oh, B. J. Mayo Clin. Proc. 55, 434–438 (1980). 2. Younossi, Z. M. et al. Hepatology 64, 73-84 (2016). 3. Rinella, M. E. JAMA 313, 2263–2273 (2015). 4. Younossi, Z. M. et al. Clin. Gastroenterol. Hepatol. 9, 524–530 (2011). 5. Lazo, M. et al. Am. J. Epidemiol. 178, 38–45 (2013).